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Phosphorinanes as Ligands for Palladium-Catalyzed Cross-Coupling Chemistry

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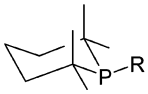
ABSTRACT



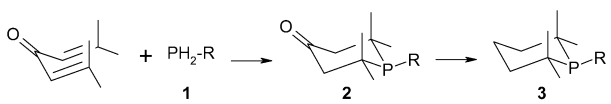
where R = isobutyl; cyclohexyl; cyclopentyl; 2-norbornyl; CH_2CH_2Ph; $CH_2CH(CH_3)CH_2C(CH_3)_3$

Phosphorinanes are presented as a class of phosphine ligand suitable for organopalladium cross-coupling chemistry. Prepared via a direct double Michael addition of a monoalkyl- or arylphosphine to phorone followed by a Wolf–Kishner reduction, phosphorinanes are relatively inexpensive to manufacture and allow modification of one of the alkyl moieties permitting steric and electronic fine-tuning of the ligands. Library screening and applications of these ligands in the Suzuki, Sonogashira, ketone arylation, and aryl amination reactions are presented.

Palladium-catalyzed cross-coupling reactions are now among the most prominent synthetic methods for mild, chemo- and stereoselective carbon−carbon and carbon−heteroatom bond-forming processes.[1] The versatility and scope of this family of cross-coupling reactions has expanded over the past few years to now include readily available but less reactive aryl chlorides and the once problematic β-hydride-containing alkyl halides. The direct coupling of aliphatic β-hydride containing electrophiles with the standard field of organometallics (including those based on B, Mg, Li, Sn, Al, Zn, and Zr) has moved from the "remarkable"[2] to now standard protocol.[3,4] The success of this chemistry hinges upon the choice of ligand employed. In particular, the popular tri-*tert*-butylphosphane, tricyclohexylphosphane,[3] and the di-*tert*-butylalkylphosphane $(^tBu)_2PR$[5−7] family have been used successfully in addition to the generally useful biaryl ligands that have emerged.[8]

In view of these developments, we were attracted to some chemistry described by Cyanamid chemists over four decades ago[9] that appeared highly applicable as a general entry to a new class of hindered aliphatic phosphane ligands. The central scaffold of interest is the phosphorinane skeleton (**3**) readily accessed through the direct double Michael addition of a monoalkyl- or arylphosphine to phorone followed by a Wolf−Kishner reduction of the central ketone (Scheme 1, **2**). There has been no interest in their development as ligands

Scheme 1



where R = isobutyl (**a**); cyclohexyl (**b**); cyclopentyl (**c**); 2-norbornyl (**d**); CH_2CH_2Ph(**e**); $CH_2CH(CH_3)CH_2C(CH_3)_3$ (**f**)

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(1) *Metal-Catalyzed Cross Coupling Reactions*; Diederich, F., Stang, P., Eds.; Wiley-VCH: New York, 1998.
(2) Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2002**, *124*, 4222.
(3) Netherton, M. R.; Dai, C.; Neuschutz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099.
(4) Powell, A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 7788.
(5) Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3910.
(6) Menzel, K.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 3718.
(7) Lee, J. Y.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 5616.
(8) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871.
(9) Welcher, R. P.; Johnson, G. A.; Wystrach, V. P. *J. Am. Chem. Soc.* **1960**, *82*, 4437. Welcher, R. P.; Day, N. E. *J. Org. Chem.* **1962**, *27*, 1824.

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and reagents until now.[10] The present paper describes the synthesis of a small library of phosphorinanes and demonstrates their utility in palladium-catalyzed cross-coupling chemistry.

Phosphorinanes (**3a**−**f**) were obtained via the two-step procedure outlined in Scheme 1. Phorone was treated with the appropriate phosphine (**1a**−**f**) to provide ketones of the general type **2**. Reduction of the carbonyl (in order to avoid any potential retro-Michael reaction) was achieved via treatment with hydrazine under basic conditions. The phosphorinane products obtained were viscous oils or low melting solids and were converted into the more easily handled, air-stable, tetrafluoroborate salts.[11] An X-ray structure for cyclopentyl-substituted phosphorinane (**3c**) was obtained and is illustrated in Figure 1.[12] Overall, the procedure is high

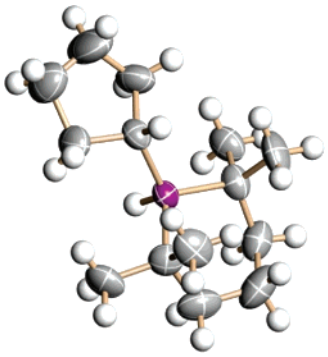
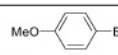
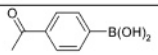
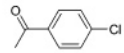
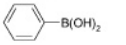
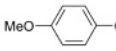
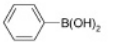
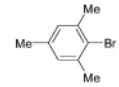
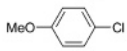
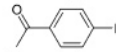
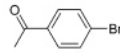
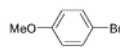
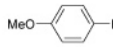
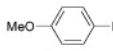
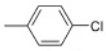
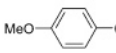


Figure 1. X-ray structure of 1-cyclopentyl-2,2,6,6-tetramethylphosphorinane (BF_4^- removed for clarity).

yielding and versatile allowing for the production of a family of ligands.

With phosphorinanes **3a**−**f** in hand, advantage was taken of our previously established approach[13] wherein the entire ligand library is screened against a particular palladium-catalyzed coupling reaction. This parallel screening quickly establishes the superior ligand to be used for the optimization of the particular reaction class. Our initial work focused on the Suzuki coupling of *p*-bromoanisole with phenylboronic acid, and while all the ligands successfully facilitated coupling, ligand **3d** revealed itself to be marginally superior (entry 1, Table 1). Optimizing the conditions for this ligand allowed for a series of Suzuki couplings to be carried out, and selected examples are shown in Table 1 (entries 1−3). Activated aryl chlorides such as 4-chloroacetophenone (entry 2) are readily coupled at room temperature, while as expected, systems such as *p*-chloroanisole (entry 3) require heating. In all cases, reaction times could be diminished at the expense of increased temperature while maintaining excellent yields.

Table 1. Selected Examples of Palladium Cross-Couplings Facilitated by Phosphorinane Ligands

Entry	Aryl Halide	Coupling Partner	Conditions[a]	Yield[b]
1			Set A; THF, rt, 48 h	95%
2			Set A; THF, rt, 40 h	83%
3			Set A; dioxane, 110C, 48 h	90%[c]
4			Set B; PhMe, rt, 24 h	95%
5			Set B; PhMe, rt, 48 h	89%
6			Set B PhMe, 50C, 48 h	68%
7			Set B; PhMe, 70C, 48 h	68%
8			Set C; dioxane, rt, 6 h	100%
9			Set C; dioxane, rt, 24 h	100%
10			Set C; dioxane, rt, 40 h	84%
11			Set D; PhMe, rt, 24 h	93%
12		Pr_2NH	Set D; PhMe, rt, 24 h	82%
13			Set E; PhMe, 70C, 24 h	97%
14			Set E; PhMe, 70C, 24 h	91%

[a] Set A: $K_3PO_4 \cdot H_2O$ (2.4 equiv), $Pd_2(dba)_3 \cdot CHCl_3$ (2%), ligand **3d** (4%), THF. Set B: NaO^{t}Bu (1.5 equiv); $Pd_2(dba)_3 \cdot CHCl_3$ (1%), ligand **3d** (2%). Set C: $^i Pr_2NH$ (1.5 equiv); $Pd(PhCN)_2Cl_2$ (3%), ligand **3a** (6%), CuI (2%). Set D: KO^{t}Bu (1.5 equiv); $Pd_2(dba)_3 \cdot CHCl_3$ (1%), ligand **3d** (2%). Set E: NaO^{t}Bu (1.5 equiv); $Pd_2(dba)_3 \cdot CHCl_3$ (1%), ligand **3d** (2%). [b] Isolated yields averaged between two runs.

Attention was turned to the coupling of enolates with aryl halides. The α-arylation of propiophenone with 4-iodotoluene was the system chosen to compare the activity of the ligand library. Using previously optimized conditions,[14] with sodium *tert*-butoxide base, $Pd_2dba_3 \cdot CHCl_3$ as the palladium source, and toluene as solvent, the norbornylphosphorinane **3d** clearly revealed itself again as the ligand of choice, showing

(10) McNulty, J.; Zhou, Y. *Tetrahedron Lett.* **2004**, *45*, 407.

(11) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295.

(12) Crystal size, 0.35 × 0.20 × 0.08 mm^3; crystal system, monoclinic; space group, $P2_1$; unit cell dimensions, a = 7.98430(10) Å, b = 13.9102(2) Å, c = 15.4291(2) Å, α = 90°, β = 91.0590(10)°, γ = 90°; volume, 1713.31(4) Å^3; empirical formula, $C_{14}H_{28}BF_4P$; formula weight, 314.14; Z 4; ρ calcd, 1.218 mg/m^3; $2\theta_{max}$, 136.32°; radiation, Cu Kα; wavelength, 1.54178 Å; scan mode, ω scans; T, 293(2) K; reflections collected, 9024; independent reflections, 4927 [R_{int} = 0.0249]; Lorentzian correction applied, polarization correction applied, absorption correction: SADABS (semiempirical from equivalents, max and min transmission, 1.00 and 0.84); absorption coefficient, 1.679 mm^{-1}; direct methods solution (SHELXS); refinement method, full-matrix least-squares on F2; refinement data [$I > -3\sigma I$]/restraints/parameters, 4927/61/432; H-atoms riding on C-atoms in calculated positions, H-atoms on P-atoms found from difference map and refined isotropically, BF_4^- disorders modeled; small disorder of C3′−C4′ orientation not refined; final R indices [$I > \sigma I$], R1 = 0.0571, wR2 = 0.1632; R indices (all data), R1 = 0.0591, wR2 = 0.1679; absolute structure parameter, 0.02(3); extinction coefficient, 0.0032(7); largest diff peak and hole, 0.296 and −0.270 e·Å^{-3}; structure deposited with CCDC.

(13) Brenstrum, T.; Gerristma, D. A.; Adjabeng, G. M.; Frampton, C. S.; Britten, J.; Robertson, A. J.; McNulty, J.; Capretta, A. *J. Org. Chem.* **2004**, *69*, 7635.

(14) Adjabeng, G. M.; Brenstrum, T.; Frampton, C. S.; Robertson, A. J.; Hillhouse, J.; McNulty, J.; Capretta, A. *J. Org. Chem.* **2004**, *69*, 5082.

complete conversion (by ^{1}H NMR) after just 6 h at room temperature. Using the optimized catalyst system containing ligand **3d**, aryl bromides such as bromobenzene (entry 4) and sterically demanding 2,4,5-trimethylbromobenzene (entry 5) were readily coupled with propiophenone at room temperature in high yields. Slightly higher temperatures were required to facilitate coupling of the aryl chlorides (entries 6 and 7) in a reasonable time period.

Screening revealed that the isobutylphosphorinane (**3a**) was the most effective ligand for the Sonogashira reaction. In addition, optimization revealed that $Pd(PhCN)_2Cl_2$ was the superior palladium source for these couplings. Quantitative yields for activated iodides and bromides (entries 8 and 9) were obtained at room temperature, while deactivated systems such as *p*-bromoanisole (entry 10) gave excellent yields of aryl alkynes at room temperature as well.

Finally, aminations of aryl halides were shown to be best promoted by ligand **3d**. Under optimized conditions, aryl bromides such as *p*-bromoanisole could be coupled readily to morpholine (entry 11) and dipropylamine (entry 12) in high yields at room temperature. Similarly, aryl chlorides could be coupled to amines in high yields (entries 13 and 14) although NaO^{t}Bu was shown to be the optimum base and higher temperatures were required in these cases.

Overall, the results above demonstrate that the phosphorinane family of trialkylphosphine ligands is clearly comparable in efficacy to other popular ligands currently employed (such as ^{t}Bu$_3$P, for example). The phosphorinanes, however, are much easier to generate, relatively inexpensive to manufacture, and allow for modification of one of the alkyl moieties permitting steric and electronic fine-tuning of the ligands. Furthermore, the intermediacy of the phosphorinones **2** (Scheme 1) allows entry to P-protected 4-hydroxyphosphorinanes[10] through hydride reduction, providing a handle by which this family of ligands could be immobilized onto a solid support.[15,16] In conclusion, the ease of preparation of this family of ligands, structural variation possible, efficacy in assisting [Pd]-mediated transformations, and potential applicability to solid supported chemistry makes this new family of ligands highly attractive. Further developments and applications along these lines are in progress in our laboratories.

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Supporting Information Available: Crystallographic information, experimental procedures, and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL052579H

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(16) Benaglia, M.; Puglisi, A.; Cozzi, F. *Chem. Rev.* **2003**, *103*, 3401.