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P,N-Type benzimidazolyl phosphine ligands for the palladium-catalyzed Suzuki coupling of potassium aryltrifluoroborates and aryl chlorides

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ABSTRACT

This study describes the efficacy of P,N-type benzimidazolyl phosphine ligands, which can be easily synthesized from commercially available and inexpensive starting materials. The application of this ligand array in palladium-catalyzed Suzuki–Miyaura coupling reaction of aryl chlorides with potassium aryltrifluoroborates is described. The air stable benzimidazolyl phosphines in combination with a palladium metal precursor provides highly effective catalysts for the Suzuki–Miyaura coupling of unactivated aryl chlorides and can achieve a catalyst loading of only 0.05 mol %.

Palladium-catalyzed Suzuki–Miyaura coupling reactions of arylboronic acids with aryl halides represent a versatile method for the preparation of diversified biaryls, which have a myriad of applications in pharmaceutical, material, and agricultural chemistry.[1] Advantages of Suzuki–Miyaura coupling include high functional group tolerance, easily separable, and nontoxic byproducts, and the commercial availability of boron coupling partners. These advantages have made Suzuki–Miyaura coupling both a popular and effective tool.[2]

In general, arylboronic acids are good nucleophilic organoboron reagents in Suzuki–Miyaura coupling reaction.[3] However, boronic acids are noted to never be ideal because they exhibit several drawbacks such as the partial formation of dimeric and cyclic trimeric boroxines (which depend on storage water content). This structural ambiguity affects the stoichiometry of boronic acids added to the intended reaction. Organotrifluoroborate salts are attractive alternatives to aryl and heteroarylboronic acids because they are usually sold in high purity from commercial sources and are readily available from other organoboron compounds.[4,5] Recently, Molander,[4,6] Buchwald,[7] and many other respected researchers[8] made superb efforts to make advancements toward transition metal-catalyzed Suzuki–Miyaura coupling using organotrifluoroborate salts as coupling partners.

Cross-coupling process efficiency has been widely recognized to be significantly affected by the structure of the ligand. Therefore, a strategic ligand modification with appropriate steric/electronic natures toward great diversity is crucial in dealing with problematic and specific substrates in this area. The advancement of some notable ligands such as t-Bu$_3$P,[9] Bellers's PAP,[10] Buchwald's biaryl-phosphines,[11] Hartwig's Q-Phos,[12] and Verkade's amino-phosphine[13] provide excellent catalytic activity in various cross-coupling of aryl halides (especially aryl chlorides)[14] (Fig. 1).[15]

Phosphine ligands that possess a potential hemilabile coordinating group have been studied in the past decade.[16] In 2004, Hor co-workers reported a study on active ferroceneyl P,N-type ligands with imino group for Suzuki–Miyaura coupling reaction.[17]

The X-ray crystal structures from the study showed that the ferrocenyl hemilabile ligands provided both P and N coordination to the palladium center. In 2005, a similar ligand using an aryl scaffold was also found to be effective in coupling processes.[18] Additionally, Liang et al. reported an amido phosphino complex as an effective catalyst for the Suzuki coupling of aryl chloride[19] and He et al. reported the use of bis(aminephosphine) palladium chelated complexes for the Suzuki coupling of aryl bromide (Fig. 2).[20]

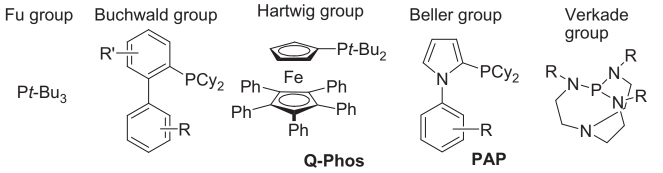

Figure 1. Recent development on effective phosphine ligands.

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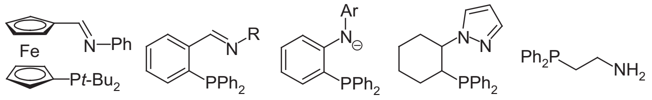


Figure 2. Recent developments on P,N ligands for Suzuki coupling reaction.

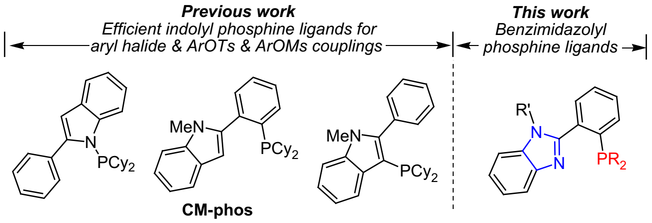
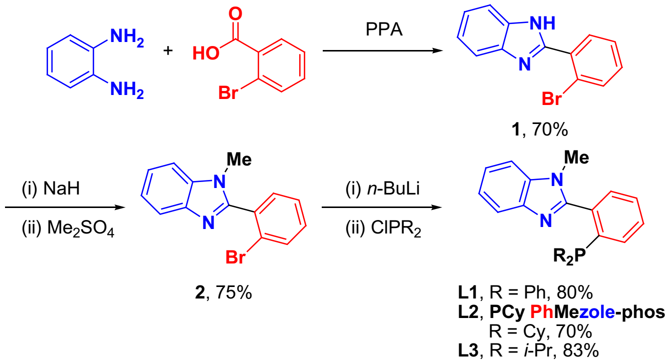


Figure 3. Efficient indolyl phosphine ligands for coupling reactions.



Scheme 1. Synthetic pathway of benzimidazolyl phosphine ligands.

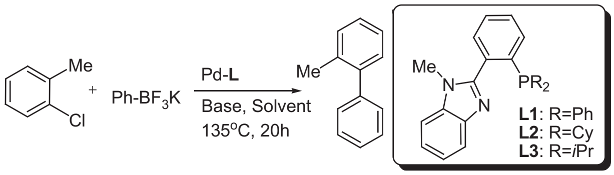
Although a variety of ligands have been introduced, a rapid assembly of structurally diverse ligand systems via simple synthetic methods is still important for the development of versatile catalysts for widespread applications of coupling reactions. In continuing our interest in developing heterocyclic phosphine ligands (Fig. 3),[21] we herein report our exploration of a benzimidazole-derived phosphine. This class of ligands contains a tunable main 2-phenylbenzimidazole skeleton. The N-chelating group on the benzimidazole ring provides weak coordinating properties for potential dynamic interaction to possibly lengthen catalyst longevity. The attached tunable phosphino group at the bottom ring can provide electron-richness and potential electronic fine-tuning.

The ligand precursor can be synthesized through simple condensation of the inexpensive *o*-phenylenediamine and 2-bromobenzoic acid in the presence of polyphosphoric acid.[22] Moreover, the phosphination of the benzimidazolyl precursor can give the corresponding benzimidazolyl phosphines in good to excellence yields (Scheme 1). It is noteworthy that this class of ligand exhibits high air stability in both solid and solution states.[23]

To test the effectiveness of the benzimidazolyl phosphine ligands, 2-chlorotoluene coupled with potassium phenyltriflouroborate was used as the benchmark entry (Table 1). Commonly used organic solvents were firstly examined. Alcoholic solvents such as *t*-BuOH and *t*-amyl alcohol showed superior result when compared to the other polar aprotic solvents (Table 1, entries 1–5). These better results of the alcoholic solvents may be due to the increasing solubility of the triflouroborate salt. Mixing *t*-BuOH with toluene gave the best results among those single solvents (Table 1, entry 6).

For the metal source, $Pd(dba)_2$ gave the best result among $Pd(OAc)_2$, $Pd(dba)_2$, and $Pd_2(dba)_3$ (Table 1, entries 7, 8, 12, 13). Upon varying the metal/ligand ratio from 1:1 to 1:4, the ratio of 1:2 provided the highest yield (Table 1, entries 7, 9–11). The use of $Pd(dba)_2$ and metal/ligand ratio 1:2 was then chosen for further screening process. Several common inorganic bases were

Table 1
Optimization of reaction conditions[a]



Entry	Pd source	Mol % Pd (%)	M:L	Solvent	Base	Yeild[b] (%)
1	$Pd(OAc)_2$	0.5	1:2	*t*-BuOH	$K_3PO_4{\cdot}H_2O$	70
2	$Pd(OAc)_2$	0.5	1:2	Toluene	$K_3PO_4{\cdot}H_2O$	16
3	$Pd(OAc)_2$	0.5	1:2	Dioxane	$K_3PO_4{\cdot}H_2O$	16
4	$Pd(OAc)_2$	0.5	1:2	DMF	$K_3PO_4{\cdot}H_2O$	15
5	$Pd(OAc)_2$	0.5	1:2	t-Amyl alcohol	$K_3PO_4{\cdot}H_2O$	60
6	$Pd(OAc)_2$	0.5	1:2	*t*-BuOH/toluene (1:1)	$K_3PO_4{\cdot}H_2O$	99
7	$Pd(OAc)_2$	0.2	1:2	*t*-BuOH/toluene (1:1)	$K_3PO_4{\cdot}H_2O$	99
8	$Pd_2(dba)_3$	0.2	1:2	*t*-BuOH/toluene (1:1)	$K_3PO_4{\cdot}H_2O$	34
9	$Pd(dba)_2$	0.2	1:2	*t*-BuOH/toluene (1:1)	$K_3PO_4{\cdot}H_2O$	44
10	$Pd(dba)_2$	0.2	1:3	*t*-BuOH/toluene (1:1)	$K_3PO_4{\cdot}H_2O$	55
11	$Pd(dba)_2$	0.2	1:4	*t*-BuOH/toluene (1:1)	$K_3PO_4{\cdot}H_2O$	37
12	$Pd(dba)_2$	0.1	1:2	*t*-BuOH/toluene (1:1)	$K_3PO_4{\cdot}H_2O$	82
13	$Pd(dba)_2$	0.1	1:2	*t*-BuOH/toluene (1:1)	$K_3PO_4{\cdot}H_2O$	28
14	$Pd(dba)_2$	0.1	1:2	*t*-BuOH/toluene (1:1)	*t*-BuONa	12
15	$Pd(dba)_2$	0.1	1:2	*t*-BuOH/toluene (1:1)	Cs_2CO_3	10
16	$Pd(dba)_2$	0.1	1:2	*t*-BuOH/toluene (1:1)	K_3PO_4	56
17	$Pd(dba)_2$	0.1	1:2	*t*-BuOH/toluene (1:1)	CsF	3
18	$Pd(dba)_2$	0.1	1:2	*t*-BuOH/toluene (1:1)	K_2CO_3	49
19	$Pd(dba)_2$	0.1	1:2	*t*-BuOH/toluene (1:1)	Na_2CO_3	44
20[c]	$Pd(dba)_2$	0.1	1:2	*t*-BuOH/toluene (1:1)	$K_3PO_4{\cdot}H_2O$	1
21[d]	$Pd(dba)_2$	0.1	1:2	*t*-BuOH/toluene (1:1)	$K_3PO_4{\cdot}H_2O$	80

[a] Reaction conditions: Pd-**L2**, 2-chlorotoluene (1.0 mmol), $PhBF_3K$ (1.5 mmol), base (3.0 mmol), solvent (3.0 mL) were stirred for 20 h at 135 °C under nitrogen.

[b] Calibrated GC yields were reported using dodecane as the internal standard.

[c] **L1** used as ligand.

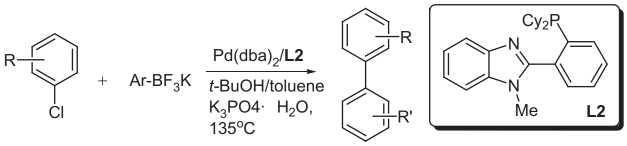
[d] **L3** used as ligand.

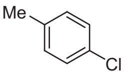
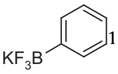
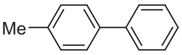
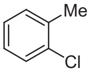
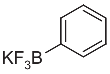
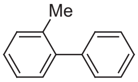
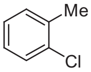
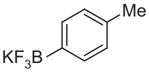
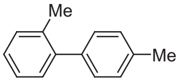
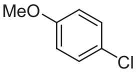
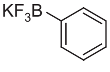
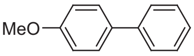
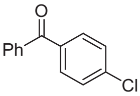
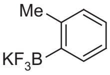
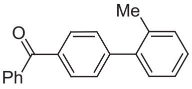
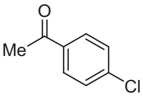
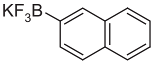
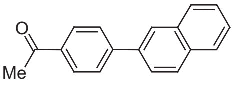
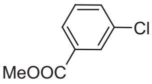
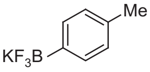
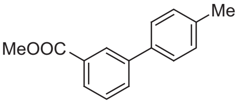
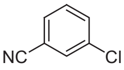
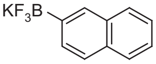
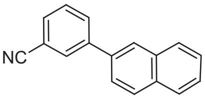
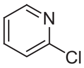
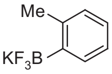
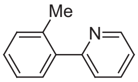
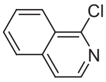
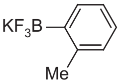
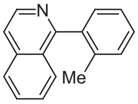
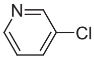
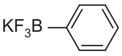
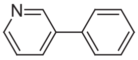
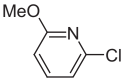
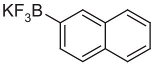
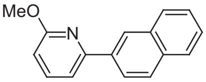
examined in the presence of ligand **L2**. $K_3PO_4{\cdot}H_2O$ was found to be the best base of choice in this catalytic system (Table 1, entries 12, 14–19). Ligand **L1** with a diphenylphosphino moiety provided trace conversion while the dicyclohexylphosphino analogue, **L2**, gave the best catalytic activity. Ligand **L3** bearing a diisopropylphosphino moiety showed a low catalytic activity toward the Suzuki coupling reaction (Table 1, entries 20 and 21).

The scope of this reaction was then investigated under the optimized conditions. A range of aryl chlorides were examined and the results are listed in Table 2. The deactivated aryl chloride containing a *para*-methoxy substituted group was found to be a feasible coupling partner (Table 2, entry 4). *ortho*-Substituted aryl chlorides and aryltrifluoroborates were also good substrates for this reaction (Table 2, entries 2, 3, 5). A variety of common functional groups were compatible under these mild reaction conditions. The functionalized aryl chlorides containing keto, ester, and nitrile groups were found to be effective electrophiles (Table 2, entries 5–8). Apart from a variety of aryl chlorides, heteroaryl chlorides were also examined. Quinolyl and pyridyl substrates could couple with potassium aryltrifluoroborate to furnish products in moderate to excellent yields. (Table 2, entries 9–12).

In conclusion, we have developed a series of efficient P,N-type benzimidazolyl phosphine ligands, which can be easily synthesized from inexpensive and commercially available starting materials. Palladium complexes derived from these ligands provide highly active catalysts for Suzuki–Miyaura coupling of aryl chlorides with potassium aryltrifluoroborates. Considering the simplicity of the ligand synthesis as well as the easy modification of the ligand

Table 2
Palladium-catalyzed Suzuki coupling of ArCl with $ArBF_3K$[a]



Entry	ArCl	Ar′-BF_3K	Product	Mol % Pd	Yeild[b] (%)
1				0.2	94
2				0.2	98
3				0.2	98
4				0.2	79
5				0.05	99
6				0.05	92
7				0.05	85
8				0.05	83
9				0.05	88
10				0.05	80
11				0.05	98
12				0.05	99

[a] Reaction conditions: $Pd(dba)_2$-L2 = 1:2, ArCl (1.0 mmol), $ArBF_3K$ (1.5 mmol), $K_3PO_4{\cdot}H_2O$ (3.0 mmol), *t*-BuOH/toluene (1:1) (3.0 mL) were stirred for 24 h at 135 °C under nitrogen. Catalyst loading and time for the reactions were not optimized.

[b] Isolated yield.

skeleton, we anticipate that further enhancements in reactivity and versatility of the ligand series will be attainable.

Acknowledgments

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References and notes

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