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Highly Active, Air-Stable Palladium Catalysts for the C−C and C−S Bond-Forming Reactions of Vinyl and Aryl Chlorides: Use of Commercially Available $[(t\text{-Bu})_2P(OH)]_2PdCl_2$, $[(t\text{-Bu})_2P(OH)PdCl_2]_2$, and $[[(t\text{-Bu})_2PO\cdots H\cdots OP(t\text{-Bu})_2]PdCl]_2$ as Catalysts

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Air-stable palladium complexes $[(t\text{-Bu})_2P(OH)]_2PdCl_2$, $[(t\text{-Bu})_2P(OH)PdCl_2]_2$, and $[[(t\text{-Bu})_2PO\cdots H\cdots OP(t\text{-Bu})_2]PdCl]_2$ serve as efficient catalysts for a variety of cross-coupling reactions of vinyl and aryl chlorides with arylboronic acids, arylzinc reagents, and thiols to yield the corresponding styrene derivatives, biaryls, and thioethers. ^{31}P NMR and mechanistic studies argue that the phosphinous acid ligands in the complexes can be deprotonated in the presence of a base to yield an electron-rich anionic species, which is likely a catalyst intermediate, and dimeric $[[(t\text{-Bu})_2PO\cdots H\cdots OP(t\text{-Bu})_2]PdCl]_2$ was isolated and cystallographically characterized. These anionic complexes are anticipated not only to accelerate the rate-determining oxidative addition of aryl chlorides but also to stabilize the palladium complexes in the catalytic cycle.

Introduction

Carbon−carbon and carbon−sulfur bond-forming reactions are important fundamental transformations in synthetic chemistry. These reactions would be even more useful and efficient if performed catalytically, rather than stoichiometrically.[1,2] The palladium-catalyzed cross-coupling reactions of vinyl and aryl halides with arylboronic acids, organozinc reagents, and thiols are versatile synthetic methods in the processes of C−C (Suzuki,[3] Negishi[4] cross-coupling), and C−S bond-forming transformations.[5] Moreover, promising catalytic systems for less expensive and readily available unactivated aryl chlorides have been studied extensively.[3,4,6−8] However, to the best of our knowledge, no air-stable phosphorus-containing ligands have ever been used in generating air-stable transition-metal complexes for the catalytic cross-coupling of unactivated aryl chlorides with arylboronic acids, organozinc reagents, and thiols.

In the course of our ongoing research on the discovery and development of new materials and industrial catalysts via combinatorial approaches, we reported the first

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(1) For general references, see: (a) Grushin, V. V.; Alper, H. In *Topics in Organometallic Chemisty*; 1999; Vol. 3, pp 193−226 and references therein. (b) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; Chapter 2. (c) Beller, M.; Riermeier, T. H. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; Vol. 1, pp 184−193. (d) Beller, M.; Riermeier, T. H.; Stark, G. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; Vol. 1, pp 208−236. (e) Negishi, E.-i.; Liu, F. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds; Wiley-VCH: Weinheim, 1998; pp 1−48. (f) Herrmann W. A. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B., Herrmann, W. A., Eds; Wiley-VCH: Weinheim, 1996; pp 764−765.

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(3) For Suzuki cross-coupling reactions of aryl chlorides mediated by palladium complexes, see: (a) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028. (b) Zapf, A.; Ehrentraut, A.; Beller, M. *Angew. Chem. Int. Ed.* **2000**, *39*, 4153−4155. (c) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168 and references therein. (d) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804−3805. Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413−2416. (e) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550−9561. (f) Bei, X.; Guram, A. S.; Turner, H. W.; Weinberg, W. H. *Tetrahedron Lett.* **1999**, *40*, 3855−3858. (g) Bei, X.; Turner, H. W.; Weinberg, W. H.; Guram, A. S. *J. Org. Chem.* **1999**, *64*, 6797−6803. (h) Firooznia, F.; Gude, C.; Chan, K.; Satoh, y. *Tetrahedron Lett.* **1998**, *39*, 3985−3988. (i) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722−9723. (j) Littke, A. F.; Fu, G. C. *Angew. Chem.* **1998**, *110*, 3586−3587. (k) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387−3388. (l) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369−7370. (m) Reetz, M. T.; Lohmer, G.; Schwickardi, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 481−483. (n) Shen, W. *Tetrahedron Lett.* **1997**, *38*, 5575−5578.

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(5) For the cross-coupling reactions of C−S bond-forming processes mediated by transition-metal complexes, see: (a) Kondo, T.; Mitsudo, T−A. *Chem. Rev.* **2000**, *100*, 3205−3220. (b) Harr, M. S.; Presley, A. L.; Thorarensen, A. *Synlett* **1999**, *10*, 1579−1581. (c) Zheng, N.; McWilliams, J. C.; Fleitz, F. J.; Armstrong, J. D., III; Volante, R. P. *J. Org. Chem.* **1998**, *63*, 9606−9607. (d) Still, I. W. J.; Toste, F. D. *J. Org. Chem.* **1996**, *61*, 7677−7680. (e) Baranano, D.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 2937−2938. (f) Takagi, K. *Chem. Lett.* **1987**, 2221−2224. (g) Kosugi, M.; Ogata, T.; Terada, M.; Sano, H.; Migita, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3657−3658. (h) Migita, T.; Shimiza, T.; Asami, Y.; Shiobara, J.; Kato, Y.; Kosugi, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1385−1389. (i) Kosugi, M.; Shimizu, t.; Migita, T. *Chem. Lett.* **1978**, 13−14.

(6) For Suzuki cross-coupling reactions of aryl chlorides mediated by palladacycle complexes, see: Beller, M.; Fischer, H.; Herrmann, W. A.; Ofele, K.; Brossmer, C. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1848−1849.

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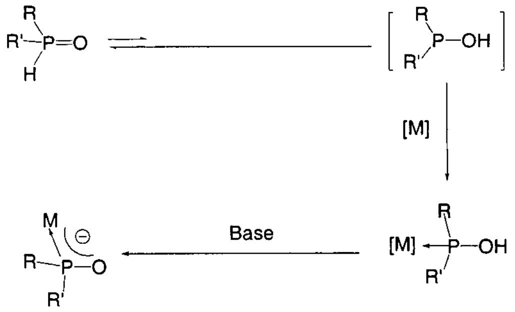
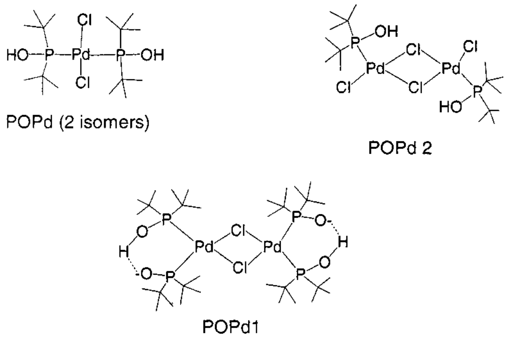
Scheme 1



air-stable phosphine oxides $[\mathrm{RR'P(H)O}]$,[8b] which were derived from the novel combinatorial technologies,[9] served as efficient ligand precursors for a variety of cross-couplings of unactivated aryl chlorides. All these transformations involving aryl chlorides (or halides) are mediated by air-stable palladium(II) complexes bearing novel phosphinous acids as ligands that are produced by tautomerization of $\mathrm{RR'P(O)H}$ to less stable phosphinous acids in the presence of transition metals (Scheme 1).[10]

Although in situ preparation of palladium catalysts has been widely utilized in the C−C bond-forming processes of aryl chlorides,[1−3] the Pd(II) complexes as only catalyst source without excess ligands in solution have been scarcely developed, principally because excess free ligands are essential to prevent transition-metal complexes from degradation in the catalytic cycle and that active catalytic species are derived from the in situ reduction of Pd(II) by excess phosphine ligands to Pd(0),[1,11] leading to difficulties in separating and purifying these complexes. Herein, we present the first investigation of cross-coupling reactions of vinyl and aryl chlorides with arylboronic acids (Suzuki reaction), organozinc reagents (Negishi reaction), and thiols catalyzed by simple, readily accessible, and air-stable palladium(II) complexes $[(t\text{-Bu})_2\mathrm{P(OH)}]_2\mathrm{PdCl_2}$ (abbreviated as POPd), $[(t\text{-Bu})_2\mathrm{P(OH)PdCl_2}]_2$ (abbreviated as POPd2), and $[[(t\text{-Bu})_2\mathrm{PO\cdots H\cdots OP}(t\text{-Bu})_2]\mathrm{PdCl}]_2$ (abbreviated as POPd1) (Scheme 2).[12]

Scheme 2. Structures of Palladium(II) Complexes Employed in the Examples of Tables 1−6


POPd (2 isomers)

POPd 2

POPd1

Results and Discussion

The principal goal of this study was to explore the possibility of cross-coupling reactions of unactivated vinyl and aryl chlorides with a variety of arylboronic acids, organozinc reagents, thiols mediated by air-stable palladium−phosphinous acids for the construction of biaryls and aryl-heteroatom-containing frameworks (e.g., unsymmetric biaryls, aryl ketones, arylthioether, and other biaryls). This study capitalized upon our previous success with in situ Pd/$\mathrm{RR'P(O)H}$ complexes-catalyzed carbon−carbon and carbon-heteroatom bond formations and upon well-characterized air-stable palladium(II) complexes-mediated Suzuki cross-coupling and C−N and C−S bond-forming transformations.[8]

In early studies, we reported that in situ $\mathrm{Pd_2(dba)_3}/(t\text{-Bu})_2\mathrm{P(H)O}$ catalysts are capable of catalyzing a variety of cross-coupling reactions of unactivated aryl chlorides with arylboronic acids, aryl Grignard reagents, amines, and thiols. We observed that both 1:1 and 1:2 ratios of Pd/$(t\text{-Bu})_2\mathrm{P(H)O}$ were effective components for these cross-coupling reactions. Encouraged by these interesting results, we decided to compare the catalytic activity of Pd/$(t\text{-Bu})_2\mathrm{P(H)O}$ with ratios of 1:1 and 1:2 and discovered that both Pd/$(t\text{-Bu})_2\mathrm{P(H)O}$ complexes could be isolated in air. We employed these isolated air-stable complexes as the only catalyst source in the absence of free $(t\text{-Bu})_2\mathrm{P(H)O}$ ligands and found that both complexes are effective catalysts for the Suzuki, Negishi cross-couplings and C−S bond formation of aryl and vinyl chlorides.

The POPd,[13] POPd1,[13] and POPd2[13] were prepared according to our reported procedures.[8,12] Well-characterized examples of this type of Pd(II) complexes are rare.[10] POPd, POPd1, and POPd2 were isolated and characterized by 1-D, 2-D, $^1\mathrm{H}/^{13}\mathrm{C}$, and $^{31}\mathrm{P}$ NMR spectroscopy, as well as elemental analysis. The structure of POPd1 was confirmed by X-ray crystallography (ORTEP view is shown in Figure 1).[14] As expected, the core structures of the POPd1 are P−Pd coordination with phosphinous acid ligands (RR′P−OH) and anionic ligand moieties forming a six-membered chelating ring with strong hydrogen bonding as part of the ring. Important features of the

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(7) For Suzuki cross-coupling reactions of aryl chlorides mediated by palladium/N-heterocyclic carbene complexes, see: (a) Zhang, C.; Trudell, M. L. *Tetrahedron Lett.* **2000**, *41*, 595−598. (b) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804−3805. (c) Weskamp, T.; Bohm, V. P. W.; Herrmann, W. A. *J. Organomet. Chem.* **1999**, *585*, 348−352. (d) Herrmann, W. A.; Reisinger, C.-P.; Spiegler, M. J. *J. Organomet. Chem.* **1998**, *557*, 93−96.

(8) For examples of cross-coupling of unactivated aryl chlorides mediated by air-stable palladium-phosphinous acid complexes, see: (a) Li, G. Y.; Zheng, G.; Noonan, A. F. *J. Org. Chem.* **2001**, *66*, 8677−8681. (b) Li, G. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1513−1516.

(9) For combinatorial approaches to the synthesis of phosphorus-containing ligands, see: (a) Li, G. Y.; Fagan, P. J.; Watson, P. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 1106−1109. (b) Li, G. Y. (E. I. Du Pont de Nemours and Company, USA). US Patent Application 60/197,031, Case No.: BC 1048 US PRV, 2000. (c) Fagan, P. J.; Li, G. Y. PCT Int. Appl WO 2000021663 A2 20000420, 169 pp. APPLICATION: WO 1999-US23509 19991013.

(10) For examples of metal−phosphinous acid complexes, see: (a) Cobley, C. J.; Heuvel, M. van den; Abbadi, A.; de Vries, J. G. *Tetrahedron Lett.* **2000**, *41*, 2467−2470. (b) Ghaffar, T.; Parkins, A. W. *Tetrahedron Lett.* **1995**, *36*, 8657−8660; UK Patent Application 9506389.7. (c) Goerlich, J. R.; Fischer, A.; Jones, P. G.; Schmutzler, R. *Z. Naturforsch., B*: *Chem. Sci.* **1994**, *49*, 801−811. (d) Heuer, L.; Jones, P. G.; Schmutzler, R. *New J. Chem.* **1990**, *14*, 891−900. (e) Arif, A. M.; Bright, T. A.; Jones, R. A. *J. Coord. Chem.* **1987**, *16*, 45−50.

(11) Amatore, C.; Jutand, A.; M'Barki, M. A. *Organometallics* **1992**, *11*, 3009−3012.

(12) (a) Li, G. Y. (E. I. Du Pont de Nemours and Company, USA). US Patent 6,291,722 B1, 2001. (a) Li, G. Y. (E. I. Du Pont de Nemours and Company, USA). US Patent Application No: 60/274,530, Case No.: BC1029 US NA PRV (2001). (b) Li, G. Y. (E. I. Du Pont de Nemours and Company, USA). US Patent 6,124,462, 2000.

(13) $[(t\text{-Bu})_2\mathrm{POH}]_2\mathrm{PdCl_2}$ (POPd), $[[(t\text{-Bu})_2\mathrm{PO\cdots H\cdots OP}(t\text{-Bu})_2]\mathrm{PdCl}]_2$ (POPd1), and $[(t\text{-Bu})_2\mathrm{P(OH)PdCl_2}]_2$ (POPd2) are available exclusively from CombiPhos Catalysts, Inc. Web site: www.combiphos.com.

(14) X-ray data for POPd1 has been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 171240. Copies of the data may be obtained from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: (+44)1223−336033. E-mail: deposit@ccdc.cam.ac.uk).

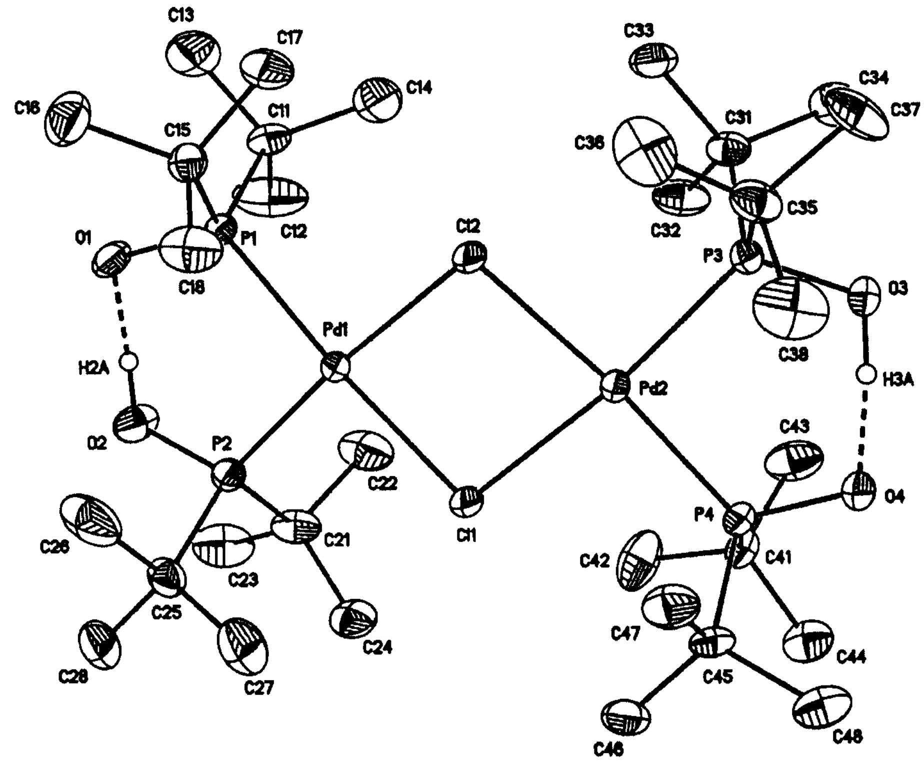
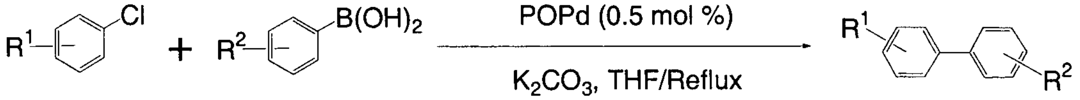
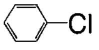
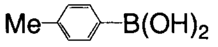
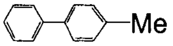
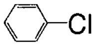
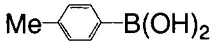
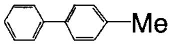
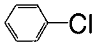
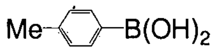
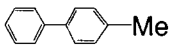
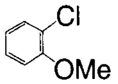
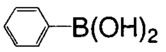
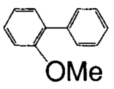
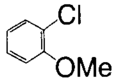
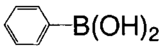
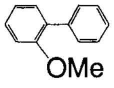


Figure 1. ORTEP view (50% probability) of dihydrogen di-μ-chlorotetrakis(di-*tert*-butylphosphinito-κ-*P*)dipalladate(2−) (**POPd1**).

Table 1. Effect of Free Ligands on the Palladium-Catalyzed Suzuki Cross-Coupling Reactions of Aryl Chlorides[a]



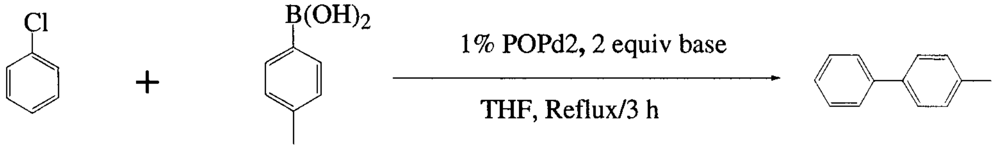
Entry	Halide	Coupling Partner	$(t\text{-Bu})_2P(O)H$	Product	Yield (%) (Isolated)
1			None		**78**[a]
2			1 eq. (0.5 mol%)		**92**[a]
3			2 eq. (1.0 mol%)		**82**[a]
4			None		**78**[b]
5			1 eq. (0.5 mol%)		**82**[b]

[a] Reaction conditions (not optimized): (a) 1.0 equiv of aryl chloride, 1.5 equiv of boronic acid, 3.0 equiv of K_2CO_3, 2 h; (b) 1.0 equiv of aryl chloride, 1.5 equiv of boronic acid, 3.0 equiv of K_2CO_3, 22 h.

structure of POPd1 include the O1−P1 (1.5478 Å) and O2−P2 (1.5543 Å) and the P−Pd bonding distance of 2.2863(5) Å between P1 and Pd1. These O−P distances are about 0.100 Å longer than a P═O double-bond distance in RRP(O)H and to a first approximation can be interpreted as a O−P single bond.

The palladium−phosphinous acid complexes POPd, POPd1, and POPd2 efficiently and regiospecifically catalyze the Suzuki cross-coupling of a variety of vinyl and aryl chlorides with arylboronic acids to yield the corresponding styrene derivatives and biaryls (Tables 1−4). The catalytic reactions in general proceed either under inert atmosphere or in open-to-air conditions (typically 0.5−2.0 mol % Pd catalyst) to completion in refluxing organic solvents (THF, dioxane, DME), in contrast to recently reported highly active Pd/ArP(t-Bu)$_2$ and Pd/P(t-Bu)$_3$ systems that are generated in situ for Suzuki cross-coupling of aryl chlorides (note: isolated phosphine complex Pd(P(t-Bu)$_3$)$_2$ does not appear to be the active catalyst for Suzuki cross-coupling process[3a]). Our isolated, air-stable POPd, POPd1, and POPd2 are all capable of catalyzing Suzuki coupling reactions of vinyl and aryl

Table 2. Effect of Base on the Air-Stable Palladium Complexes-Catalyzed Suzuki Cross-Coupling Results of Aryl Chlorides[a]



Entry	Base	Yield % (Isolated))	Entry	Base	Yield % (Isolated))
1	None	3	6	CsF	95
2	Et_3N	9	7	KF	54
3	Na_2CO_3	41	8	NaF	39
4	K_2CO_3	62	9	NaO-*t*-Bu	95
5	Cs_2CO_3	56	10	K_3PO_4	55

[a] Reaction conditions (not optimized): 1.0 equiv of aryl chloride, 1.5 equiv of arylboronic acid.

chlorides (or halides) to yield the corresponding biaryls in high yields (Tables 1–4).

In regard to comparisons of catalytic effects of POPd, POPd1, and POPd2, entries 4, 5, and 7 of Table 3 offer data comparing these catalysts to those (Table 3, entries 1–3) which are generated in-situ. It can be seen that the transformations are equally effective under comparable conditions of catalyst, concentration, and temperature. Interestingly, and in marked contrast to the typical catalytic systems employing excess free ligands to prevent catalysts from degradation in the catalytic processes, the present results (Table 1) demonstrate that the air-stable Pd-complex (POPd) for Suzuki cross-couplings of aryl chlorides are the same efficiency as those catalytic systems with excess ligands. More importantly, from the standpoint of organic synthesis, the direct use of POPd, POPd1, and POPd2 as catalysts would be more practical owing to the difficulties in generating in situ catalysts and in handling extremely air-sensitive phosphine ligands.

The required cross-coupling products of vinyl and aryl chlorides with arylboronic acids are produced in the presence of a variety of bases. Among the bases listed in Table 2, it would likely appear that CsF and NaO-*t*-Bu are the bases of choice (Table 2, entries 6 and 9); however, from the standpoint of organic synthesis, nonhalogenated reagents and mild bases would have a broad application. Therefore, we examined several nonhalogenated bases that were effected to mediate Suzuki cross-coupling of aryl chlorides; a variety of bases (Na_2CO_3, K_2CO_3, Cs_2CO_3, and K_3PO_4) have proved to be effective for cross-coupling of aryl chlorides (Table 2); of these, Na_2CO_3 and K_2CO_3 would be more suitable for industrial applications.

The catalytic results of Suzuki cross-coupling reactions of vinyl chlorides and arylboronic acids are summarized in Table 4. It can be seen that our air-stable palladium complexes mediate C–C bond formation efficiently to generate styrene derivatives in good yields. Interestingly, and in marked contrast to the $Pd_2(dba)_3/P(t\text{-}Bu)_3$ catalyst (Table 4, entry 2),[3a] using air-stable POPd as only catalyst source provides higher catalytic efficiencies in Suzuki cross-coupling of vinyl chlorides under comparable conditions of palladium concentration, temperature, and reaction time (Table 4, entries 3 and 5). The result of entry 4 (Table 4) reveals that POPd2 is also an efficient catalyst for Suzuki cross-coupling of vinyl chlorides.

Based on the successful Kumada–Tamao–Corriu cross-coupling of aryl chlorides with aryl Grignard reagents mediated by POPd at room temperature,[15] we also examined the Negishi cross-coupling of aryl chlorides with arylzinc reagents (Table 5). The reaction of aryl chlorides with organozinc reagents proceeds with diminished efficiency without the catalyst (Table 5, entry 1); however, a variety of biaryls are indeed produced efficiently in the presence of catalysts in refluxing THF/NMP solvents. Our air-stable catalysts can couple not only chlorobenzene (Table 5, entry 2) but also electron-rich substrates 4-chloroanisole (Table 5, entries 3 and 7) and 4-bromothioanisole (Table 5, entry 6). Entries 4 and 5 (Table 5) show that a ketone-containing substrate is tolerated by our catalysts as demonstrated by 4-chloroacetophenone. Also noteworthy is that an organic sulfur compound is tolerated and coupled with arylzinc reagents to form a biaryl containing thioethers, as illustrated by entry 6 (Table 5).

It has been known that organic sulfur compounds strongly bind to the transition-metal centers through M–S bonding, thus poisoning them and making catalytic reactions ineffective.[16] However, our air-stable palladium-phosphinous acid complexes, as illustrated in Table 6, can be employed catalytically for the C–S bond-forming reactions of vinyl chlorides generating thioethers. For example, thiophenols undergo coupling with 1-chloro-1-

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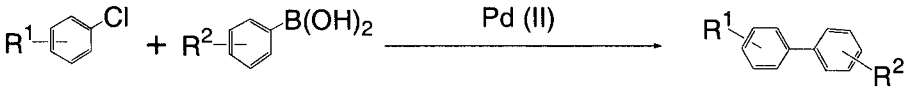
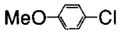
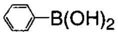
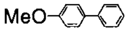
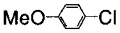
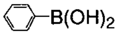
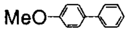
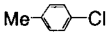
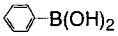
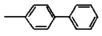
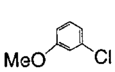
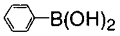
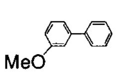
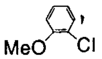
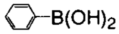
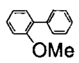
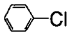
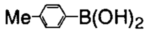
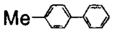
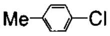
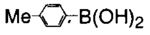
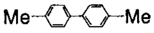
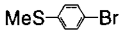
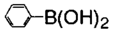
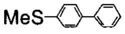
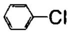
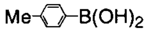
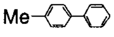
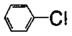
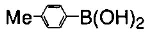
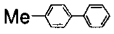
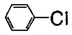
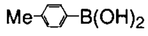
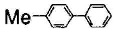
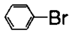
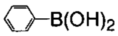
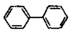
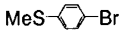
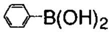
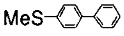
(15) For examples of Kumada–Tamao–Corriu cross-coupling of unactivated aryl chlorides with aryl Grignard reagents mediated by air-stable palladium–phosphinous acid or nickel-phosphinothious acid complexes, see: (a) Li, G. Y. *J. Organomet. Chem.* (Special Issue on Cross-Coupling Reaction) **2002**, in press. (b) Li, G. Y.; Marshall, W. J. *Organometallics* **2002**, *21*, 590–591.

(16) Ogawa, A.; Ikeda, T.; Kimura, K.; Hirao, T. *J. Am. Chem. Soc.* **1999**, *121*, 5108–5114.

Table 3. Air-Stable Palladium Complex Catalyzed Suzuki Cross-Coupling Results[a]



Entry	Halide	Coupling Partner	Catalyst	Base/Solvent	Product	Yield (%) (Isolated)
1			$Pd_2(dba)_3$/$(t\text{-}Bu)_2P(O)H$	CsF/dioxane		97[8b]
2			$Pd(OAc)_2$/$(t\text{-}Bu)_2PCl$/H_2O	CsF/dioxane		86[a]
3			$Pd(OAc)_2$/$(t\text{-}Bu)_2PCl$/H_2O	CsF/dioxane		73[a]
4			POPd	CsF/DME		94[a]
5			POPd	CsF/dioxane		90[a]
6			POPd2	CsF/dioxane		94[a]
7			POPd2	CsF/dioxane		84[a]
8			POPd	K_2CO_3/dioxane-H_2O		95[a]
9			POPd1	K_2CO_3/THF		92[b]
10			POPd1	CsF/THF		97[b]
11			POPd1	K_3PO_4/THF		99[b]
12			POPd2	K_2CO_3/THF-H_2O		65[c]
13			POPd2	CsF/dioxane		84[d]

[a] Reaction conditions (not optimized): 1.0 equiv of aryl chloride, 1.5 equiv of boronic acid, 3.0 equiv of base; (a) 1.5−3 mol % catalyst, 100 °C; (b) 0.50 mol % catalyst, 65 °C/2 h; (c) 0.05mol % catalyst, 1.0 equiv of bromobenzene, 1.2 equiv of boronic acid, 1.2 equiv of K_2CO_3, room temperature; (d) 0.5 mol % catalyst, 1.0 equiv of aryl bromide, 1.5 equiv of boronic acid, 3.0 equiv of CsF, room temperature.

cyclopentene in the presence of palladium-phosphinous acid complexes (Table 6, entries 2−4), and alkylthiol can also be coupled with vinyl chlorides in generating thioethers (Table 6, entry 5). It would thus appear that all the substrate thiols and the product thioethers are tolerated by these palladium complexes in the catalytic cycle. The reasons likely reflect a combination of ligand steric bulk, differing substrate and/or product molecule coordination, less electrophilic metal centers (anionic species) generated by the deprotonalysis of phosphinous acid ligands in the presence of bases.

With regard to a plausible mechanism, ^1H and ^{31}P NMR studies of the reaction of POPd2 with CsF in CD_3OD or D_2O solution argue that the palladium(II) chloride dimer (POPd2) is subject to cleavage and deprotonolysis giving mononuclear species at room temperature in the presence of bases,[17−19] yielding an electron-rich phosphine-containing anionic complex that would be anticipated not only to accelerate the rate-determining oxida-

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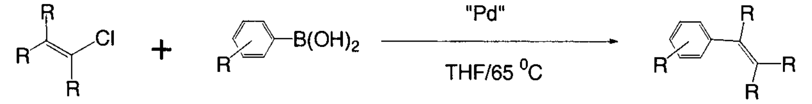
[17] A reaction of POPd2 (100 mg, 0.147 mmol, ^{31}P NMR (CD_3OD): δ 148.0 (singlet) ppm) and CsF (50.0 mg, 0.329 mmol) in 1.0 mL of CD_3OD at room temperature for 5 min generates an insoluble mixture.

[18] Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*, 5th ed.; John Wiley & Sons: New York, 1988; pp 921−922.

[19] For an excellent paper on tricoordinated anionic complexes $Pd^0L_2Cl^-$ as the real active catalysts, see: Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314−321.

Table 4. Air-Stable Palladium-Catalyzed Cross-Coupling Results of Vinyl Chlorides



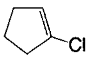
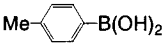
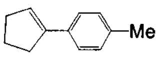
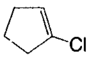
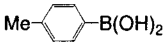
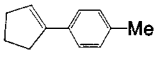
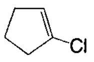
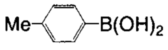
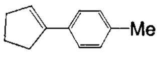
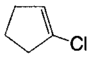
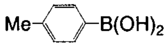
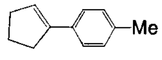
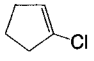
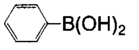
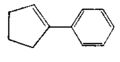
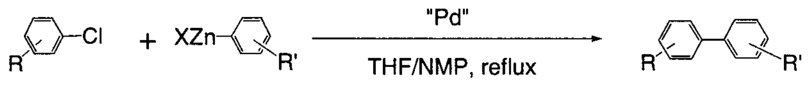
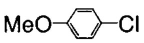
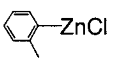
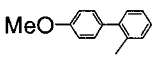
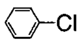
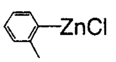
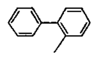
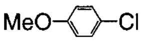
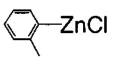
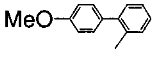
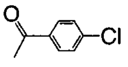
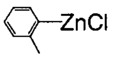
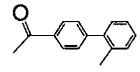
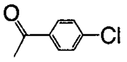
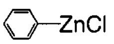
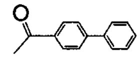
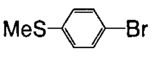
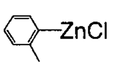
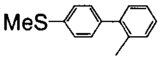
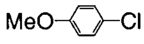
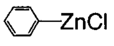
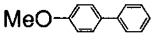
Entry	Halide	Coupling Partner	Catalyst	Base	Product	Yield (%) (Isolated)
1			None	K_2CO_3		5>
2			1.5% $Pd_2(dba)_3$ 3.6%$P(t\text{-}Bu)_3$	KF		87[3a]
3			POPd (1 % mol)	K_2CO_3		92
4			POPd **2** (0.5 % mol)	K_2CO_3		53
5			POPd (1 % mol)	K_2CO_3		86

Table 5. Air-Stable Palladium-Catalyzed Negishi Cross-Coupling of Aryl Chlorides



Entry	Halide	Coupling Partner	Catalyst	Time (h)	Product	Yield (%) (Isolated)
1			None	16		~0
2			POPd (5 mol%)	2		83
3			POPd (5 mol%)	14		57
4			POPd2 (2 mol%)	2		45
5			POPd (5 mol%)	2		40
6			POPd (5 mol%)	2		72
7			POPd (5 mol%)	14		55

tive addition of aryl chlorides[20] but also to stabilize the transition-metal complexes in the catalytic cycle. Further evidence for the proposed anionic species is derived from the direct reaction of POPd with Et_3N in organic solvent at room temperature to yield an anionic palladium dimer POPd1 (Scheme 3), which has been isolated and characterized by single-crystal X-ray analysis.[14]

Conclusions

In summary, air-stable palladium (II) complexes (POPd, POPd1, and POPd2) possessing phosphinous acid ligands were found to be highly active catalysts in the cross-coupling reactions of vinyl and aryl chlorides with arylboronic acids, organozinc reagents, and thiols. The use of phosphine oxide [$R_2P(H)O$] as a ligand precursor instead of phosphine ligand (R_3P) is the key to generate these air-stable complexes. Of note is the attraction of generating catalytically active electron-rich anionic species in the presence of bases, these anionic complexes can

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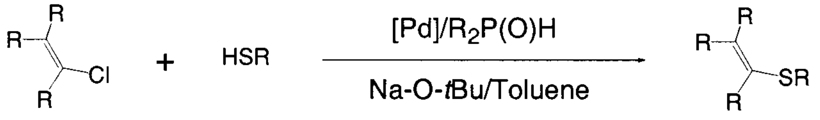
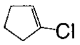
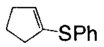
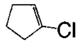
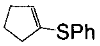
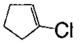
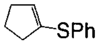
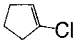
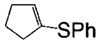
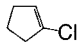
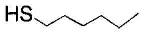
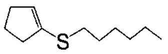
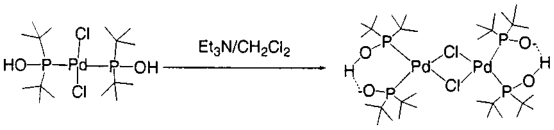
[20] The low catalytic reactivity of aryl chlorides in cross-coupling reactions is usually attributed to their reluctance toward oxidative addition to Pd(0). For a discussion, see: (a) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047–1062, and reference therein. (b) Grushin, V. V. *Organometallics* **2000**, *19*, 1888–1900.

Table 6. Air-Stable Palladium-Catalyzed C−S Bond Formation of Vinyl Chlorides



Entry	Halide	Coupling Partner	Catalyst	Temp (°C)	Time (h)	Product	Yield (%) (Isolated)
1		HSPh	None	110	18		~0
2		HSPh	POPd (3.0 % mol)	110	18		88
3		HSPh	POPd2 (1.5 % mol)	110	18		75
4		HSPh	POPd1 (3.0 % mol)	100	15		38
5			POPd (3.0 % mol)	110	18		97

Scheme 3



POPd (2 isomers)

POPd1

be incorporated into catalytic processes for cross-coupling reactions of vinyl and aryl halides by not only facilitating the rate-limiting oxidative addition of unactivated aryl chlorides with palladium complexes, but also stabilizing transition-metal complexes in the catalytic cycle. Also noteworthy are the high efficiency for vinyl and aryl chlorides; simplicity of use, low cost, air-stability, and ready accessibility of these separable complexes. Additional applications are currently under investigation.

Experimental Section

POPd, POPd1, and POPd2 are available from CombiPhos Catalysts, Inc. Alternatively, they may be prepared according to our reported procedures.[12]

Preparation of Dihydrogen Di-μ-chlorotetrakis(di-*tert*-butylphosphinito-κ-*P*)dipalladate(2−) (POPd1).[13] A solution of dichloro[bis(di-*tert*-butylphosphinous acid)]palladium(II) (POPd) (7.40 g, 14.77 mmol) in 40 mL of CH_2Cl_2 was treated with Et_3N (7.4 g, 73.1 mmol) at room temperature under open-to-air conditions over a period of 3 min. The resulting yellowish solution was stirred at room temperature for 4 h before the solvent and excess Et_3N were removed by rotary evaporation. The residue was washed with H_2O (3 × 50 mL) and hexane (2 × 50 mL). The crude product was purified by column chromatography on silica gel with CH_2Cl_2/hexane to afford 6.0 g (87% yield) of $[[(t\text{-Bu})_2PO\cdots H\cdots OP(t\text{-Bu})_2]PdCl]_2$. It was >95% pure by ^1H NMR and GC/MS. ^1H NMR (300 MHz, $CDCl_3$): δ 1.37 (d, $J = 14.6$ Hz) ppm. ^{13}C NMR (76 MHz, $CDCl_3$): δ 41.9 (t, $J = 14.4$ Hz), 29.48 (s) ppm. ^{31}P NMR (121 MHz, $CDCl_3$): δ 124.0 ppm. ^1H-coupled ^{31}P NMR (121 MHz, $CDCl_3$): δ 124.9 (s) ppm. Anal. Calcd for $C_{32}H_{74}O_4Cl_2P_4Pd_2$: C, 41.30; H, 8.02; P, 13.31; Cl, 7.62. Found: C, 41.21; H, 8.66; P, 13.28; Cl, 7.54. The crystallographic sample was obtained by slow recrystallization from a mixture of dichloromethane and hexane.[14]

General Procedure for the Reaction of Vinyl and Aryl Chlorides with Arylboronic Acids (Entry 1, Table 1). POPd (25.0 mg, 0.05 mmol, 0.5 mol %), chlorobenzene (1.13 g, 10.0 mmol), $Me\text{-}C_6H_4B(OH)_2$ (2.04 g, 15.0 mmol), and K_2CO_3 (4.15 g, 30.0 mmol) were weighed in air and transferred to a 50 mL reactor equipped with a magnetic stir bar and 20 mL of THF. The reaction mixture was refluxed under N_2 for 2 h. The reaction was transferred to a separatory funnel and diluted with 300 mL of hexane and 100 mL of H_2O. The layers were separated, the organic layer was washed with H_2O (100 mL) and brine (100 mL), dried over $MgSO_4$, and filtered, and solvents were removed from the filtrate by rotary evaporation. The resulting residue was chromatographed on silica gel using hexane as eluant. The eluate was concentrated by rotary evaporation followed by high vacuum to give 1.31 g (78% yield) of the final product.

Synthesis of 4-Phenylanisole[8b] (Entry 2, Table 3). In the drybox, 110 mg (0.609 mmol) of $(Me_3C)_2P{-}Cl$, 67 mg (0.299 mmol) of $Pd(OAc)_2$, and 3.0 mL of CH_2Cl_2 were loaded into a reactor (10 mL) equipped with a magnetic stir bar. The resulting mixture was stirred at room temperature for 4 h before 60 mg (3.3 mmol) of H_2O was added. The mixture above was stirred at room temperature for 12 h. After removal of solvent and excess H_2O, the residue was dissolved in 15.0 mL of 1,4-dioxane and transferred into a reactor (100 mL). Next, 1.43 g (10.0 mm) of 4-chloroanisole, 1.83 g (15.0 mm) of $PhB(OH)_2$, and 4.56 g (30.0 mm) of CsF were added into the mixture above. The resulting mixture was then taken out from the drybox and refluxed for 18 h. The reaction mixture was then cooled to room temperature, quenched with 50 mL of H_2O, and extracted with 300 mL of diethyl ether. The organic extracts were washed with H_2O (2 × 80 mL) and brine (80 mL), dried over $MgSO_4$, and filtered, and the ether and dioxane were removed from the filtrate by rotary evaporation. The resulting residue was chromatographed on silica gel using hexane as eluant. The eluate was concentrated by rotary evaporation followed by high vacuum to yield 1.58 g (86% yield) of 4-phenylanisole.

1-(1-Cyclopenten-1-yl)-4-methylbenzene (Entry 3, Table 4).[3a] The general procedure was followed with use of POPd (47 mg, 0.10 mmol, 0.94% mol), 1-chloro-1-cyclopentene (1.03 g, 10.0 mmol), 4-Me-$C_6H_4B(OH)_2$ (2.04 g, 15.0 mmol), and K_2CO_3 (4.16 g, 30.0 mmol) in 15 mL of THF. The reaction mixture was refluxed for 15 h until the starting material was completely consumed as judged by TLC. Workup and column chromatography (hexane) yielded 1.45 g (92% yield) of the final product.

General Procedure for the Reaction of Aryl Chlorides with Arylzinc Reagents (Entry 3, Table 5).[8] In the drybox, 15 mL of *o*-tolylmagnesium chloride (15 mmol, 1.0 M solution in THF) was treated with 32.0 mL of $ZnCl_2$ (16 mmol, 0.5 M solution in THF) dropwise over a period of 5 min. The resulting mixture was stirred at room temperature for 20 min before 1-methyl-2-pyrrolidinone (NMP, 22 mL) was added. After the mixture was stirred for an additional 5 min, 250.0 mg (0.50 mm) of POPd and 1.43 g (10.0 mm) of 4-chloroanisol were added into the mixture above. The resulting mixture was refluxed for 14 h before it was allowed to cool to room temperature, and aqueous HCl was added (1.0 M; 60 mL). The resulting mixture was extracted with Et_2O (4 × 100 mL), and the extracts were washed with H_2O (5 × 100 mL) and 100 mL of brine, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The crude product was purified by column chromatography on silica gel (95:5 hexane/diethyl ether) to afford 1.12 g (57% yield) of 4-(2-tolyl)anisole.

General Procedure for the Reaction of Vinyl Chlorides with Thiols (Entry 2, Table 6).[21] A 50 mL of reactor equipped with magnetic stir bar was charged with 270 mg (0.54 mmol) of POPd, 1.89 g (18.47 mmol) of 1-chloro-1-cyclopentene, 1.98 g (18.0 mmol) of PhSH, and 3.46 g (36.0 mmol) of NaO-*t*-Bu in 10.0 mL of toluene. The resulting mixture was heated to 120 °C for 18 h before the mixture was cooled to room temperature and quenched with 100 mL of H_2O. The mixture was transferred to a separatory funnel and extracted with EtOAc (2 × 200 mL). The layers were separated, the organic layer was washed with H_2O (2 × 100 mL) and brine (150 mL), dried over $MgSO_4$, and filtered, and the solvents were removed from the filtrate by rotary evaporation. The final product was chromatographed on silicon gel using *tert*-butylmethyl ether/hexane (1% volume ratio) as eluant. The eluate was concentrated by rotary evaporation followed by high vacuum to yield 2.8 g (88% yield) of 1-phenylthio-1-cyclopentene.

Acknowledgment. I thank Dr. Patrick Y. S. Lam and Dr. Rafael Shapiro for helpful discussions and suggestions. I also thank Mr. William J. Marshall for expert assistance with X-ray crystallographic work and Mr. Gang Zheng for excellent technical assistance.

Supporting Information Available: X-ray data of dihydrogen di-μ-chlorotetrakis(di-*tert*-butylphosphinito-κ-P)dipalladate(2−) (POPd1), experimental procedures for all reactions, as well as characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO010983Y

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[21] Martinez, A. G.; Barcina, J. O.; de Fresno C. A.; Subramanian, L. R. *Synlett* **1994**, (*7*), 561−562.