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Oxaphosphole-Based Monophosphorus Ligands for Palladium-Catalyzed Amination Reactions

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Abstract: A novel class of C-2-substituted oxaphosphole-based monophosphines **1–4** has been synthesized. Palladium complexes derived from these ligands and their C-2-unsubstituted analogs provide general catalysts for amination reactions of challenging aryl and heteroaryl halides with sterically hindered anilines and alkylamines.

Keywords: *N*-arylamination; C–N coupling; palladium

The development of new, general methodology for the formation of aromatic carbon-nitrogen bonds is of great significance in many areas of organic synthesis. Due to the versatility and high functional group tolerance of most palladium catalysts, the palladium-catalyzed amination of aryl halides has evolved as a viable alternative to traditional nucleophilic aromatic substitution and various other classical methods of introducing arylamines.[1] Recent advances have focused on the development of novel catalysts to provide broad substrate scope, wide functional group tolerance and at low catalyst loadings. Examples of novel families of ligands include Li's POPd complexes,[2] Nolan's N-heterocyclic carbenes,[3] Verkade's triaminophosphines,[4] Singer's *N*-phenylpyrrole and pyrazole phosphines,[5] Beller's N-substituted heteroarylphosphines,[6] Zhang's triazole phosphines,[7] Kwong's benzamine-derived phosphines,[8] Suzuki's tri-*tert*-alkylphosphines,[9] and Swamy's cyclodiphosphozane.[10] Extensions of well established catalytic systems such as Beller's, Buchwald's, Hartwig's and Kwong's have also been reported to include aryl tosylates,[11] aryl mesylates,[12] and heteroaryl systems[13] as electrophiles, and ammonia[14] and amides[15] as nucleophiles. Palladium-catalyzed aminations have also been developed utilizing continuous flow chemistry.[16] Despite all these advances, the arylation of hindered arylamines with hindered aryl halides has been less explored.[3a,17] Few successful results have been shown for the preparation of tetra-*ortho*-substituted diarylamines from such extremely hindered partners. Therefore, the development of new, efficient and general ligands for amination reactions is important for dealing with the challenging substrates in this area such as deactivated hindered (hetero)aryl halides, sterically hindered arylamines and alkylamines. Herein, we report a new series of *trans*-C-2-substituted oxaphosphole-based monophosphorus ligands **1–4** (Figure 1) and

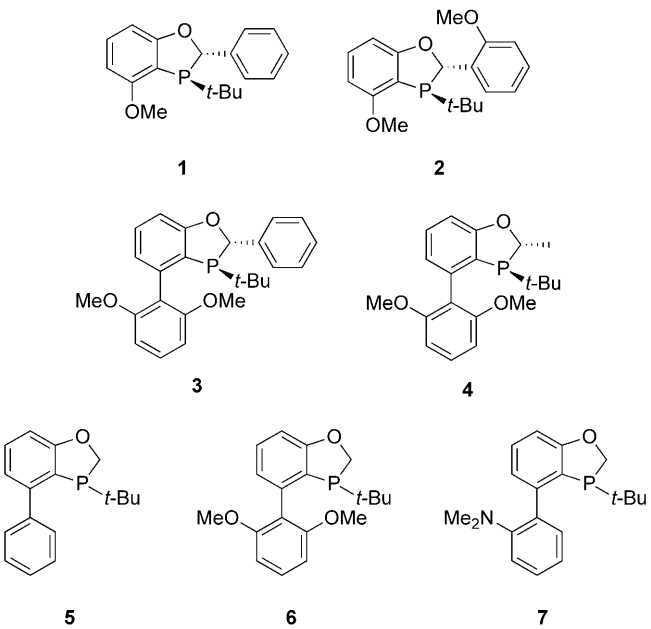
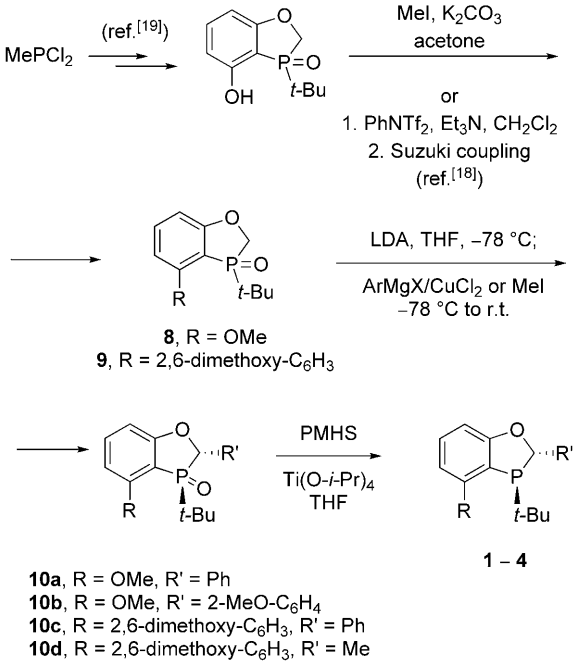


Figure 1. Novel oxaphosphole-based ligands.

their application in palladium-catalyzed amination reactions of challenging aryl and heteroaryl halides with sterically demanding aryl- and alkylamines.

Recently, we described a novel class of biaryl monophosphorus ligands, that is, **5**–**7** (Figure 1), containing a 2,3-dihydrobenzo[*d*][1,3]oxaphosphole core.[18] The effectiveness of ligand **6** (BI-DIME) was demonstrated in palladium-catalyzed Suzuki–Miyaura coupling reactions of various aryl and heteroaryl bromides and chlorides with sterically congested and electron-poor arylboronic acids. The application of monophosphines **5**–**7** in amination reactions was also the subject of the present investigation.

The syntheses of C-2-substituted ligands **1**–**4** were accomplished in two steps from aryl methyl ether **8** or biphenyl **9** (Scheme 1), which was prepared from

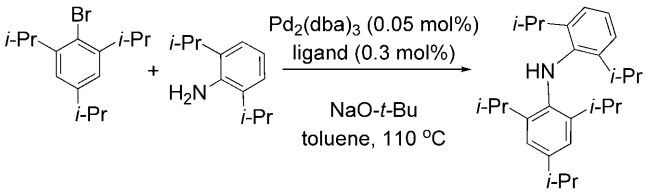


Scheme 1. Synthesis of C-2-substituted oxaphosphole monophosphine ligands **1**–**4**.

methyldichlorophosphine at kilogram scale using our previously reported procedure.[19] The $CuCl_2$-mediated oxidative cross-coupling of lithiated **8** or **9** with various aryl organometallic reagents provided phosphine oxides **10a–c** in approximately 50% yield.[20] For the synthesis of the C-2-methyl substituted ligand **4**, the lithiated **9** was reacted with MeI to afford **10d** in 61% isolated yield. Reduction of the phosphine oxides with polymethyl hydrosiloxane (PMHS) in the presence of $Ti(O\text{-}i\text{-}Pr)_4$[21] afforded 50–90% yields of racemic ligands **1**–**4** which proved to be air-stable solids at room temperature.[22]

To evaluate the effectiveness of these ligands in the Pd-catalyzed amination of challenging aryl halides, we first investigated the reaction between 2,4,6-triisopropylbromobenzene and 2,6-diisopropylaniline (Table 1). Standard conditions for the reactions were

Table 1. Amination of 2,4,6-triisopropylbromobenzene with various ligands.[a]



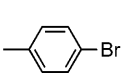
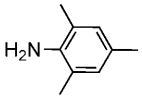
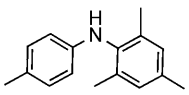
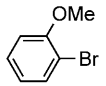
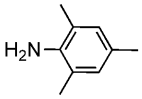
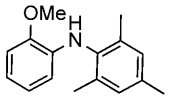
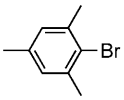
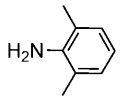
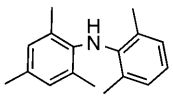
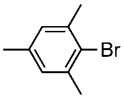
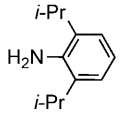
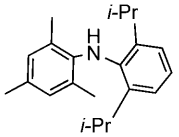
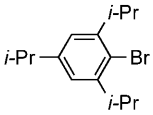
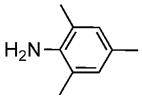
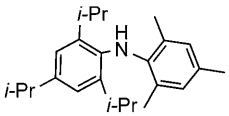
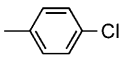
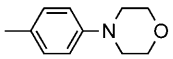
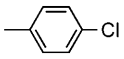
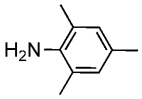
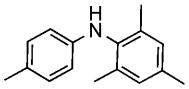
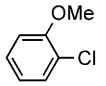
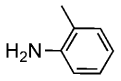
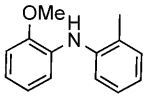
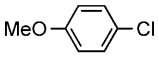
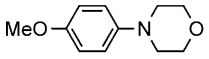
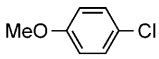
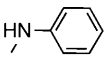
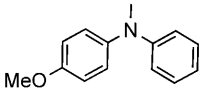
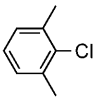
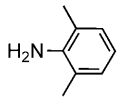
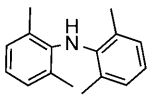
Entry	Ligand	Conversion [%][b]	Yield [%][c]
1	**1**	24	–
2	**2**	61	–
4	**3**	24	–
5	**4**	100	96
6	**5**	72	–
7	**6**	100	98
8	**7**	70	–
9	BINAP	0	–
10	Xantphos	46	–
11	JohnPhos	0	–
12	XPhos	5	–
13	SPhos	18	–

[a] *Conditions:* aryl bromide (1.0 equiv.), amine (1.2 equiv.), Pd/Ligand 1:3, NaO-*t*-Bu (1.5 equiv.), toluene, 110 °C, 20 h.
[b] Conversion by HPLC at 220 nm.
[c] Isolated yields.

2,4,6-triisopropylbromobenzene (1 equiv.), 2,6-diisopropylaniline (1.2 equiv.), NaO-*t*-Bu (1.5 equiv.), $Pd_2(dba)_3$/phosphine (Pd/L 1:3) in toluene (0.5 M solution relative to aryl halide) at 110 °C. While commonly used commercially available ligands such as BINAP, xantphos, JohnPhos, XPhos and SPhos afforded low conversions at 0.1 mol% Pd loading, ligands **4** and **6** provided superior performance with excellent conversions and yields. It is noteworthy that the cross-coupling product is one of the most sterically congested secondary amines reported to date *via* palladium-catalyzed aminations with all four branched *ortho*-substituents.[23] The high performance of ligands **4** and **6** clearly demonstrated the advancement of dihydrobenzooxaphosphole-based ligands for amination of sterically demanding substrates. Both $Pd_2(dba)_3$ and $Pd(OAc)_2$ could be used as palladium sources although the latter provided slightly lower yields of the arylated amine.

Subsequently, the scope of the amination reaction between various aryl halides and aryl- or alkylamines was studied with the simpler ligand **6** (BI-DIME).

Table 2. Amination reactions of aryl bromides and chlorides.[a]

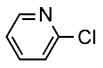
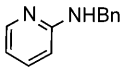
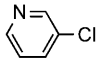
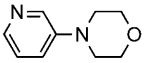
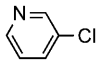
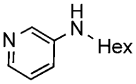
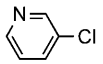
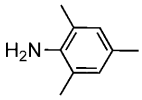
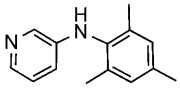
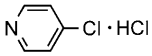
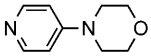
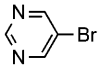
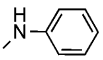
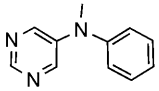
Entry	Halide	Amine	Product	$Pd_2(dba)_3$ (mol%)	Yield [%][b]
1				1.5	90
2				0.5	99
3				0.05	98
4				0.5	97
5				0.5	90
6				0.25	90
7				0.25	95
8				1.0	92[c]
9				2.5	81[c]
10				1.0	94
11				2.5	99

[a] *Conditions:* halide (1.0 equiv.), amine (2 equiv.), $Pd_2(dba)_3$ (0.05–2.5 mol%), ligand **6** (0.3–10 mol%), NaO-*t*-Bu (2 equiv.), toluene, 110 °C, 20 h.
[b] Isolated yields.
[c] *m*-Xylene, 130 °C.

Particular emphasis was given to sterically demanding substrate combinations. The results are summarized in Table 2. Sterically hindered aniline derivatives were efficiently converted (Table 2, entries 1–6 and 11). Furthemore, high yields of isolated product were obtained with electron-rich, thereby electronically deactivated, aryl chlorides and bromides. *ortho*-Substituents on the aryl bromides and chlorides were tolerated as well, leading to the corresponding hindered coupling products in high yields (Table 2, entries 2–5, 10–11). Thus, tetra-*ortho*-substituted diarylamines were prepared in 90–99% yields (Table 2, entries 3–5 and 11). These results demonstrate the broad substrate scope of the $Pd_2(dba)_3$/oxaphosphole systems for amination reactions and its particular effectiveness for sterically demanding substrates.

We also evaluated the scope of the oxaphosphole monophosphine ligands in amination reactions of het-

Table 3. Amination reactions of heteroaryl halides.[a]

Entry	Halide	Amine	Product	Yield [%][b]
1				72
2				82
3				75
4				95
5				99
6				78

[a] *Conditions:* halide (1.0 equiv.), amine (2 equiv.), $Pd_2(dba)_3$ (2.5 mol%), ligand **6** (10 mol%), NaO-*t*-Bu (2 equiv.), toluene, 110 °C, 12–20 h.
[b] Isolated yields.

eroaryl halides (Table 3). 2-, 3- and 4-chloropyridines were viable substrates for catalytic amination reactions using ligand **6** (entries 1–5). A variety of amines proved to be suitable coupling partners including acyclic alkylamines which are usually difficult substrates due to β-hydride elimination of their palladium amide complexes (Table 3, entry 3) and hindered 2,4,6-trimethylaniline (Table 3, entry 4). 5-Bromopyrimidine also reacted with *N*-methylaniline to form the desired coupling product in 78% isolated yield (Table 3, entry 6).

In summary, we have developed a series of dihydrobenzooxaphosphole-based monophosphorus ligands **1–4** bearing a C-2-substituted oxaphosphole backbone. These ligands and their C-2-unsubstituted analogs **5–7** were evaluated in palladium-catalyzed amination reactions of a variety of (hetero)aryl bromides and chlorides with diverse amines including sterically hindered anilines and alkyl amines. In particular, ligand **6** (BI-DIME) proved to be highly efficient in the amination reaction of a wide variety of challenging substrates.

Experimental Section

Typical Procedure for the Amination of 2,4,6-Triisopropylbromobenzene with 2,6-Diisopropylamine

To a mixture of $Pd_2(dba)_3$ (1.1 mg, 0.0012 mmol, 0.05 mol%), ligand **6** (2.5 mg, 0.004 mmol, 0.3 mol%,) and NaO-*t*-Bu (356 mg, 3.71 mmol, 1.5 equiv.) in toluene (4 mL) under argon was added 2,4,6-triisopropylbromobenzene (0.62 mL, 2.47 mmol) and 2,6-diisopropylamine (0.56 mL, 2.96 mmol, 1.2 equiv.). The resulting mixture was stirred at 110 °C for 20 h, and after cooling to room temperature, the mixture was filtered through a pad of celite washing with EtOAc. The filtrate was concentrated to give a residue, which was purified by column chromatography (silica gel, 0–20% EtOAc in hexanes) to provide *N*-(2,4,5-triisopropylphenyl)-*N*-(2,6-diisopropylphenyl)amine as white solid; yield: 919 mg (2.42 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.06$ (d, $J = 7.6$ Hz, 2H), 6.96 (t, $J = 7.6$ Hz, 1H), 6.93 (s, 1H), 4.77 (s, 1H), 3.11 (sept, $J = 6.8$ Hz, 2H), 3.05 (sept, $J = 6.8$ Hz, 2H), 2.86 (sept, $J = 6.8$ Hz, 1H), 1.23 (d, $J = 6.8$ Hz, 6H), 1.08 (d, $J = 6.8$ Hz, 12H), 1.07 (d, $J = 6.8$ Hz, 12H).

See Supporting Information for experimental details, characterization of products and copies of product ^{1}H and ^{13}C NMR spectra.

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[22] The *trans*-relative stereochemistry between the C-2 and the P centers of ligands **1–4** was established by NOE and by analogy to the parent BIBOP and POP ligands described in refs.[19a,19b], respectively. The stereochemistry of MeO-BOP and POP ligands was confirmed by X-ray analysis of their Rh complexes.

[23] Preparation of tetra-branched-*ortho*-substituted diarylamine was previously reported by Verkade using 1 mol% palladium.[17d].

