Buchwald–Hartwig Amination of Aryl Chlorides Catalyzed by Easily Accessible Benzimidazolyl Phosphine-Pd Complexes

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Abstract: This study describes the efficacy of benzimidazolyl phosphine ligands, which are easily synthesized from inexpensive and commercially available *o*-phenylenediamine, 2-bormobenzoic acid, and chlorophosphines, in the Buchwald–Hartwig amination of aryl chlorides. Primary and secondary aromatic/aliphatic amines are effective substrates in this catalytic system. Functional groups such as keto and esters are also compatible. The catalyst loading can be reduced to 0.1 mol% Pd.

Key words: palladium, cross-coupling, amination, aryl chlorides, phosphine

Buchwald–Hartwig amination is one of the most powerful tools available for constructing aromatic carbon–nitrogen bonds in synthetic organic chemistry.[1] This method has been widely used in the synthesis of pharmaceutically useful intermediates and biologically active compounds and materials.[1] Since the first catalytic amination protocol was discovered,[2] efforts toward increasing the reaction efficacy have been actively pursued.[3] Recently, aryl iodides and bromides were reported to be successfully converted into the corresponding aryl amines by employing simple copper[4] or iron salts[5] with various ligands as catalysts. However, the use of easily available and inexpensive aryl chlorides still requires a highly active palladium catalyst for the amination reactions. For cross-coupling processes, it has been recognized that the efficiency is significantly affected by the structure of the ligand. Therefore, flexible modifications that result in ligands with appropriate steric/electronic nature are crucial in dealing with problematic and specific substrates in this area. The advancement of some notable ligands such as *t*-Bu_3P,[6] Bellers's PAP,[7] Buchwald's biaryl-phosphines,[8] Hartwig's Q-Phos,[9] and Verkade's amino-phosphine[10] provide excellent catalytic activity in various cross-coupling reactions of aryl halides and, especially, aryl chlorides (Figure 1).[11]

Phosphine ligands that possess a potentially hemilabile coordinating group have been studied in the past decade.[12] In 1999, Guram, Bei and co-workers reported a preliminary study of *P*,*N*-type ligands (Figure 2) for amination reactions of aryl chlorides.[13] Although these *P*,*N*-type ligands only showed low to moderate activity, they demonstrated the possibility of using *P*,*N*-type ligands in amination reactions. Recently, Stradiotto and co-workers reported a series of highly effective DalPhos *P*,*N*-ligands for amination reactions (Figure 2).[14]

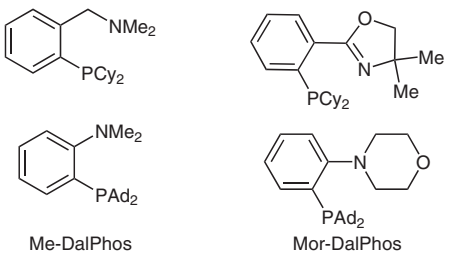

Figure 2 Recently developed *P*,*N*-ligands for amination reactions

Although a variety of ligands have been developed, the rapid assembly of structurally diverse ligand scaffolds through simple synthetic methods is still important for the development of versatile catalysts for widespread applications of coupling reactions. In a continuation of our interest in developing heterocyclic phosphine ligands,[15] we herein report our exploration of a benzimidazole-derived phosphine that contains attractive features of a resourceful ligand: (i) a tunable 2-phenylbenzimidazole skeleton providing potential diversification; (ii) a hemilabile chelating

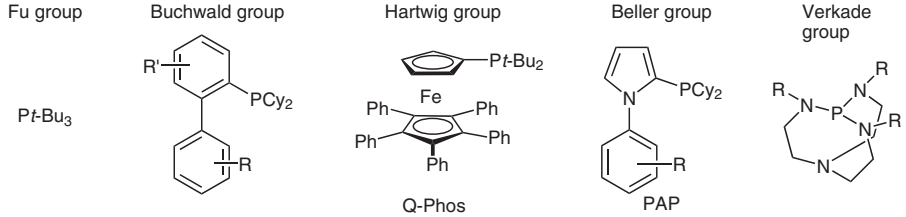

Figure 1 Some recently developed effective phosphine ligands

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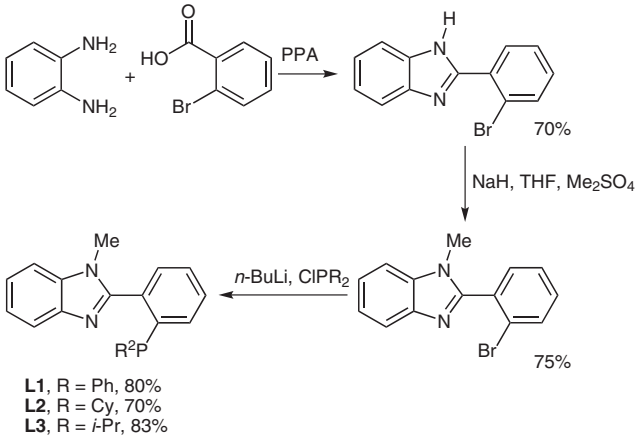
group that can provide weak coordinating properties for dynamic interaction of metal centers that could increase catalyst longevity, and (iii) a tunable phosphino group on the aryl ring that could provide electron density and potential electronic fine-tuning.



Scheme 1 Synthetic pathway to benzimidazolyl phosphine ligands

The ligand precursor of these heterocyclic phosphine ligands was efficiently obtained through simple condensation between commercially available and inexpensive *o*-phenylenediamine and 2-bromobenzoic acid in the presence of polyphosphoric acid.[16] Notably, a practical scale-up synthesis of up to 100 mmol was possible without difficulties in either synthetic or purification processes. The methylated ligand precursors were then lithiated by treatment with *n*-BuLi and trapped with $ClPR_2$, affording the corresponding benzimidazolyl phosphines in good to excellence yields (Scheme 1). **L2** was recrystallized from ethyl acetate and was subjected to an X-ray diffraction study (Figure 3).[17] It is worth noting that this class of ligand exhibits high air-stability in both solid and solution states.[18]

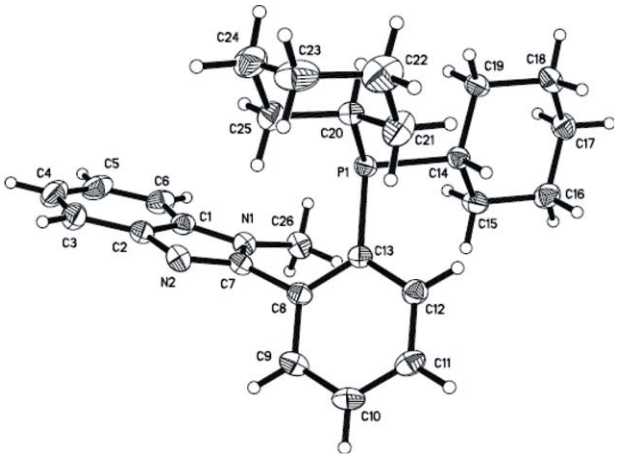
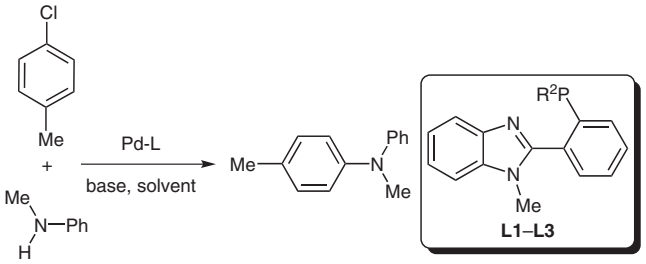


Figure 3 ORTEP representation of benzimidazolyl phosphine ligand **L2** (30% probability ellipsoids). Hydrogen atoms have been omitted for clarity. Selected bond distances (Å) and angles (deg): P(1)–C(13), 1.8536(14); P(1)–C(20), 1.8597(15); P(1)–C(14), 1.8583(15); C(13)–P(1)–C(14), 101.22(6); C(13)–P(1)–C(20), 102.88(7); C(14)–P(1)–C(20), 104.06(7).

To test the effectiveness of the benzimidazole-derived ligands, 4-chlorotoluene with *N*-methylaniline were used as model substrates. A catalyst loading of 0.5 mol% Pd was initially applied in probing the ligand efficacy (Table 1).

With the benzimidazolyl ligands **L1**–**L3** in hand, a survey of Pd sources was subsequently started using toluene as

Table 1 Investigations on the Effectiveness of the Benzimidazolyl Phosphine Ligands in the Amination of Aryl Chlorides[a]



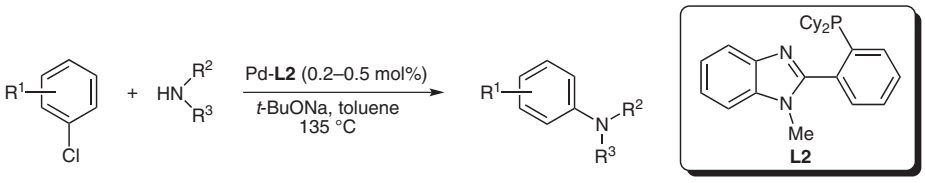
Entry	Pd source	Pd (%)	Base	Solvent	Yield (%)[b]
1[c]	$Pd(OAc)_2$	0.5	*t*-BuONa	toluene	84
2[c]	$Pd(dba)_2$	0.5	*t*-BuONa	toluene	86
3[c]	$Pd_2(dba)_3$	0.5	*t*-BuONa	toluene	99
4[c]	$PdCl_2(MeCN)_2$	0.5	*t*-BuONa	toluene	84
5[d]	$Pd(OAc)_2$	0.5	*t*-BuONa	toluene	62
6[e]	$Pd(OAc)_2$	0.5	*t*-BuONa	toluene	92
7	$Pd(OAc)_2$	0.5	*t*-BuONa	toluene	96
8	$Pd(OAc)_2$	0.2	*t*-BuONa	toluene	83
9	$Pd_2(dba)_3$	0.2	*t*-BuONa	toluene	94
10	$Pd_2(dba)_3$	0.2	*t*-BuONa	dioxane	93
11	$Pd_2(dba)_3$	0.1	*t*-BuONa	toluene	74
12	$Pd_2(dba)_3$	0.1	*t*-BuONa	dioxane	66
13	$Pd_2(dba)_3$	0.1	*t*-BuONa	*p*-xylene	67
14	$Pd_2(dba)_3$	0.1	K_3PO_4	toluene	65
15	$Pd_2(dba)_3$	0.2	K_3PO_4	toluene	85
16	$Pd_2(dba)_3$	0.1	Cs_2CO_3	toluene	34
17	$Pd_2(dba)_3$	0.1	K_2CO_3	toluene	4
18[f]	$Pd_2(dba)_3$	0.2	*t*-BuONa	toluene	1
19[g]	$Pd_2(dba)_3$	0.2	*t*-BuONa	toluene	81

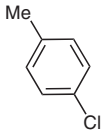
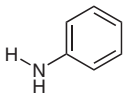
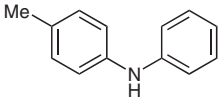
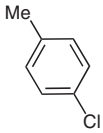
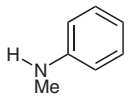
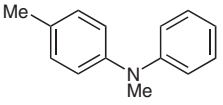
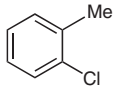
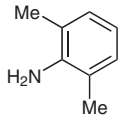
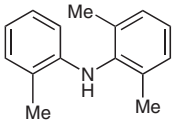
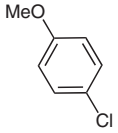
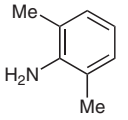
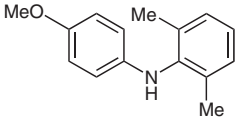
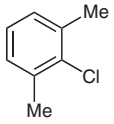
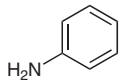
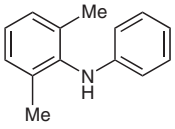
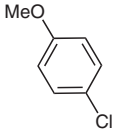
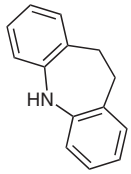
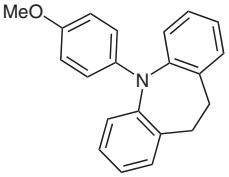
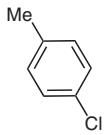
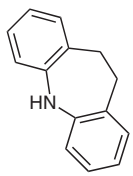
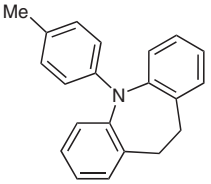
[a] Reaction conditions: Pd, ligand **L2**, Pd/L ratio1:4, ArCl (1.0 mmol), *N*-methylaniline (1.5 mmol), base (2.5 mmol), solvent (3.0 mL), 20 h, 135 °C under nitrogen.
[b] Calibrated GC yields were calculated using dodecane as the internal standard.
[c] Pd/L ratio 1:2.
[d] Pd/L ratio 1:1.
[e] Pd/L ratio 1:3.
[f] Ligand = **L1**.
[g] Ligand = **L3**.

the solvent and *t*-BuONa as the base. Use of $Pd_2(dba)_3$ gave the best result among $Pd(OAc)_2$, $Pd(dba)_2$ and $PdCl_2(MeCN)_2$ (Table 1, entries 1–4), and a metal/ligand ratio of 1:4 provided the highest yield (Table 1, entries 1 and 5–7). These conditions were then chosen for further screening. Among the commonly used organic solvents examined, toluene gave the best result (Table 1, entries 9–13). Several bases were examined in the presence of ligand **L2**, and *t*-BuONa was found to be the base of choice in this catalytic system (Table 1, entries 11 and 14–17). It is worth noting that the weaker base K_3PO_4 was also effective in this system. Ligand **L1**, with a diphenylphosphino moiety, provided trace amounts of substrate conversion, whereas the dicyclohexylphosphino analogue, **L2**, showed the best performance (Table 1, entries 9, 18, and 19). Ligand **L3**, bearing a diisopropylphosphino moiety, gave a lower catalytic activity in the amination reaction.

We first employed the preliminary optimized reaction conditions for the amination of aryl chlorides with aromatic amines (Table 2).[19] Aniline and *N*-methylaniline were effective substrates that gave the corresponding

Table 2 Palladium-Catalyzed Amination of ArCl with Aromatic Amines[a]



Entry	ArCl	Amine	Product	Pd (mol%)	Time (h)	Yield (%)[b]
1				0.2	20	99
2				0.2	20	90
3				0.2	20	99
4				0.2	20	90
5				0.5	24	90
6				0.2	20	99
7				0.2	20	94

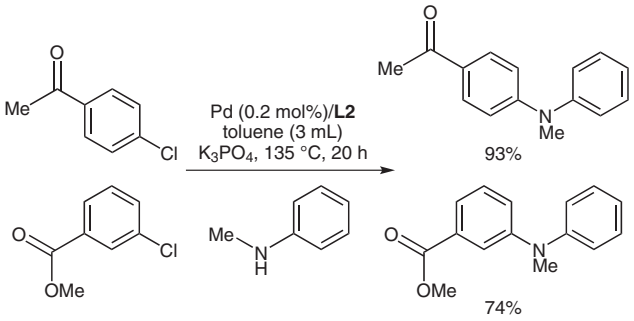
[a] Reaction conditions: ArCl (1.0 mmol), amine (1.5 mmol), *t*-BuONa (2.5 mmol), $Pd_2(dba)_3$/**L2** = 1:4, toluene (3.0 mL), 135 °C under nitrogen.
[b] Isolated yield.

products in excellent yields (Table 2, entries 1 and 2). A sterically hindered amine was also found to be a suitable coupling partner in this C–N bond formation, generating the tri-*ortho*-substituted product (Table 2, entry 3). Amination of a deactivated aryl chloride did not diminish the desired product yields when compared with amination of neutral aryl chloride (Table 2, entry 4). Furthermore, a fused cyclic amine also coupled well with chloroarenes (Table 2, entries 6 and 7).

We than examined the reactivity of the Pd-**L2** system towards the amination of aryl chlorides with cyclic and aliphatic amines (Table 3). Morpholine and piperidine showed excellent reactivity in the amination reaction (Table 3, entries 1–3). An acyclic secondary amine such as dihexylamine was also compatible with this system (Table 3, entry 4).

The coupling of heteroaryl chlorides was also studied. The results showed that 2-chloropyridine was an effective substrate for the amination reaction (Table 4). Under 0.5 mol% Pd loading, cyclic, aromatic and aliphatic amines were transformed into the corresponding coupled products in excellent yields. In the absence of the $Pd_2(dba)_3$, no coupling product between 2-chloropyridine and dibenzylamine was observed (Table 4, entries 5 and 6).

Functional group compatibility is one of the major concerns for the effectiveness of an amination system since

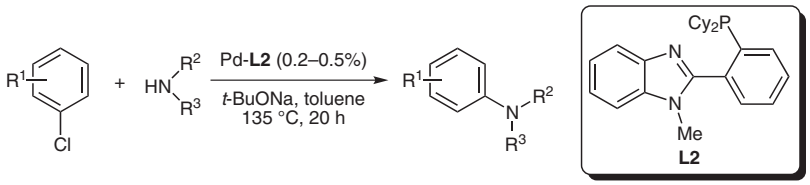


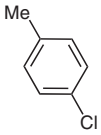
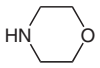
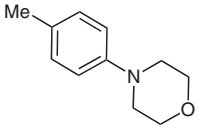
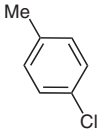
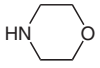
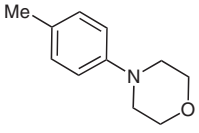
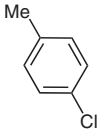
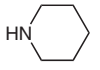
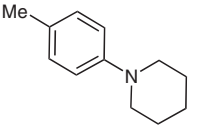
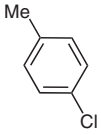
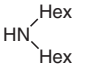
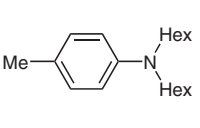
Scheme 2 Palladium-catalyzed amination of functionalized aryl chloride

one of the important applications of amination reactions is to synthesize pharmaceutically useful intermediates that usually contain reactive functional groups. In this system, using K_3PO_4 as base, reactive functional groups such as keto and ester moieties were also compatible and the desired products were obtained in good yield (Scheme 2).

In conclusion, we have developed a series of efficient benzimidazolyl phosphine ligands that can be used in aromatic C–N bond-forming reactions. These ligands can be easily accessible on large scales using inexpensive and commercially available starting materials. Palladium complexes derived from these ligands provide highly active catalysts for amination of aryl chlorides with aromatic

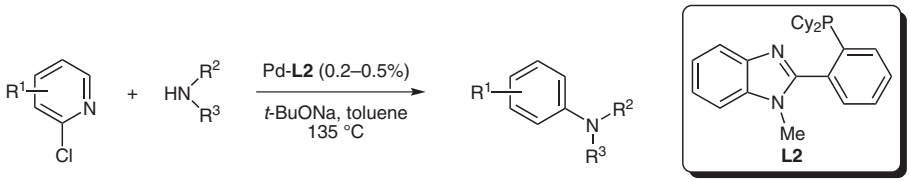
Table 3 Palladium-Catalyzed Amination of ArCl with Aliphatic Amines[a]

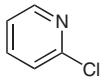
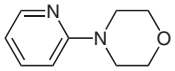
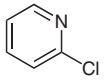
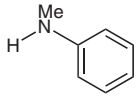
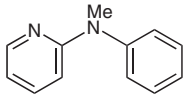
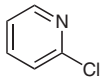
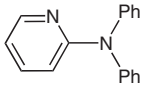
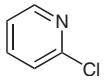
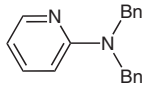
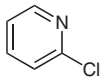
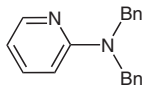
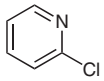
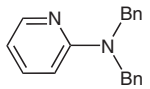
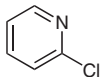
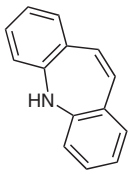
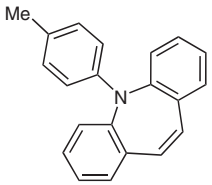


Entry	ArCl	Amine	Product	Pd (mol%)	Yield (%)[b]
1				0.2	89
2				0.2	86
3				0.5	80
4				0.5	73

[a] Reaction conditions: ArCl (1.0 mmol), amine (1.5 mmol), *t*-BuONa (2.5 mmol), $Pd_2(dba)_3$/**L2** = 1:4, toluene (3.0 mL), 20 h, 135 °C under nitrogen.
[b] Isolated yield.

Table 4 Palladium-Catalyzed Amination of Heteroaryl Chlorides[a]



Entry	ArCl	Amine	Product	Pd (mol%)	Time (h)	Yield (%)[b]
1				0.2	20	92
2				0.2	20	99
3				0.5	24	98
4				0.5	24	95
5[c]				0.5	24	0
6[d]				0.5	24	0
7				0.5	24	97

[a] Reaction conditions: ArCl (1.0 mmol), amine (1.5 mmol), *t*-BuONa (2.5 mmol), $Pd_2(dba)_3$/**L2** = 1:4, toluene (3.0 mL), 20 h, 135 °C under nitrogen.
[b] Isolated yield.
[c] Without $Pd_2(dba)_3$ and **L2**.
[d] Without $Pd_2(dba)_3$.

and aliphatic amines. Functional groups such as keto and ester moieties are compatible with the use of K_3PO_4 as base. In view of the simplicity of the ligand synthesis, we anticipate that further diversification of the ligand scaffold will be attainable.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(16) According to the list price from Aldrich (21-2-2011), *o*-phenylenediamine costs 0.18 USD/G and 2-bromobenzoic acid costs 0.88 USD/G.

(17) CCDC-865333 contains the supplementary crystallographic data for **L2**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(18) There was no detectable phosphine oxide signal of **L2** in the ^{31}P NMR spectrum when the solid form of the ligand was allowed to stand under air for one month.

(19) **Palladium-Catalyzed Amination of Aryl Chlorides; General Procedure:** A stock solution of $[Pd_2(dba)_3]$ (0.023 g, 0.10 mmol) and ligand **L** (Pd/**L** = 1:4) were loaded into a reaction tube equipped with a Teflon-coated magnetic stir bar. The tube was evacuated and flushed with nitrogen (3 cycles). A stock solution was prepared by adding freshly distilled toluene (5.0 mL). Bases (2.5 mmol) were loaded into an array of Schlenk tubes. The tubes were evacuated and flushed with nitrogen (3 cycles). Aryl chlorides (1.0 mmol), amines (1.5 mmol) and the stock solution (0.1 mol% Pd per 0.5 mL stock solution) were loaded into the tubes. Toluene was then added to give a total volume of 3.0 mL in each tube. The solutions were stirred at room temperature for several minutes and then placed into a preheated oil bath (135 °C) for the time period indicated in the Tables. After completion of reaction as judged by GC analysis, the reaction tube was allowed to cool to room temperature and the reaction was quenched with water and diluted with EtOAc. The organic layer was separated and the aqueous layer was washed with EtOAc. The combined organic layer was dried, filtered and concentrated under reduced pressure and the crude products were purified by flash column chromatography on silica gel (230–400 mesh) to afford the desired product.
4-Methyl-*N*-phenylaniline (Table 2, entry 1): ^1H NMR (400 MHz, $CDCl_3$): δ = 2.50 (s, 3 H), 5.70 (s, 1 H), 7.05–7.09 (m, 1 H), 7.16–7.19 (m, 4 H), 7.26–7.30 (m, 2 H), 7.40–7.46 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.6, 116.8, 118.8, 120.1, 129.2, 129.7, 130.7, 140.2, 143.9; MS (EI): *m/z* (%) = 183.1 (100) $[M]^+$, 167.1 (20), 91.0(14), 77.1 (10).

