JOC Article

Phosphaadamantanes as Ligands for Palladium Catalyzed Cross-Coupling Chemistry: Library Synthesis, Characterization, and Screening in the Suzuki Coupling of Alkyl Halides and Tosylates Containing β-Hydrogens with Boronic Acids and Alkylboranes

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A 15-member library of phosphaadamantane ligands has been prepared via *P*-arylation of 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phosphaadamantane. Screening of this tertiary phosphine collection has allowed for the rapid determination of the most suitable ligand, specifically 1,3,5,7-tetramethyl-6-(2,4-dimethoxyphenyl)-2,4,8-trioxa-6-phosphaadamantane, for facilitating Suzuki-type couplings of alkyl halides or tosylates containing β-hydrogens with either boronic acids or alkylboranes.

Organopalladium cross-coupling reactions are among the most useful and reliable methods for carbon−carbon bond formation.[1] The renewed interest in this chemistry has been driven, to a great extent, by the development of synthetic protocols employing sterically demanding, electron-rich phosphine ligands.[2] Utilization of catalytic systems incorporating these bulky phosphines has allowed for the successful coupling of even the least-reactive partners in the Suzuki,[3] Stille,[4] Sonogashira,[5] aryl amination,[6] and ketone arylation[7] reactions among others. A recent addition to the organopalladium family of reactions involves the Suzuki-type couplings of alkyl halides or tosylates containing β-hydrogens with either boronic acids or alkylboranes. While aryl and alkenyl halides have been routinely used in the Suzuki reaction, halides bonded to sp^3-hybridized carbons have been generally overlooked due to the slower rate of oxidative addition of alkyl halides to palladium and their propensity to undergo β-hydride elimination rather than the desired coupling reaction. Fu has shown[8] that the application of palladium catalyst systems utilizing bulky alkylphosphines allows for the Suzuki coupling of alkyl-halides with a variety of boronic acids and alkylboranes with little concomitant elimination product.

Overall, however, a review of the current chemical literature reveals that while certain phosphines accelerate a particular reaction, the same phosphine may have little effect on a different palladium-catalyzed cross-coupling. Although some phosphines show a greater versatility than others, a ligand that can successfully be employed in all organopalladium coupling reactions has yet to be described. In our lab, for example, catalyst systems incorporating 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane (Figure 1, **2**) have allowed for effective Suzuki cross-coupling of a variety of

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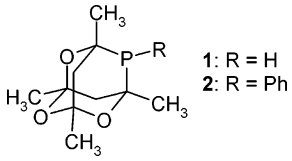


FIGURE 1. Phosphaadamantane.

aryl halides and boronic acids under mild conditions.[9] This same ligand can also be used for solid-phase Suzuki couplings involving immobilized reaction partners.[10] In addition, an air-stable palladium complex of this phenylphosphaadamantane ligand has been shown to be an effective, versatile catalyst for use in the Suzuki and Sonogashira reactions and the α-arylation of ketones.[11] However, attempts to use the ligand in Suzuki couplings of alkyl halides containing *β*-hydrogens with alkylboranes have met with less than satisfactory results.

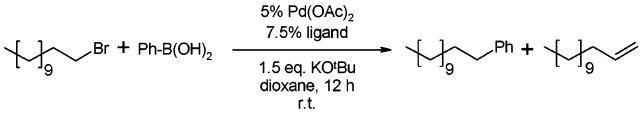
Our search for a "one-size-fits-all" ligand has, therefore, evolved into the following combinatorial approach. With the phosphaadamantanes, the parent, secondary system (Figure 1, **1**) affords the opportunity for introduction of variable aryl or alkyl moieties at the phosphorus. Each new tertiary phosphine thus generated has different electronic and steric properties. Parallel screening of the phosphaadamantane library quickly establishes the superior ligand to be used for the optimization of the particular reaction. The present paper illustrates the successful application of this new approach and describes the synthesis, characterization, and parallel screening of a collection of tertiary phosphaadamantanes in the Suzuki coupling of alkyl systems containing *β*-hydrogens.

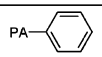
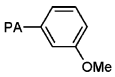
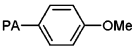
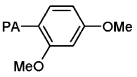
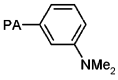
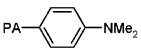
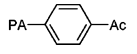
Results and Discussion

Ligands 5−15 (Table 1)[12] are prepared via derivitization of the parent secondary phosphaadamantane[13] (1,3,5,7-tetramethyl-2,4,8-trioxa-6-phosphaadamantane, Figure 1, **1**), using previously developed protocols. Treatment of **1** with an equivalent or slight excess of the appropriate aryl halide in the presence of $Pd(PPh_3)_4$ and potassium carbonate in xylenes affords the tertiary phosphines in good to excellent yields. The compounds were fully characterized with ^1H, ^{13}C, and ^{31}P NMR as well as MS. In addition, each of the derivatized phosphaadamantanes was air-stable and many crystallized to allow for X-ray structure determination.[14]

With the phosphaadamantane library in hand, our attention was turned to the parallel screening of the ligands for their effectiveness in Suzuki cross-coupling involving alkyl halides possessing *β*-hydrogens. Ligands were tested for their ability to affect the coupling of 1-bromododecane and phenylboronic acid in the presence of $Pd(OAc)_2$ and potassium *tert*-butoxide in dioxane at room temperature. The reactions were carried out in parallel then subjected to GC/MS analysis to determine

TABLE 1. Screening the Phosphaadamantane Library



	Ligand[a]	Yield (%)[b]	
		Coupled Product	Elimination
2		5	23
3		6	17
4		2	7
5		71	15
6		34	5
7		64	26
8		96	4
9		40	33
10		23	45
11		51	17
12		34	37
13		44	21
14		6	23
15		3	45

[a] PA = phosphaadamantane. [b] Percent coupled product and percent elimination product determined by GC/MS.

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(12) Preparation of ligands **2**, **3**, and **4** is described in ref 9.

(13) Epstein, M.; Buckler, S. A. *J. Am. Chem. Soc.* **1961**, *83*, 3279−3282.

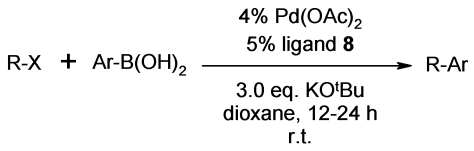
(14) Details regarding the crystal structure of ligands **4** (deposition number 246300), **5** (deposition number 246301), **6** (deposition number 246304), **11** (deposition number 246302), and **15** (deposition number 246303) may be obtained from the Cambridge Crystallographic Data Centre.

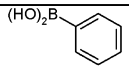
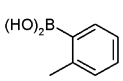
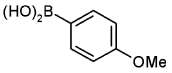
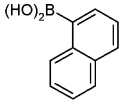
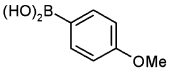
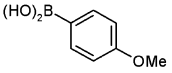
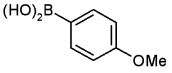
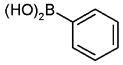
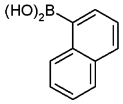
the relative amounts of coupled product (1-dodecylbenzene) and the byproduct from elimination (1-dodecene). The results appear in Table 1. Ligands containing aryl moieties substituted with electron-donating groups performed better than the unsubstituted phenylphosphaadamantane (**2**) and alkyl-substituted system (**3**). As expected, the 4-acetylphenyl system (**15**) gave only small amounts of the desired coupled product while the 2-pyridinyl system did marginally better. The best results were obtained with the methoxyphenyl-containing phosphaadamantanes with the ortho- (**5**) and para-substituted systems (**7**) facilitating the coupling in 71% and 64%, respectively. Introduction of a second methoxy group provided the best ligand of the series **8** providing a 96% yield of the desired coupled product with the remainder being the product from elimination. Contrasting the effectiveness of **5** and **7** with **8**, it is clear that both OMe substituents are required for optimal efficiency. Attempts to prepare the trimethoxy analogue with two ortho and one para substituent have not been successful to date. A few additional points are worth noting. Phosphaadamantane **8** contains the same *o*-methoxy substitutuent contained in Buchwald's latest ligand.[15] The methoxy group seems to have the correct steric and electronic properties needed for the reaction since neither the *o*-benzyloxy moiety of **12** nor the dimethylamino substituents of **9**, **10**, and **11** perform nearly as well.

Optimization of the reaction parameters revealed $Pd(OAc)_2$ to be the best palladium source and potassium *tert*-butoxide to be the best base. While both toluene and benzene could be used as solvent, dioxane consistently gave the superior coupling yields while minimizing the elimination products. Finally, a slight excess of ligand with respect to palladium was determined to be necessary. With the conditions in hand, a variety of alkyl bromides and chlorides were coupled to a series of boronic acids and the results appear in Table 2. Use of ligand **8** allowed for the Suzuki coupling of 1-bromododecane to electron-neutral (entries 1 and 2), more sterically demanding (entry 2), and electron-rich (entry 3) aryl boronic acids in excellent yields with minimal elimination products. Not surprisingly, entry 7 revealed that the catalytic species was more selective for the C−Br bond over the C−Cl allowing for the 95% yield of 1-(5-chloropentyl)-4-methoxybenzene. Limited success was achieved in the coupling of secondary alkyl bromides. Using 5 equiv of cyclohexyl bromide (relative to *p*-methoxyphenylboronic acid), 44% coupling could be obtained (entry 6). Under the reaction conditions used, rapid β-hydride elimination gave substantial amounts of cyclohexene. Alkyl boronic acids could also be used with butylboronic acid coupling to 1-bromododecane with moderate success (entry 5). Monitoring via GC/MS, however, revealed that cross-coupling, β-hydride elimination, and boronic acid decomposition were all occurring at similar rates and as a result only 54% of the desired product could be obtained. The alkyl chlorides required elevated temperatures and resulted in modest yields of coupled products (entries 8 and 9).

The dimethoxyphenylphosphaadamantane ligand **8** was shown to be equally effective in facilitating the Suzuki coupling of alkyl halides and tosylates with alkyl boranes. The requisiste alkyl boranes were easily accessed via hydroboration of the appropriate alkene with 9-borabicyclo[3.3.1]nonane (9-BBN). The coupling of alkyl bromides with alkyl-9-BBN derivatives (entries 1, 2, 3, and 4 of Table 3) progressed smoothly and in good yields at room temperature in THF with $Pd(OAc)_2$ as the palladium source and $K_3PO_4 \cdot H_2O$ as base. The reaction conditions were compatible with a variety of functional groups including alkenes, esters, and nitriles. Slightly different conditions were required for the coupling of alkyl tosylates, with dioxane, NaOH, and a temperature of 50 °C proving optimal (entries 5, 6, 7, and 8 in Table 3). The conditions were mild enough to tolerate ketone and ester functionalities, although the yields for these

TABLE 2. Suzuki Coupling of Alkyl Halides and Boronic Acids



Entry	Alkyl Halide	Boronic Acid	Yield[a]
1			97
2			97
3			94
4			96
5			54
6			44
7			95
8[b]			72
9[b]			65
10			59

[a] Isolated yield and average of two runs. [b] Reaction carried out at 90 °C.

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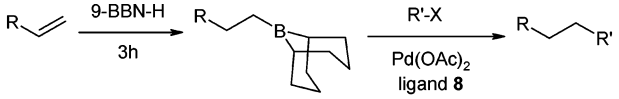
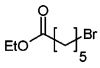
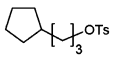
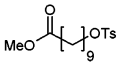
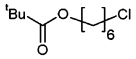
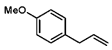
TABLE 3. Suzuki Coupling of Alkyl Halides or Tosylates with Alkylboranes



Entry	R	R'-X	Yield[a]
1[b]			93
2[b]			84
3[b]			62
4[b]			66
5[c]			73
6[c]			76
7[c]			46
8[c]			55
9[d]			77
10[d]			73
11[e]			51
12[d]			74
13[d]			80

[a] Isolated yield and average of two runs. [b] 4% $Pd(OAc)_2$, 5% ligand **8**, 1.2 equiv of $K_3PO_4 \cdot H_2O$, THF, rt, 24 h. [c] 4% $Pd(OAc)_2$, 16% ligand **8**, 1.2 equiv NaOH, dioxane, 50 °C, 24 h. [d] 10% $Pd(OAc)_2$, 20% ligand **8**, 1.1 equiv $CsOH \cdot H_2O$, dioxane, 90 °C, 48 h. [e] 10% $Pd(OAc)_2$, 20% ligand **8**, 1.1 equiv KOH, dioxane, 90 °C, 48 h.

were moderate. For the alkyl chlorides more vigorous conditions were required, with a temperature of 90 °C and $CsOH \cdot H_2O$ generally affording excellent results (entries 9−13, Table 3). At these temperatures, catalystand ligand decomposition became an issue and, therefore, higher catalyst loading was deemed necessary.

Overall, the 1,3,5,7-tetramethyl-6-(2,4-dimethoxyphenyl)-2,4,8-trioxa-6-phosphaadamantane ligand (**8**) has demonstrated itself to be effective in facilitating the Suzuki-type couplings of alkyl halides or tosylates containing β-hydrogens with either boronic acids or alkylboranes. In contrast to the other ligands used in these transformations, the phosphaadamantane offers a number of distinct advantages. Ligand **8** is air-stable, crystalline, easy to prepared, and is easily handled. Furthermore, the approach involving the screening of a ligand library has allowed for the rapid determination of the most suitable ligand for a particular reaction. Applications of this approach to other palladium-promoted cross-coupling reactions are currently under investigation.

Experimental Section

For each of the coupling protocols described, a general procedure is provided as well as one specific example. All other experimental procedures are available in the Supporting Information.

General Procedure for the Arylation of 1,3,5,7-Tetramethyl-2,4,8-trioxa-6-phosphaadamantane. The aryl bromide (9.26 mmol), 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phosphaadamantane (**1**, 2.0 g, 9.26 mmol), $Pd(PPh_3)_4$ (321 mg, 0.28 mmol), and potassium carbonate (3.8 g, 27.8 mmol) are stirred in xylenes (50 mL) under an argon atmosphere and heated at 110 °C for 20 h. The mixture is diluted with diethyl ether (20 mL) and filtered through a plug of silica (2 cm × 2 cm), and the solvent is removed at reduced pressure. Flash chromatography (using 20% diethyl ether/hexanes) allows for the isolation of the pure tertiary phosphine ligand. **1,3,5,7-Tetramethyl-6-(2-methoxyphenyl)-2,4,8-trioxa-6-phosphaadamantane (Table 1, Entry 5):** synthesized as per the general procedure with 2-bromoanisole (865 mg, 9.26 mmol). Flash chromatography with 20% diethyl ether/hexanes afforded the title compound (2.365 g, 79%) as white needles, mp 167−170 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.23 (3H, d, J = 12.0 Hz), 1.33 (3H, s), 1.35 (3H, s), 1.39 (1H, dd, J = 13.4, 1.4 Hz), 1.45 (3H, d, J = 12.6 Hz), 1.78 (1H, d, J = 13.4 Hz), 1.86 (1H, dd, J = 25.3, 13.1 Hz), 2.03 (1H, dd, J = 13.1, 7.4 Hz), 3.78 (3H, s), 6.82 (1H, dd, J = 8.2, 4.6 Hz), 6.91 (1H, t, J = 7.5 Hz), 7.2 (1H, ddd, J = 8.2, 7.5, 0.9 Hz), 8.02 (1H, dd, J = 7.5, 0.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.8 (d, J = 18.9 Hz), 27.9 (s), 28.0 (d, J = 21.2 Hz), 28.1 (s), 36.8 (d, J = 1.8 Hz), 46.0 (d, J = 18.9 Hz), 55.5 (s), 73.1 (d, J = 22.4 Hz), 73.9 (d, J = 8.8 Hz), 96.2, 96.8 (s), 110.5 (d, J = 2.0 Hz), 121.0 (s), 122.1 (d, J = 27.9 Hz), 130.8 (s), 134.1 (d, J = 3.6 Hz), 134.1 (d, J = 16.9 Hz); ^{31}P NMR ($CDCl_3$, 81 MHz) δ −41.3; EIMS m/z (RI%) 322 (19), 222 (100), 207 (37), 179 (19), 138 (17), 85 (17), 43 (67). HRMS molecular weight for $C_{17}H_{23}O_4P$ calcd 322.1334, obsd 322.1324.

General Procedure for Suzuki Couplings of Alkyl Halides and Aryl Boronic Acids. A reaction vessel containing $Pd(OAc)_2$ (4%, 9.0 mg, 0.04 mmol), 1,3,5,7-tetramethyl-6-(2,4-dimethoxyphenyl)-2,4,8-trioxa-6-phosphaadamantane (ligand **8**, 4%, 11.7 mg, 0.04 mmol), potassium *tert*-butoxide (337 mg, 3.0 mmol), and boronic acid (1.0 mmol) was sealed with a rubber septum and its contents placed under an argon atmosphere. Toluene (dry, degassed, 1.5 mL) and the alkyl bromide (1.2 to 5.0 mmol as indicated) were added via a syringe. The flask was stirred at room temperature and the reaction was monitored via TLC (5% EtOAc in hexane). Once the reaction was judged as completed, the toluene was diluted with diethyl ether (10 mL) and washed with distilled water (1 × 10 mL) and brine (1 × 10 mL). The organic solution was concentrated under reduced pressure and the residue purified via flash silica gel chromatography (5% ethyl acetate in hexane). **1-Dodecylbenzene (Table 2, Entry 1):** synthesized as per the general procedure above with 1-bromododecane (299.1 mg, 288.1 μL, 1.2 mmol) and phenylboronic acid (121.9 mg, 1.0 mmol). After 26 h the reaction was stopped. Chromatography resulted in a 97% yield of 1-dodecylbenzene (239.0 mg, 97 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.94 (3H, m), 1.32 (18H, br m), 1.67 (2H, m), 2.65 (2H, t, J = 7.18 Hz), 7.21−7.32 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 22.8, 29.4, 29.5, 29.6, 29.7, 29.8, 29.8, 29.8, 31.7, 32.1, 36.1, 125.6, 127.3,

128.3, 143.0. EIMS *m*/*z* (RI%) 57 (13), 92 (100), 105 (12), 246. (87); HRMS molecular weight for $C_{18}H_{30}$ calcd 246.2347, obsd 246.2353.

General Cross-Coupling Procedure of Alkyl Halides/Tosylates with 9-BBN Adducts. For the alkyl bromide substrates, the following procedure was employed. A reaction vessel containing $Pd(OAc)_2$ (9.0 mg, 0.040 mmol), 1,3,5,7-tetramethyl-6-(2,4-dimethoxyphenyl)-2,4,8-trioxa-6-phosphaadamantane (ligand **8**, 17.6 mg, 0.050 mmol), and $K_3PO_4 \cdot H_2O$ (276 mg, 1.2 mmol) was sealed with a rubber septum and its contents placed under an argon atmosphere. The alkyl bromide (1.0 mmol) and organoborane (1.2 mmol) were added in turn via syringe and the mixture stirred at the indicated temperature for the indicated time. The reaction was then diluted with Et_2O, filtered through silica gel with copious washing (Et_2O), concentrated, and purified by column chromatography. For the alkyl tosylate substrates, the above procedure was employed but with 1,3,5,7-tetramethyl-6-(2,4-dimethoxyphenyl)-2,4,8-trioxa-6-phosphaadamantane (ligand **8**, 56.3 mg, 0.16 mmol), NaOH (24 mg, 1.2 mmol), alkyl tosylate (1.0 mmol), and additional dioxane (4.0 mL). For the alkyl chloride substrates, the above procedure was employed but with $Pd(OAc)_2$ (22.5 mg, 0.10 mmol), 1,3,5,7-tetramethyl-6-(2,4-dimethoxyphenyl)-2,4,8-trioxa-6-phosphaadamantane (ligand **8**, 70.4 mg, 0.20 mmol), $CsOH \cdot H_2O$ (184 mg, 1.1 mmol), and alkyl chloride (1.0 mmol). ***n*-Octadecane (Table 3, entry 1):** synthesized as per the general procedure above with *n*-bromododecane (249 mg, 1.00 mmol) and the organoborane (2.4 mL of a 0.50 M solution in THF; 1.2 mmol) prepared from hydroboration of 1-hexene with 9-BBN. After 24 h, workup followed by column chromatography (hexanes) afforded the title compound as a white, waxy solid (236 mg, 93%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.26 (32H, br s), 0.88 (6H, t, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 2 × 3.1, 10 × 29.9, 2 × 29.5, 2 × 22.8, 2 × 14.2. EIMS *m*/*z* (RI%) 254 (7), 231 (15), 117 (38), 99 (35), 85 (67), 71 (100), 57 (60); HRMS molecular weight for $C_{18}H_{38}$ calcd 254.2974, obsd 254.2949.

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Supporting Information Available: ORTEP and crystallographic data for **8** (CIF); experimental procedures for compounds shown in Table 1 (entries 6−15), Table 2 (entries 2−10) and Table 3 (entries 2−13) and ^{1}H NMR spectra for all compounds described. This material is available free of charge via the Internet at http://pubs.acs.org.

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