JOC Article

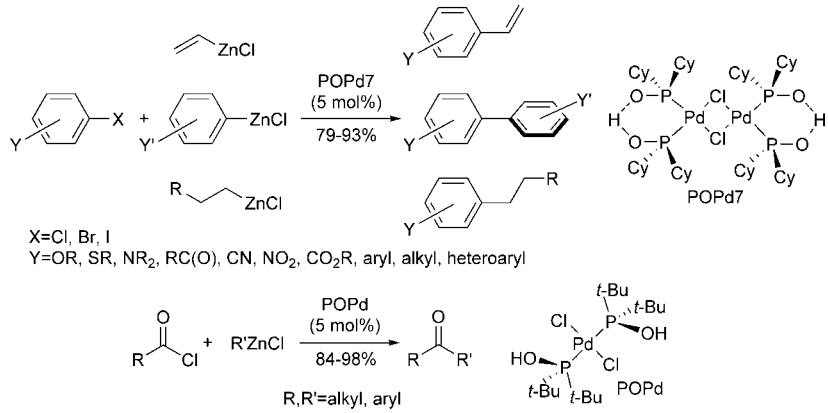
Palladium−Phosphinous Acid-Catalyzed Cross-Coupling of Aryl and Acyl Halides with Aryl-, Alkyl-, and Vinylzinc Reagents

Hanhui Xu, Kekeli Ekoue-Kovi, and Christian Wolf*

Department of Chemistry, Georgetown University, Washington, D.C. 20057

cw27@georgetown.edu

Received July 1, 2008



Several palladium−phosphinous acids have been prepared and employed in cross-coupling reactions of aryl or acyl halides with aliphatic and aromatic organozinc reagents. The POPd7-catalyzed reaction of aryl halides, including electron-rich aryl chlorides, and arylzinc reagents was found to afford biaryls exhibiting alkoxy, alkylthio, amino, ketone, cyano, nitro, ester, and heteroaryl groups in 75−93% yield. Excellent results were obtained with sterically hindered substrates which gave di- and tri-ortho-substituted biaryls in up to 92% yield. Aryl halides also undergo POPd7-catalyzed aryl−vinyl and aryl−alkyl bond formation under mild conditions. Styrenes and alkylarenes were prepared in 79−93% yield from aryl halides and vinyl or alkylzinc reagents. The replacement of aryl halides by acyl halides provides access to ketones which were produced in up to 98% yield when POPd was used as catalyst. This approach overcomes the limited substrate scope, reduced regiocontrol, and low functional group tolerance of traditional Friedel−Crafts acylation methods.

Introduction

Transition-metal-catalyzed cross-coupling of aryl halides with boronic acids, organostannanes, organosiloxanes, organozinc compounds, and Grignard reagents have found widespread popularity during recent years.[1]The impressive progress in this area has been paved by the development of electron-rich, bulky phosphines[2] and *N*-heterocyclic carbene ligands that form highly active nickel and palladium catalysts.[3] Similarly, phosphinous acids have been successfully applied as ligands in transition-metal-catalyzed Suzuki, Stille, Hiyama, Kumada, Sonogashir a and other cross-coupling reactions.[4] In particular, palladium−phosphinous acids have found a wide range of synthetic applications and proved to be remarkably stable to air and water, which facilitates operation and catalyst recycling, handling, and storage.[5]

(1) (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4177–4211. (b) Miyaura, N., Ed. *Cross-Coupling Reactions*; Springer: Berlin, 2002. (c) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131–209.

(2) (a) Yamamoto, T.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 2367–2370. (b) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387–3388. (c) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 2411–2413. (d) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473–1478. (e) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369–4378. (f) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550–9561. (g) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413–2416. (h) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028. (i) Yin, J.; Rainka, M. P.; Zhang, X.-X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162–1163. (j) Hooper, M. W.; Hartwig, J. F. *Organometallics* **2003**, *22*, 3394–3403. (k) Hooper, M. W.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2003**, *68*, 2861–2873. (l) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653–6655. (m) Walker, S. D.; Barder, T. E.; Martinelli, J. R; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871–1876. (n) Christmann, U.; Vilar, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 366–374. (o) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674–688.

10.1021/jo801445y CCC: $40.75 © 2008 American Chemical Society
Published on Web 09/04/2008

In comparison to carbon−carbon bond formation with boronic acids and stannanes, relatively few examples using organozinc reagents have been described to date, and the use of palladium−phosphinous acids in Negishi reactions has barely been investigated.[6] Li et al. demonstrated the potential of this class of catalysts for the coupling of aryl chlorides with arylzinc reagents, but only moderate yields were obtained.[7] To the best of our knowledge, there are no reports on palladium−phosphinous acid-catalyzed couplings of acyl chlorides with organozinc compounds and aryl−alkenyl and aryl−alkyl bond formation in the literature. We therefore decided to investigate the possibility of efficient palladium−phosphinous acid-catalyzed synthesis of biaryls, aryl ketones, styrene derivatives, and alkylbenzenes from aromatic, vinylic, and aliphatic organozinc reagents.

Results and Discussion

Based on our previous experience with palladium−phosphinous acid catalysis, we decided to screen the suitability of POPd, POPd1, POPd2, POPd5, POPd6, and POPd7 and the chlorophosphine-derived analogue PXPd for the coupling reaction of 4-chloroanisole, **1**, and 2-tolylzinc chloride, **2** (Figure 1). In addition, we prepared several new phosphine oxides, **L1**−**L9**, bearing bulky, electron-rich aliphatic and aromatic substituents. These ligands readily form the corresponding tautomeric phosphinous acids in the presence of a transition metal, thus producing active palladium catalysts after stirring with Pd_2dba_3 for 2−4 h at room temperature (Figure 2).

We found that ligands **L1**, **L4**, **L6**, **L7**, **L8**, and **L9** can be readily obtained from a Grignard or organolithium precursor upon treatment with *tert*-butyldichlorophosphine and subsequent hydrolysis (Scheme 1). For example, **L1** and **L6** were synthesized from phenylethyl bromide and 2,4-dimethoxyphenyl bromide via Grignard formation and reaction with *t*-$BuPCl_2$ in

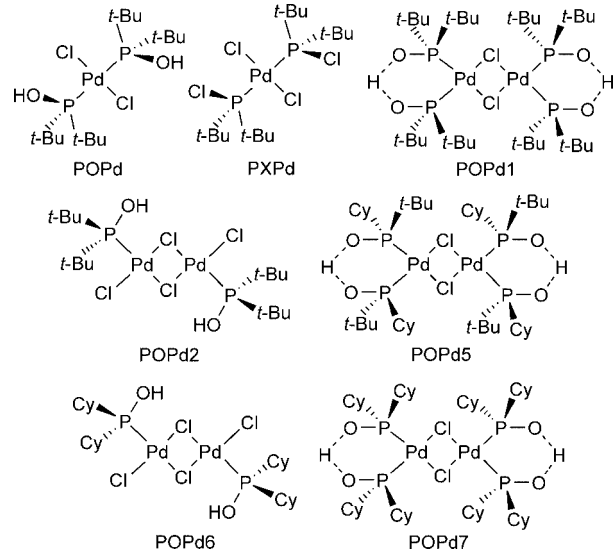


FIGURE 1. Structures of the palladium−phosphinous acids and a chlorophosphine analogue used in this study.

67 and 64% yield, respectively. Direct lithiation of 1,3-diisopropoxybenzene, 1,3,5-trimethoxybenzene, and ferrocene followed by the same reaction sequence gave **L4**, **L7**, and **L9**. For the synthesis of Buchwald-type ligand **L8**, 2-bromo-2′,6′-dimethoxybiphenyl was first prepared from 1,3-dimethoxybenzene and 1,2-dibromobenzene in 95% yield. Lithiation of the biaryl bromide, reaction with *t*-$BuPCl_2$, and aqueous workup furnished **L8** in 85% yield.

The synthesis of phosphine oxides using the reaction of Grignard or organolithium compounds with *tert*-butyldichlorophosphine as the key step proved less successful for the preparation of ligands **L2**, **L3**, and **L5**. We therefore resorted to triethyl phosphite as an alternative electrophile. As shown in Scheme 2, addition of 2 equiv of 2,4-dimethoxyphenylmagnesium bromide to $P(OEt)_3$ and subsequent acidic hydrolysis gave **L2** in 73% yield. We found that this reaction can be controlled when 1 equiv of 1-naphthyllithium or 2-biphenyllithium is used, thus providing the corresponding diethyl arylphosphinate in 60−65% yield. Addition of *tert*-butylmagnesium chloride then gave *tert*-butyl(1-naphthyl)phosphine oxide, **L3**, and 2-biphenyl(*tert*-butyl)phosphine oxide, **L5**, in 60−70% yield.

Initial optimization of typical reaction parameters including solvent, temperature, and concentration of the substrates showed that excellent results can be achieved for the cross-coupling of 4-chloroanisole, **1**, and 2-tolylzinc chloride, **2**, when POPd is employed in *N*-methylpyrrolidinone, NMP, at 65 °C while the presence of any additives and base was unnecessary. Using 5 mol % of POPd under these conditions, 4-methoxy-2′-methylbiphenyl, **3**, was obtained in 89% yield after 4 h (entry 1, Table 1). All catalysts shown in Figure 1 were then tested under the same reaction conditions. With the exception of POPd5, other palladium−phosphinous acids showed catalytic activity comparable to that of POPd (entries 3−7). Most importantly, biphenyl **3** was produced in 93% yield within 4 h when POPd7 was used (entry 7). Among the catalysts that were generated in situ by premixing of stoichiometric amounts of **L1**−**L9** and Pd_2dba_3, the metal complexes derived from **L1**, **L2**, **L3**, and **L8** showed remarkable activity, generating biphenyl **3** in 81−90% yield within 4 h (entries 8−10, and 15). We assume that deprotonation of the palladium−phosphinous acid ligands

(3) (a) Herrmann, W. A.; Reisinger, C.-P.; Spiegler, M. *J. Organomet. Chem.* **1998**, *557*, 93–96. (b) Selvakumar, K.; Zapf, A.; Beller, M. *Org. Lett.* **2002**, *4*, 3031–3033. (c) Viviu, M. S.; Kissling, R. M.; Stevens, E. D.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 2229–2231. (d) Gstöttmayr, C. W. K.; Bohm, V. P. W.; Herdtweck, E.; Grosche, M; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1363–1365. (e) Viviu, M. S.; Kelly, R. A., III; Stevens, E. D.; Naud, F.; Studer, M.; Nolan, S. P. *Org. Lett.* **2003**, *5*, 1479–1482. (f) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 3690–3693. (g) De Lewis, A. K.; Caddick, S.; Cloke, F. G. N.; Billingham, N. C.; Hitchcock, P. B.; Leonard, J. *J. Am. Chem. Soc.* **2003**, *125*, 10066–10073. (h) Navarro, O.; Kelly, R. A., III; Nolan, S. P. *J. Am. Chem. Soc.* **2003**, *125*, 11818–11819.

(4) (a) Li, G. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1513–1516. (b) Li, G. Y. *J. Organomet. Chem.* **2002**, *653*, 63–68. (c) Wolf, C.; Lerebours, R.; Tanzini, E. H. *Synthesis* **2003**, *206*, 9–2073. (d) Wolf, C.; Lerebours, R *J. Org. Chem.* **2003**, *68*, 7077–7084. (e) Wolf, C.; Lerebours, R *J. Org. Chem.* **2003**, *68*, 7551–7554. (f) Wolf, C.; Lerebours, R *Org. Lett.* **2004**, *6*, 1147–1150. (g) Wolf, C.; Lerebours, R *Org. Biomol. Chem.* **2004**, *2*, 2161–2164. (h) Lerebours, R.; Wolf, C. *Synthesis* **2005**, *228*, 7–2292. (i) Bigeault, J.; Giordano, L.; Buono, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4753–4757. (j) Wolf, C.; Ekoue-Kovi, K. *Eur. J. Org. Chem.* **2006**, *191*, 7–1925. (k) Wolf, C.; Xu, H. *J. Org. Chem.* **2008**, *73*, 162–167.

(5) (a) Ackermann, L. *Synthesis* **2006**, 1557–1571. (b) Lerebours, R.; Wolf, C. *J. Am. Chem. Soc.* **2006**, *128*, 13052–13053. (c) Ekoue-Kovi, K.; Wolf, C. *Org. Lett.* **2007**, *9*, 3429–3432.

(6) (a) Selected examples: Vettel, S.; Vaupel, A.; Knochel, P *J. Org. Chem.* **1996**, *61*, 7473–7481. (b) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719–2724. (c) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12527–12530. (d) Walla, P.; Kappe, O. *Chem. Commun.* **2004**, 564–565. (e) Malosh, C.; Ready, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 10240–10241. (f) Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028–13032. (g) Tan, Z.; Negishi, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 762–765. (h) Kondolff, I.; Doucet, H.; Santelli, M. *Organometallics* **2006**, *25*, 5219–5222. (i) Gavryushin, A.; Kofink, C.; Manolikakes, G.; Knochel, P. *Tetrahedron* **2006**, *62*, 7521–7533. (j) Akao, A.; Tsuritani, T.; Kii, S.; Sato, K.; Nonoyama, N.; Mase, T.; Yasuda, N. *Synlett* **2007**, 31–36. (k) Wang, L.; Wang, Z.-X. *Org. Lett.* **2007**, *9*, 4335–4338.

(7) Li, G. Y. *J. Org. Chem.* **2002**, *67*, 3643–3650.

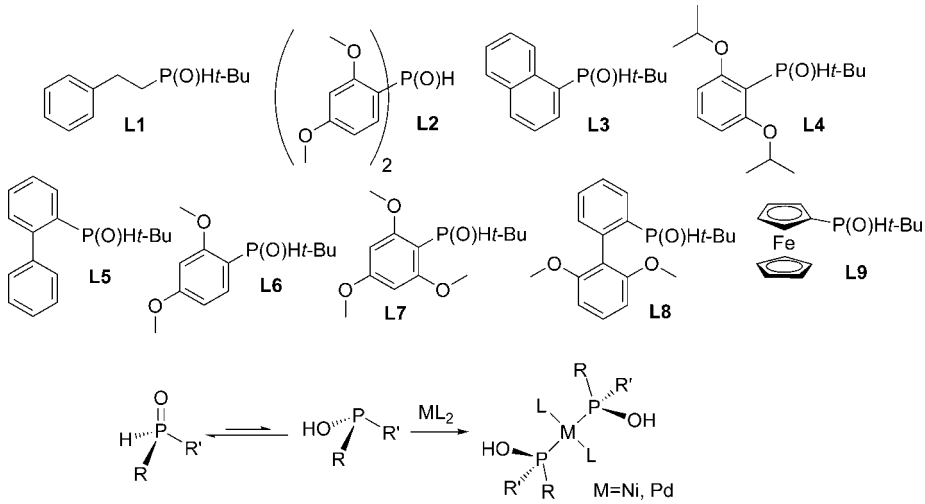
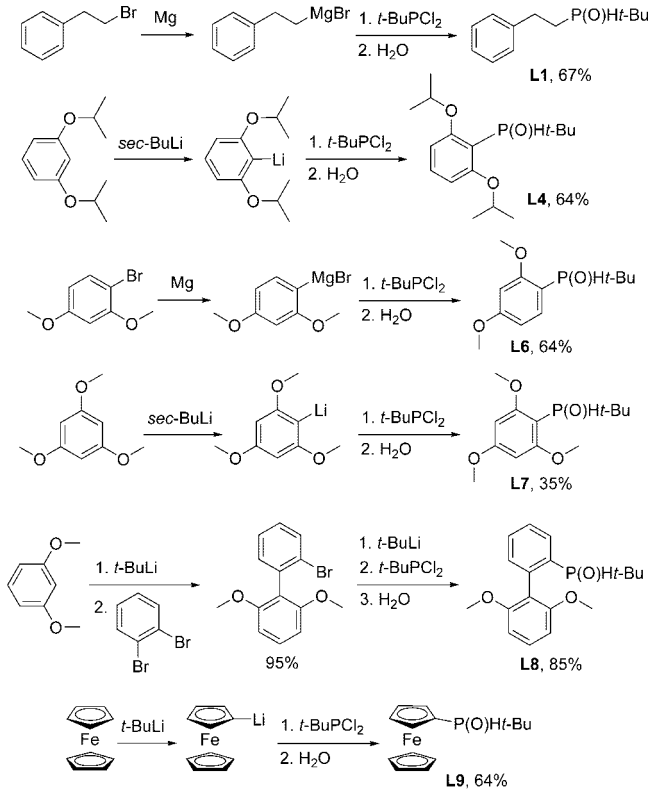


FIGURE 2. Structures of new phosphine oxides **L1**−**L9** (top) and formation of $(RR'POH)_2ML_2$ (bottom).

SCHEME 1. Synthesis of Phosphine Oxides Using *t*-BuPCl$_2$



by the organozinc reagent facilitates oxidative addition of the nonactivated halide **1** to the metal center which is probably the rate-limiting step in the Negishi cross-coupling reaction when electron-rich aryl chlorides are used. Although the actual structure of the catalytically active palladium species is not known, it has generally been assumed that the formation of negatively charged ligands plays a crucial role in generating a catalytically active metal complex.[4] Comparison of the results obtained with POPd and PXPd, which carries two chlorophosphine ligands that cannot undergo deprotonation, shows that the latter has very low catalytic activity producing only 20% of biphenyl **3** after 20 h (entry 2, Table 1). A nickel analogue of POPd, which was generated in situ by premixing of $(t\text{-Bu})_2P(O)H$ and $Ni(cod)_2$, gave **3** in only 60% yield even after 20 h.

Based on our screening results summarized in Table 1, we continued to evaluate the substrate scope of the palladium−phosphinous acid-catalyzed Negishi reaction using 5 mol % of POPd7 in NMP at 65 °C. Coupling of electron-rich 2-chloroanisole, **4**, and 4-methylthiochlorobenzene, **15**, with arylzinc **2** gave 2-methoxy-2′-methylbiphenyl and 2-methyl-4′-methylthiobiphenyl, **16**, in 89% and 86% yield, respectively (entries 2 and 7, Table 2). As expected, ketone, ester, and heteroaryl groups are well tolerated. The POPd7-catalyzed Negishi coupling reaction of ester **6**, ketone **13**, thiophene **17**, pyridine **20**, and quinoline **24** gave the corresponding biaryls in 75−93% yield (entries 3, 6, 8, 9, and 11). Noteworthy, excellent results were achieved with sterically hindered arylzinc reagents **11**, **18**, and **22** (entries 5, 8, and 10). For example, 2,2′,6-trimethylbiphenyl was produced from 2-tolyl chloride, **10**, and 2,6-dimethylzinc chloride, **11**, in 90% yield within 12 h.

High yields ranging from 83 to 92% were also obtained with aryl bromides and iodides (Table 3). In comparison to aryl chlorides, reaction times were generally shorter but yields improved only in some cases (compare entries 4−7 and 10 in Table 2 with entries 4−6, 8, and 10 in Table 3). Cross-coupling of sterically hindered substrates gave 2-methyl-2′-isopropylbiphenyl, **27**, 2-cyclohexyl-2′-isopropylbiphenyl, **32**, 2,2′,6-trimethylbiphenyl, **12**, 2-isopropyl-2′-phenylbiphenyl, **37**, and 9-(2-tolyl)anthracene, **23**, in 85−92% yield (entries 1, 3, 5, 7, and 10).

Despite the general availability and high reactivity of acyl halides toward oxidative addition, few examples of transition-metal-catalyzed cross-coupling reactions with stannanes,[8] boronic acids,[9] and organozinc,[10] arylbismuth,[11] and Grignard reagents[12] have been reported to date. Common drawbacks of some of these methods include the need for high reaction temperatures and long reaction times that do not take advantage of the inherently high reactivity of acyl chlorides and incompatibility with several functional groups, in particular, carbonyl and aryl and alkyl halide groups. Encouraged by the high yields

(8) (a) Labadie, J. W.; Tueting, D.; Stille, J. K. *J. Org. Chem.* **1983**, *48*, 4634–4642. (b) Labadie, J. W.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 6129–6137. (c) Bumagin, N. A.; Ponomaryov, A. B.; Beletskaya, I. P. *J. Organomet. Chem.* **1985**, *291*, 129–132. (d) Ye, J.; Bhatt, R. K.; Falck, J. R. *J. Am. Chem. Soc.* **1994**, *116*, 1–5. (e) Thibonnet, J.; Abarbri, M.; Parrain, J.-L.; Duchêne, A. *J. Org. Chem.* **2002**, *67*, 3941–3944. (f) Davis, J. L.; Dhawan, R.; Arndtsen, B. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 590–594. (g) Kells, K. W.; Chong, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 15666–15667. (h) Lerebours, R.; Camacho-Soto, A.; Wolf, C. *J. Org. Chem.* **2005**, *70*, 8601–8604.

SCHEME 2. Synthesis of Phosphine Oxides Using $P(OEt)_3$

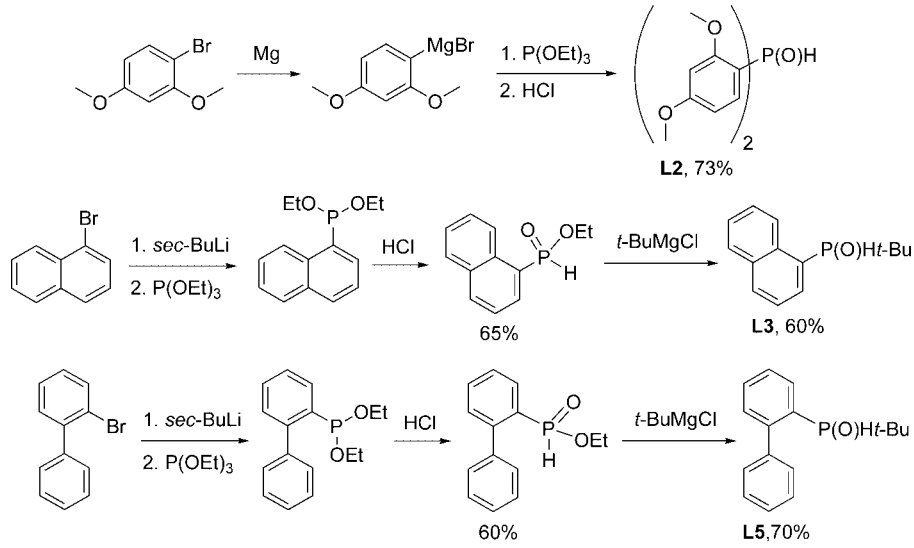
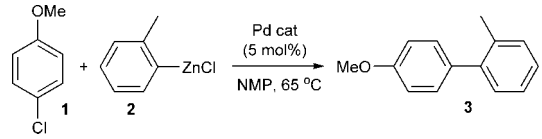


TABLE 1. Negishi Coupling of 4-Chloroanisole, 1, and 2-Tolylzinc Chloride, 2, in the Presence of Palladium−Phosphinous Acids[a]



entry	catalyst	time (h)	yield (%)
1	POPd	4	89
2	PXPd	20	25
3	POPd1	4	82
4	POPd2	4	87
5	POPd5	20	37
6	POPd6	15	83
7	POPd7	4	93
8	**L1** + Pd_2dba_3	4	81
9	**L2** + Pd_2dba_3	4	84
10	**L3** + Pd_2dba_3	4	86
11	**L4** + Pd_2dba_3	18	50
12	**L5** + Pd_2dba_3	5	78
13	**L6** + Pd_2dba_3	18	18
14	**L7** + Pd_2dba_3	18	55
15	**L8** + Pd_2dba_3	4	90
16	**L9** + Pd_2dba_3	18	26

[a] Reaction conditions: 4-chloroanisole (1.0 mmol), catalyst (5 mol %), 2-tolylzinc chloride (2.0 mmol) in NMP, 65 °C.

obtained with palladium−phosphinous acid-catalyzed Negishi coupling, we extended our study to acyl chlorides. Screening of the palladium complexes shown in Figure 1 revealed that POPd, POPd1, and POPd7 effectively catalyze the conversion of benzoyl chloride, **46**, and 2-tolylzinc chloride, **2**, toward 2-methyl benzophenone, **47**, at room temperature (entry 1, Table 4).[13] Using 5 mol % of POPd in NMP, we found that a wide range of aromatic and aliphatic acyl chlorides undergo fast cross-coupling with several organozinc reagents. For example, benzoyl chloride, **46**, 1-naphthoyl chloride, **48**, and 2-toluyl chloride, **50**, react with several arylzinc compounds carrying methoxy, cyano, and ester groups to the corresponding benzophenones with 91−98% yield (entries 1−3 and 9−11). In addition, acetophenones were obtained in high yields from aliphatic acyl chlorides **69** and **71** (entries 12 and 13). The reaction also proceeds smoothly with aliphatic zinc reagents. Coupling of benzoyl chloride and Et_2Zn gave propiophenone, **74**, in 98% yield (entry 14). The superior control of chemo- and regioselectivity and the suitability of the POPd-catalyzed ketone formation to electron-deficient arenes that would not react under traditional Friedel−Crafts acylation (FCA) conditions are important features of this reaction. For example, the presence of alkyl halides is tolerated (see entry 13), and ketones **49**, **51**, **53**, **55**, and **62** can generally not be produced in such high yields via FCA due to formation of substantial amounts of regioisomers. While palladium-catalyzed cross-coupling of **2** and **50** furnished 3-chloro-2′-methylbenzophenone, **55**, in 95% yield, Lewis acid-promoted acylation of toluene with 3-chlorobenzoyl chloride would generate a mixture of two major regioisomers **55** and **73** that are difficult to separate and the use of 2-toluyl chloride and chlorobenzene would almost exclusively afford benzophenones **74** and **75** (Scheme 3). Our POPd-catalyzed method therefore nicely complements the scope of traditional FCA synthesis.

We were pleased to find that the palladium−phosphinous acid POPd7 also catalyzes the cross-coupling reaction of aryl halides with vinylzinc and alkylzinc reagents (Table 5). The aryl−vinyl bond formation proceeds smoothly with aryl iodides, bromides, and chlorides at 50 °C in the presence of 5 mol % of the catalyst. For example, 2-methylstyrene, **76**, was obtained from 2-bromo- and 2-chlorotoluene in 91 and 84% yield, respectively (entries 1 and 2). Ethyl 3-iodobenzoate, **79**, 3-bromoacetophenone, **35**, and 2-chlorobenzonitrile, **82**, gave the corresponding styrenes **80**, **81**, and **83** in 82−93% yield (entries 4−6). The reaction of

(9) (a) Selected examples: Chen, H.; Deng, M.-Z. *Org. Lett.* **2000**, *2*, 1649–1651. (b) Urawa, Y.; Ogura, K. *Tetrahedron Lett.* **2003**, *44*, 271–273. (c) Nishihara, Y.; Inoue, Y.; Fujisawa, M.; Takagi, K. *Synlett* **2005**, 2309–2312. (d) Bandgar, B. P.; Patil, A. V. *Tetrahedron Lett.* **2005**, *46*, 7627–7630. (e) Polackova, V.; Toma, S.; Augustinova, I. *Tetrahedron* **2006**, *62*, 11675–11678. (f) Xin, B.; Zhang, Y.; Cheng, K. *J. Org. Chem.* **2006**, *71*, 5725–5731.

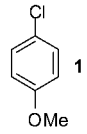
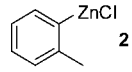
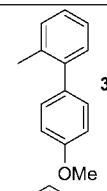
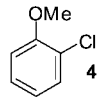
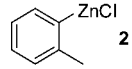
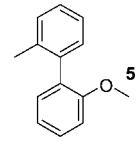
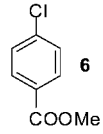
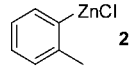
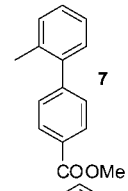
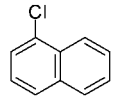
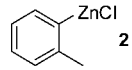
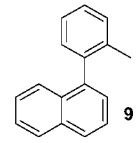
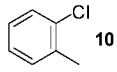
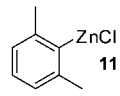
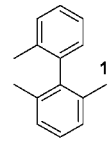
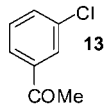
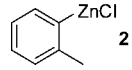
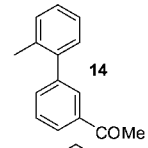
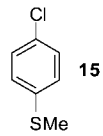
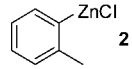
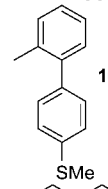
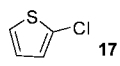
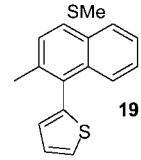
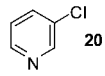
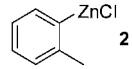
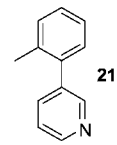
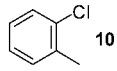
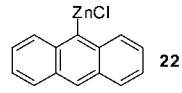
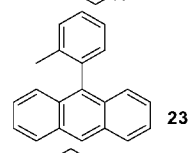
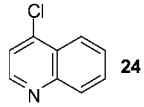
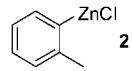
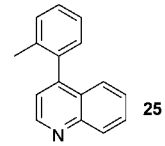
(10) (a) Evans, P. A.; Nelson, J. D.; Stanley, A. L. *J. Org. Chem.* **1995**, *60*, 2298–2301. (b) Østergaard, N.; Skjaerbaek, N.; Begtrup, M.; Vedso, P. *J. Chem. Soc., Perkin Trans. 1* **2002**, 428–433. (c) Zhang, Y.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 15964–15965.

(11) (a) Rao, M. L. N.; Venkatesh, V.; Jadhav, D. N. *Tetrahedron Lett.* **2006**, *47*, 6975–6978. (b) Rao, M. L. N.; Venkatesh, V.; Banerjee, D. *Tetrahedron* **2007**, *63*, 12917–12926.

(12) Wang, X.-J.; Zhang, L.; Sun, X.; Xu, Y.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2005**, *7*, 5593–5595.

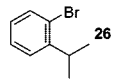
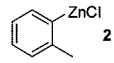
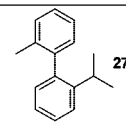
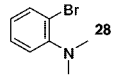
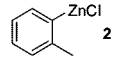
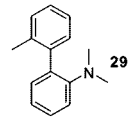
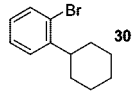
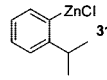
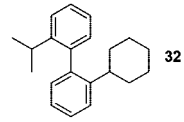
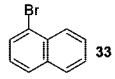
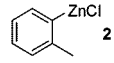
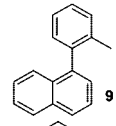
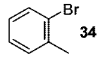
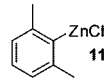
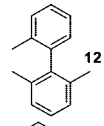
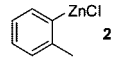
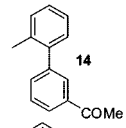
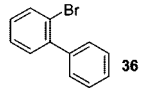
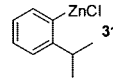
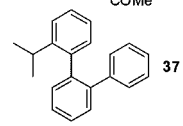
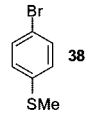
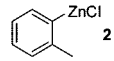
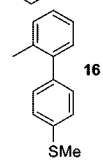
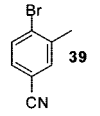
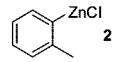
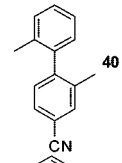
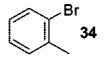
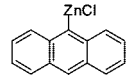
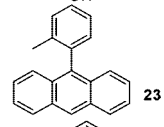
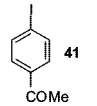
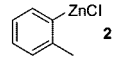
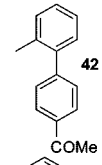
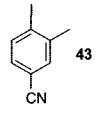
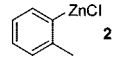
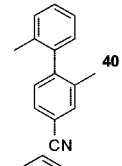
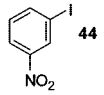
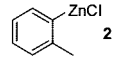
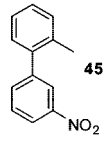
(13) This reaction is sluggish in the absence of a palladium catalyst, and only 2−5% of **47** was obtained after 30 minutes under the same reaction conditions.

TABLE 2. POPd7-Catalyzed Negishi Cross-Coupling Using Aryl Chlorides[a]

entry	aryl chloride	organozinc reagent	biaryl	time (h)	yield (%)[b]
1	 1	 2	 3	4	93
2	 4	 2	 5	3	89
3	 6	 2	 7	5	91
4	 8	 2	 9	3	91
5	 10	 11	 12	12	90
6	 13	 2	 14	15	75
7	 15	 2	 16	24	86
8	 17	 18	 19	8	93
9	 20	 2	 21	4	93
10	 10	 22	 23	8	91
11	 24	 2	 25	4	89

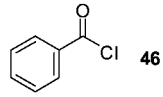
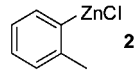
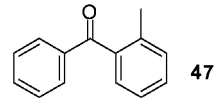
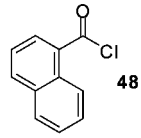
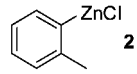
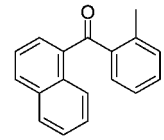
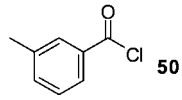
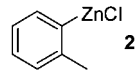
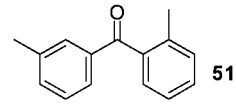
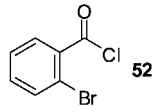
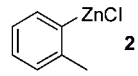
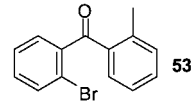
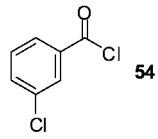
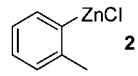
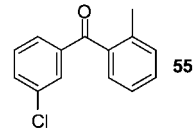
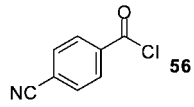
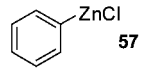
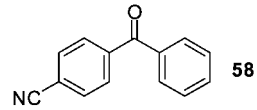
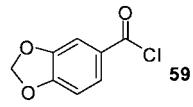
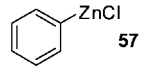
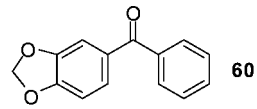
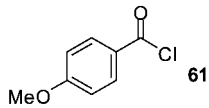
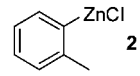
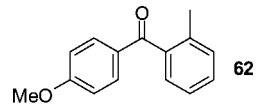
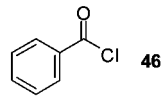
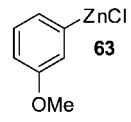
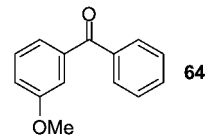
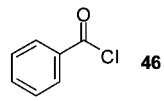
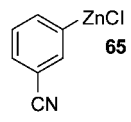
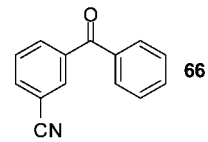
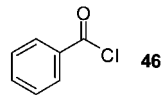
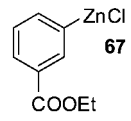
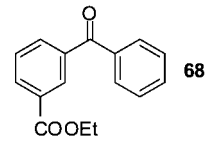
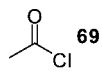
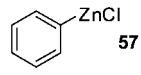
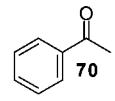
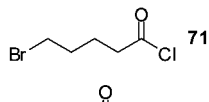
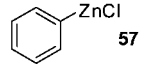
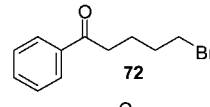
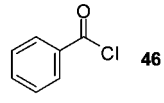
[a] Reaction conditions: aryl chloride (1.0 mmol), POPd7 (5 mol %), arylzinc chloride (2.0 mmol) in NMP, 65 °C, 3−24 h. [b] Isolated yields.

TABLE 3. POPd7-Catalyzed Negishi Cross-Coupling Using Aryl Bromides and Iodides[a]

entry	aryl bomide or iodide	organozinc reagent	biaryl	time (h)	yield (%)[b]
1	 **26**	 **2**	 **27**	3	86
2	 **28**	 **2**	 **29**	7	83
3	 **30**	 **31**	 **32**	2	85
4	 **33**	 **2**	 **9**	2	91
5	 **34**	 **11**	 **12**	8	92
6	 **35** COMe	 **2**	 **14** COMe	5	84
7	 **36**	 **31**	 **37**	2	88
8	 **38** SMe	 **2**	 **16** SMe	3	92
9	 **39** CN	 **2**	 **40** CN	2	88
10	 **34**	 **22**	 **23**	4	89
11	 **41** COMe	 **2**	 **42** COMe	2	87
12	 **43** CN	 **2**	 **40** CN	2	86
13	 **44** NO_2	 **2**	 **45** NO_2	3	90

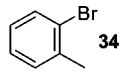
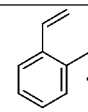
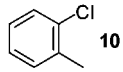
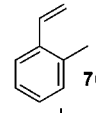
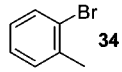
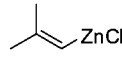
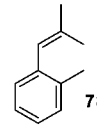
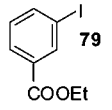
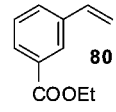
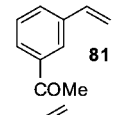
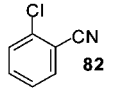
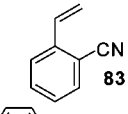
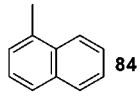
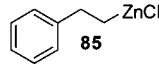
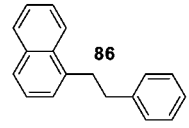
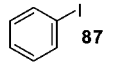
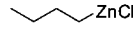
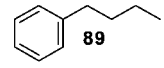
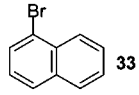
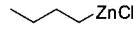
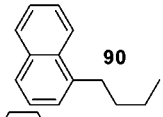
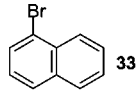
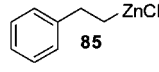
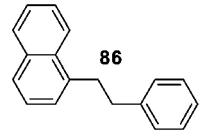
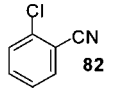
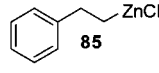
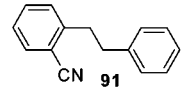
[a] Reaction conditions: aryl bromide or iodide (1.0 mmol), POPd7 (5 mol %), arylzinc chloride (2.0 mmol) in NMP, 65 °C, 2−8 h. [b] Isolated yields.

TABLE 4. POPd-Catalyzed Coupling of Acyl Chlorides and Organozinc Reagents[a]

entry	acyl chloride	organozinc reagent	ketone	yield (%)[b]
1	 **46**	 **2**	 **47**	98, 97[c]
2	 **48**	 **2**	 **49**	97
3	 **50**	 **2**	 **51**	95
4	 **52**	 **2**	 **53**	92
5	 **54**	 **2**	 **55**	95
6	 **56**	 **57**	 **58**	91
7	 **59**	 **57**	 **60**	89
8	 **61**	 **2**	 **62**	96
9	 **46**	 **63**	 **64**	93
10	 **46**	 **65**	 **66**	91
11	 **46**	 **67**	 **68**	96
12	 **69**	 **57**	 **70**	90
13	 **71**	 **57**	 **72**	84
14	 **46**	Et_2Zn **73**	**74**	98

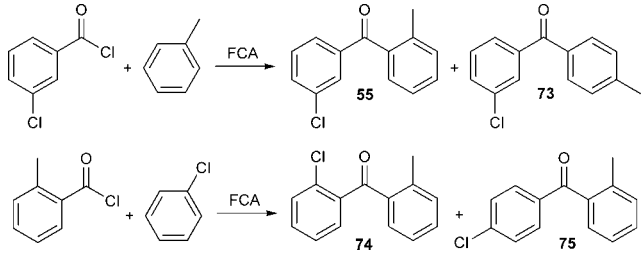
[a] Reaction conditions: acyl chloride (1.0 mmol), POPd (5 mol %), arylzinc chloride (1.5 mmol) in NMP, 25 °C, 30 min. [b] Isolated yields. [c] POPd1 and POPd7.

TABLE 5. POPd7-Catalyzed Coupling of Aryl Halides with Vinylzinc and Alkylzinc Reagents[a]

entry	aryl halide	organozinc reagent	biaryl	time (h)	yield (%)[b]
1	 **34**	 **75**	 **76**	1	91
2	 **10**	 **75**	 **76**	3	84
3	 **34**	 **77**	 **78**	1	92
4	 **79** COOEt	 **75**	 **80** COOEt	1	82
5	 **35** COMe	 **75**	 **81** COMe	1	93
6	 **82**	 **75**	 **83**	1	89
7	 **84**	 **85**	 **86**	1	82
8	 **87**	 **88**	 **89**	1	87
9	 **33**	 **88**	 **90**	2	79
10	 **33**	 **85**	 **86**	3	84
11	 **82**	 **85**	 CN **91**	20	81[c]

[a] Reaction conditions: aryl halide (1.0 mmol), POPd7 (5 mol %), vinylzinc chloride (2.0 mmol) in NMP at 50 °C or alkylzinc chloride (2.0 mmol) in NMP at 25 °C. [b] Isolated yields. [c] 70 °C.

SCHEME 3. FCA Routes toward 3-Chloro-2′-methylbenzophenone, 55, and Some Regioisomers



aryl bromides and aryl iodides **33**, **84**, and **87** with aliphatic organozinc compounds **85** and **88** occurred at room temperature and was generally completed within 1−3 h (entries 7−10). However, the cross-coupling of 2-chlorobenzonitrile, **82**, and phenylethylzinc chloride, **85**, required heating to 70 °C, and 2-phenylethylbenzonitrile, **92**, was isolated after 20 h in 81% yield (entry 11).

Conclusion

The screening of POPd, PXPd, POPd1, POPd2, POPd5, POPd6, POPd7, complexes formed in situ from Pd_2dba_3, and ligands **L1**−**L9** revealed that palladium−phosphinous acids are efficient catalysts for the cross-coupling of aryl and acyl halides with a wide range of organozinc reagents. Using 5 mol % of POPd7 in NMP, we have prepared a series of biaryls carrying alkoxy, alkylthio, amino, ketone, cyano, nitro, ester, and heteroaryl groups from aryl halides, including electron-rich aryl

chlorides, and arylzinc reagents in 75−93% yield. In addition to the expected wide functional group compatibility, this catalyst also tolerates sterically hindered aryl halides and arylzinc reagents without compromising yields. The same catalyst allows coupling of aryl halides with vinyl and alkylzinc reagents, producing styrenes and alkylarenes in 79−93% yield. The POPd-catalyzed coupling of acyl halides and organozinc reagents gives ketones in up to 98% yield. This method tolerates functional groups that are not compatible with general FCA reaction conditions, proceeds with superior regiocontrol, and is suitable to aliphatic and both electron-rich and electron-deficient aromatic substrates.

Experimental Section

All chemicals used were of reagent grade, and reactions were carried out under nitrogen. Flash chromatography was performed on Kieselgel 60, particle size 0.032−0.063 mm. NMR spectra were obtained at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR) using $CDCl_3$ as solvent. Chemical shifts are reported in ppm relative to TMS.

General Procedure for the Negishi Cross-Coupling of Aryl Halides and Arylzinc Chloride Reagents. Anhydrous $ZnCl_2$ (2.2 mmol) and 3.0 mL of anhydrous *N*-methylpyrrolidinone (NMP) were placed in a 50 mL round-bottom flask under nitrogen. Then, *o*-tolylmagnesium chloride (2.0 M solution in diethyl ether; 1.0 mL, 2.0 mmol) was added dropwise to the colorless solution. The resulting mixture was heated to 60 °C and purged with nitrogen for 20 min to remove the ether. The mixture was cooled to room temperature and stirred for 1 h. After addition of the aryl halide (1.0 mmol) and POPd7 (0.05 mmol) in NMP (1.0 mL), the reaction mixture was heated to 65 °C. Upon completion, the reaction mixture was cooled to 25 °C, quenched with water, extracted with diethyl ether, and dried over anhydrous $MgSO_4$. The solvents were removed under vacuum, and the crude products were purified by flash chromatography on silica gel as described below.

4-Methoxy-2′-methylbiphenyl, 3.[14] Purification by flash chromatography (hexanes/CH_2Cl_2 8:2) gave 184.4 mg of a colorless oil (0.93 mmol, 93%). ^{1}H NMR: δ 2.25 (s, 3H), 3.78 (s, 3H), 6.92 (d, J = 8.8 Hz, 2H), 7.18−7.24 (m, 6H). ^{13}C NMR: δ 21.2, 55.8, 114.1, 126.4, 127.6, 130.5, 130.8, 130.9, 135.0, 136.0, 142.2, 159.1.

2-Methoxy-2′-methylbiphenyl, 5.[15] Purification by flash chromatography (hexanes/CH_2Cl_2 10:1) gave 176.4 mg of a colorless oil (0.89 mmol, 89%). ^{1}H NMR: δ 2.13 (s, 3H), 3.70 (s, 3H), 6.90−7.33 (m, 8H). ^{13}C NMR: δ 20.3, 55.7, 111.1, 120.9, 125.9, 127.7, 129.0, 130.0, 130.4, 131.3, 131.4, 137.2, 139.1, 157.0.

Methyl 2′-Methylbiphenyl-4-carboxylate, 7.[16] Purification by flash chromatography (hexanes/ethyl acetate 10:1) gave 205.9 mg of a colorless oil (0.91 mmol, 91%). ^{1}H NMR: δ 2.25 (s, 3H), 3.92 (s, 3H), 7.21−7.26 (m, 4H), 7.38 (d, J = 8.8 Hz, 2H), 8.08 (d, J = 8.8 Hz, 2H). ^{13}C NMR: δ 21.0, 52.7, 126.5, 128.4, 129.2, 130.0, 130.1, 131.0, 135.7, 141.4, 147.3, 167.6.

1-(2-Tolyl)naphthalene, 9.[2] Purification by flash chromatography (hexanes) gave 198.6 mg of colorless crystals (0.91 mmol, 91%). ^{1}H NMR: δ 2.00 (s, 3H), 7.21−7.36 (m, 6H), 7.41−7.51 (m, 3H), 7.83 (d, J = 8.3 Hz, 1H), 7.83 (d, J = 8.5 Hz, 1H). ^{13}C NMR: δ 20.7, 126.0, 126.2, 126.4, 126.6, 126.8, 127.3, 128.1, 128.2, 128.9, 130.5, 131.0, 132.7, 134.2, 137.4, 140.4, 140.9.

2,2′,6-Trimethylbiphenyl, 12.[2] Purification by flash chromatography (hexanes) gave 176.7 mg of a colorless oil (0.90 mmol, 90%). ^{1}H NMR: δ 1.94 (s, 6H), 1.96 (s, 3H), 7.00−7.27 (m, 7H). ^{13}C NMR: δ 20.1, 21.0, 126.7, 127.6, 127.7, 127.9, 129.5, 130.6, 136.2, 136.5, 141.2, 141.7.

3-Acetyl-2′-methylbiphenyl, 14. Purification by flash chromatography (hexanes/ethyl acetate 10:1) gave 157.7 mg of a colorless oil (0.75 mmol, 75%). ^{1}H NMR: δ 2.32 (s, 3H), 2.66 (s, 3H), 7.26−7.34 (m, 4H), 7.51−7.59 (m, 2H), 7.98−8.02 (m, 2H). ^{13}C NMR: δ 20.9, 27.2, 126.5, 127.3, 128.3, 128.9, 129.5, 130.2, 131.0, 134.3, 135.7, 137.6, 141.3, 142.9, 198.5. Anal. Calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.47; H, 6.63.

4-(2-Tolyl)thioanisole, 16.[17] Purification by flash chromatography (hexanes/CH_2Cl_2 8:2) gave 184.3 mg of a colorless oil (0.86 mmol, 86%). ^{1}H NMR: δ 2.26 (s, 3H), 2.50 (s, 3H), 7.18−7.30(m, 8H). ^{13}C NMR: δ 16.5, 21.1, 126.4, 126.9, 127.9, 130.3, 130.4, 131.0, 136.0, 137.5, 139.4, 141.9.

2-(2-Methyl-1-naphthyl)thiophene, 19. Purification by flash chromatography (hexanes) gave 208.6 mg of a colorless oil (0.93 mmol, 93%). ^{1}H NMR: δ 2.311 (s, 3H), 6.94 (dd, J = 3.4 Hz, 1.2 Hz, 1H), 7.15 (dd, J = 5.1 Hz, 3.4 Hz, 1H), 7.31−7.37 (m, 3H), 7.41 (dd, J = 5.1 Hz, 1.2 Hz, 1H), 7.58−7.61 (m, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.77 (dd, J = 6.0 Hz, 2.7 Hz, 1H). ^{13}C NMR: δ 21.6, 125.6, 126.5, 126.9, 127.8, 128.3, 128.4, 128.8, 129.0, 130.9, 132.5, 134.8, 136.6, 140.7. Anal. Calcd for $C_{15}H_{12}S$: C, 80.31; H, 5.39. Found: C, 79.97; H, 5.13.

3-(2-Tolyl)pyridine, 21.[18] Purification by flash chromatography (hexanes/ethyl acetate 10:1) gave 157.4 mg of a colorless oil (0.93 mmol, 93%). ^{1}H NMR: δ 2.25 (s, 3H), 7.18 (d, J = 7.3 Hz, 1H), 7.19−7.29 (m, 3H), 7.30 (dd, J = 7.6 Hz, 4.8 Hz, 1H), 7.61 (ddd, J = 7.6 Hz, 2.1 Hz, 1.5 Hz, 1H), 8.57 (m, 2H). ^{13}C NMR: δ 20.8, 123.5, 126.5, 128.6, 130.3, 131.0, 136.0, 136.9, 137.9, 138.5, 148.5, 150.3.

9-(2-Tolyl)anthracene, 23.[2] Purification by flash chromatography (hexanes/CH_2Cl_2 10:1) gave 244.2 mg of white crystals (0.91 mmol, 91%). ^{1}H NMR: δ 1.84 (s, 3H), 7.21−7.41 (m, 8H), 7.50 (d, J = 8.8 Hz, 2H), 7.97 (d, J = 8.6 Hz, 2H), 8.42 (s, 1H). ^{13}C NMR: δ 20.41, 125.8, 126.1, 126.5, 127.1, 127.2, 128.5, 129.1, 130.6, 130.7, 131.9, 132.1, 137.1, 138.4, 138.8.

4-(2-Tolyl)quinoline, 25. Purification by flash chromatography (hexanes/ethyl acetate 10:1) gave 195.2 mg of colorless crystals (0.89 mmol, 89%). ^{1}H NMR: δ 2.00 (s, 3H), 7.17 (d, J = 8.6 Hz, 1H), 7.25 (d, J = 4.4 Hz, 1H), 7.25−7.42 (m, 4H), 7.48 (dd, J = 8.6 Hz, 1.8 Hz, 1H), 7.67 (ddd, J = 8.3 Hz, 2.1 Hz, 1.5 Hz, 1H), 8.18 (d, J = 8.3 Hz, 1H), 8.93 (d, J = 4.4 Hz, 1H). ^{13}C NMR: δ 20.4, 121.9, 126.3, 126.5, 127.1, 127.8, 128.9, 129.9, 130.0, 130.3, 130.7, 136.5, 137.9, 148.9, 149.0, 150.5. Anal. Calcd for $C_{16}H_{13}N$: C, 87.64; H, 5.98; N, 6.39. Found: C, 87.21; H, 5.93; N, 6.48.

2-Isopropyl-2′-methylbiphenyl, 27.[2] Purification by flash chromatography (hexanes) gave 180.9 mg of a colorless oil (0.86 mmol, 86%). ^{1}H NMR: δ 1.07 (d, J = 6.8 Hz, 3H), 1.14 (d, J = 6.8 Hz, 3H), 2.05 (s, 3H), 2.69 (sept, J = 6.8 Hz, 1H), 7.04−7.40 (m, 8H). ^{13}C NMR: δ 20.2, 23.2, 24.7, 29.8, 125.3, 125.5, 127.1, 127.6, 129.3, 129.4, 129.6, 129.7, 136.0, 140.3, 141.5, 146.5.

2-Dimethylamino-2′-methylbiphenyl, 29.[2] Purification by flash chromatography (hexanes CH_2Cl_2 9:1) gave 175.4 mg of a colorless oil (0.83 mmol, 83%). ^{1}H NMR: δ 2.15 (s, 3H), 2.50 (s, 6H), 6.95−7.30 (m, 8H). ^{13}C NMR: δ 20.6, 43.8, 118.1, 121.7, 126.3, 127.4, 128.6, 130.6, 130.7, 132.4, 135.2, 136.8, 142.4, 152.2.

2-Cyclohexyl-2′-isopropylbiphenyl, 32.[2] Purification by flash chromatography (hexanes) gave 236.7 mg of a colorless oil (0.85 mmol, 85%). ^{1}H NMR: δ 0.86−1.34 (m, 8H), 1.46−1.74 (m, 8H), 2.29 (m, 1H), 2.70 (sept, J = 6.8 Hz, 1H), 7.03−7.38 (m, 8H). ^{13}C NMR: δ 23.8, 25.4, 26.8, 27.4, 30.5, 34.1, 36.0, 41.2, 125.7, 125.8, 126.5, 126.6, 128.0, 128.2, 130.3, 130.4, 140.8, 141.1, 146.4, 147.3.

2-Isopropyl-2′-phenylbiphenyl, 37.[2] Purification by flash chromatography (hexanes) gave 239.7 mg of colorless crystals (0.88 mmol, 88%).^{1}H NMR: δ 0.64 (d, J = 6.8 Hz, 3H), 0.95 (d, J =

(14) Rostovtsev, V. V.; Bryman, L. M.; Junk, C. P.; Harmer, M. A.; Carcani, L. G. *J. Org. Chem.* **2008**, *73*, 711–714.
(15) Wolf, C.; Xu, H. *J. Org. Chem.* **2008**, *73*, 162–167.
(16) Okamoto, K.; Akiyama, R.; Kobayashi, S. *Org. Lett.* **2004**, *6*, 1987–1990.
(17) Li, G. Y. *J. Org. Chem.* **2002**, *67*, 3643–3650.
(18) Kudo, N.; Perseghini, M.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1282–1284.

6.8 Hz, 3H), 2.66 (sept, $J = 6.8$ Hz, 1H), 7.06−7.46 (m, 13H). ^{13}C NMR: δ 22.4, 25.6, 30.0, 125.3, 125.5, 126.7, 127.3, 127.8, 127.9, 128.0, 130.0, 131.1, 140.3, 140.6 141.3, 141.6, 146.7.

4-Cyano-2,2′-dimethylbiphenyl, 40. Purification by flash chromatography (hexanes/ethyl acetate 10:1) gave 182.4 mg of a colorless oil (0.88 mmol, 88%). ^{1}H NMR: δ 2.03(s, 3H), 2.08 (s, 3H), 7.03 (d, $J = 7.3$ Hz, 1H), 7.19 (d, $J = 7.8$ Hz, 1H), 7.21−7.31 (m, 3H), 7.48−7.52 (m, 1H), 7.55 (dd, $J = 1.2$ Hz, 0.8 Hz, 1H). ^{13}C NMR: δ 20.2, 111.6, 119.6, 126.4, 128.6, 129.1, 129.9, 130.7, 133.8, 133.9, 135.7, 138.1, 140.2, 147.2. Anal. Calcd for $C_{15}H_{13}N$: C, 86.92; H, 6.32; N, 6.76. Found: C, 86.61; H, 6.38; N, 6.83.

4-Acetyl-2′-methylbiphenyl, 42.[19] Purification by flash chromatography (hexanes/ethyl acetate 10:1) gave 182.9 mg of a colorless oil (0.87 mmol, 87%). ^{1}H NMR: δ 2.25 (s, 3H), 2.62 (s, 3H), 7.18−7.28 (m, 4H), 7.40 (d, $J = 8.5$ Hz, 2H), 7.99 (d, $J = 8.5$ Hz, 2H). ^{13}C NMR: δ 20.9, 27.2, 126.5, 128.5, 128.8, 130.0, 130.1, 131.1, 135.7, 136.1, 141.3, 147.5, 198.5.

3-Nitro-2′-methylbiphenyl, 45.[20] Purification by flash chromatography (hexanes/ethyl acetate 9:1) gave 191.9 mg of a yellow oil (0.90 mmol, 90%). ^{1}H NMR: δ 2.26 (s, 3H), 7.18−7.31 (m, 4H), 7.53−7.66 (m, 2H), 8.16−8.19 (m, 2H). ^{13}C NMR: δ 20.9, 122.4, 124.6, 126.7, 128.9, 129.6, 130.1, 131.2, 135.7, 135.9, 139.9, 144.1, 148.6.

General Procedure for the POPd-Catalyzed Cross-Coupling of Acyl Chlorides and Organozinc Reagents. Anhydrous $ZnCl_2$ (1.6 mmol) and 3.0 mL of anhydrous *N*-methylpyrrolidinone (NMP) were placed in a 50 mL round-bottom flask under nitrogen. Then, *o*-tolylmagnesium chloride (2.0 M solution in diethyl ether; 0.75 mL, 1.5 mmol) was added dropwise to the colorless solution. The resulting mixture was heated to 60 °C and purged with nitrogen for 20 min to remove the ether. The mixture was cooled to room temperature and stirred for 1 h. After addition of benzoyl chloride (1.0 mmol) and POPd (0.05 mmol) in NMP (1.0 mL), the reaction mixture was stirred at room temperature for 30 min, quenched with water, extracted with diethyl ether, and dried over anhydrous $MgSO_4$. The solvents were removed under vacuum, and the crude products were purified by flash chromatography on silica gel as described below.

2-Methylbenzophenone, 47.[21] Purification by flash chromatography (hexanes/ethyl acetate 10:1) gave 192.3 mg of a colorless oil (0.98 mmol, 98%). ^{1}H NMR: δ 2.32 (s, 3H), 7.18−7.30 (m, 3H), 7.34 (dd, $J = 7.1$ Hz, 1.6 Hz, 1H), 7.38−7.44 (m, 2H), 7.50−7.56 (m, 1H), 7.78 (d, $J = 7.1$ Hz, 2H). ^{13}C NMR: δ 20.5, 125.7, 128.9, 129.0, 130.6, 130.8, 131.5, 133.6, 137.2, 138.2, 139.1, 199.0.

2-(1-Naphthoyl)toluene, 49.[22] Purification by flash chromatography (hexanes/ethyl acetate 10:1) gave 238.9 mg of a colorless oil (0.97 mmol, 97%). ^{1}H NMR: δ 2.44 (s, 3H), 7.07−7.15 (m, 1H), 7.23 (d, $J = 6.8$ Hz, 1H), 7.30−7.35 (m, 3H), 7.43−7.54 (m, 3H), 7.82 (d, $J = 8.1$ Hz, 1H), 7.90 (d, $J = 8.1$ Hz, 1H), 8.56 (d, $J = 8.1$ Hz, 1H). ^{13}C NMR: δ 21.2, 124.8, 125.9, 126.3, 127.0, 128.3, 129.0, 130.7, 130.9, 131.5, 131.6, 131.9, 133.0, 134.4, 136.9, 138.6, 140.0, 200.7.

2,3′-Dimethylbenzophenone, 51.[23] Purification by flash chromatography (hexanes/ethyl acetate 10:1) gave 199.8 mg of a colorless oil (0.95 mmol, 95%). ^{1}H NMR: δ 2.32 (s, 3H), 2.35 (s, 3H), 7.18−7.38 (m, 6H), 7.53−7.57 (m, 1H), 7.65 (dd, $J = 1.2$ Hz, 0.7 Hz, 1H). ^{13}C NMR: δ 20.5, 21.8, 125.7, 128.1, 128.8, 129.0, 130.7, 130.9, 131.5, 134.4, 137.1, 138.3, 138.8, 139.3, 199.2.

2-Bromo-2′-methylbenzophenone, 53.[24] Purification by flash chromatography (hexanes/ethyl acetate 10:1) gave 253.1 mg of a colorless oil (0.92 mmol, 92%). ^{1}H NMR: δ 2.58 (s, 3H), 7.12−7.18 (m, 1H), 7.26−7.41 (m, 6H), 7.56−7.60 (m, 1H). ^{13}C NMR: δ 21.9, 120.6, 126.1, 127.8, 130.3, 132.0, 132.2, 132.5, 132.7, 133.9, 136.9, 140.4, 142.1, 198.4.

3-Chloro-2′-methylbenzophenone, 55.[10] Purification by flash chromatography (hexanes/ethyl acetate 10:1) gave 219.2 mg of a colorless oil (0.95 mmol, 95%). ^{1}H NMR: δ 2.33 (s, 3H), 7.19−7.40 (m, 5H), 7.48−7.51 (m, 1H), 7.80 (dd, $J = 2.1$ Hz, 1.6 Hz, 1H). ^{13}C NMR: δ 20.5, 125.8, 128.8, 129.1, 130.3, 131.2, 131.7, 132.5, 133.4, 135.2, 137.5, 138.2, 139.9, 197.4.

4-Cyanobenzophenone, 58.[25] Purification by flash chromatography (hexanes/ethyl acetate 10:1) gave 188.6 mg of colorless crystals (0.91 mmol, 91%). ^{1}H NMR: δ 7.48−7.54 (m, 2H), 7.61−7.67 (m, 1H), 7.77−7.80 (m, 4H), 7.85−7.89 (m, 2H). ^{13}C NMR: δ 116.0, 118.4, 129.0, 130.4, 130.6, 132.6, 133.7, 136.7, 141.5, 195.3.

Piperonyloylbenzene, 60.[26] Purification by flash chromatography (hexanes/ethyl acetate 10:1) gave 201.3 mg of a colorless oil (0.89 mmol, 89%). ^{1}H NMR: δ 6.00 (s, 2H), 6.81 (d, $J = 8.3$ Hz, 1H), 7.32−7.35 (m, 2H), 7.40−7.46 (m, 2H), 7.49−7.55 (m, 1H), 7.70−7.74 (m, 2H). ^{13}C NMR: δ 102.2, 107.9, 110.1, 127.1, 128.4, 129.9, 132.0, 132.2, 138.4, 148.2, 151.8, 195.2.

4-Methoxy-2′-methylbenzophenone, 62.[27] Purification by flash chromatography (hexanes/ethyl acetate 10:1) gave 217.2 mg of a colorless oil (0.96 mmol, 96%). ^{1}H NMR: δ 2.29 (s, 3H), 3.84 (m, 3H), 6.89−6.93 (m, 2H), 7.19−7.38 (m, 4H), 7.76−7.80 (m, 2H). ^{13}C NMR: δ 20.3, 56.1, 114.3, 125.7, 128.5, 130.3, 131.1, 131.4, 133.0, 136.7, 139.8, 164.3, 197.9.

3-Methoxybenzophenone, 64.[8] Purification by flash chromatography (hexanes/ethyl acetate 10:1) gave 197.3 mg of a colorless oil (0.93 mmol, 93%). ^{1}H NMR: δ 3.80 (m, 3H), 7.08−7.12 (m, 1H), 7.30−7.37 (m, 3H), 7.40−7.46 (m, 2H), 7.51−7.57 (m, 1H), 7.77−7.80 (m, 2H). ^{13}C NMR: δ 55.8, 114.8, 119.2, 123.3, 128.7, 129.7, 130.5, 132.9, 138.0, 139.3, 160.0, 196.8.

3-Cyanobenzophenone, 66.[28] Purification by flash chromatography (hexanes/ethyl acetate 10:1) gave 188.6 mg of colorless crystals (0.91 mmol, 91%). ^{1}H NMR: δ 7.48−7.54 (m, 2H), 7.61−7.67 (m, 2H), 7.76−7.79 (m, 2H), 7.85−7.88 (m, 1H), 8.00−8.06 (m, 2H). ^{13}C NMR: δ 113.2, 118.4, 129.1, 129.8, 130.4, 133.7, 133.8, 134.3, 135.8, 136.7, 139.0, 194.8.

Ethyl 3-benzoylbenzoate, 68.[29] Purification by flash chromatography (hexanes/ethyl acetate 10:1) gave 244.1 mg of a colorless oil (0.96 mmol, 96%). ^{1}H NMR: δ 1.38 (t, $J = 7.1$ Hz, 3H), 4.39 (q, $J = 7.1$ Hz, 2H), 7.45−7.62 (m, 4H), 7.78−7.81 (m, 2H), 7.94−7.98 (m, 1H), 8.23−8.27 (m, 1H), 8.46 (t, $J = 1.7$ Hz, 1H). ^{13}C NMR: δ 14.7, 61.8, 128.9, 130.4, 131.3, 133.2, 133.5, 134.4, 137.4, 138.3, 166.1, 196.0.

Acetophenone, 70.[30] Purification by flash chromatography (hexanes/ethyl acetate 10:1) gave 108.1 mg of a colorless oil (0.90 mmol, 90%). ^{1}H NMR: δ 2.57 (s, 3H), 7.40−7.46 (m, 2H), 7.50−7.57 (m, 1H), 7.92−7.96 (m, 2H). ^{13}C NMR: δ 27.0, 128.7, 129.0, 133.5, 137.5, 198.6.

5-Bromo-1-phenylpentan-1-one, 72.[31] Purification by flash chromatography (hexanes/ethyl acetate 10:1) gave 202.5 mg of

(19) Schweizer, S.; Becht, J.; Le Drian, C. *Org. Lett.* **2007**, *9*, 3777–3780.
(20) He, H. S.; Yan, J. J.; Shen, R.; Zhuo, S.; Toy, P. H. *Synlett* **2006**, 563–566.
(21) Rao, M.L. N.; Venkatesh, V.; Banerjee, D. *Tetrahedron* **2007**, *63*, 12917–12926.
(22) Yamamoto, J.; Nakane, I.; Nakashima, M.; Asano, M.; Akamatsu, H.; Okamoto, Y.; Sugita, K. *Nippon Kagaku Kaishi* **1989**, *9*, 1587–92.
(23) Kikukawa, K.; Idemoto, T.; Katayama, A.; Kono, K.; Wada, F.; Matsuda, T. *J. Chem. Soc., Perkin Trans. 1* **1987**, *7*, 1511–14.
(24) Karagoz, S.; Astley, D. K.; Astley, S. T. *Appl. Organomet. Chem.* **2000**, *14*, 341–344.
(25) Qin, C.; Chen, J.; Wu, H.; Cheng, J.; Zhang, Q.; Zuo, B.; Su, W.; Ding, J. *Tetrahedron Lett.* **2008**, *49*, 1884–1888.
(26) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 1557–1565.
(27) Andrus, M. B.; Ma, Y.; Zang, Y.; Song, C. *Tetrahedron Lett.* **2002**, *43*, 9137–9140.
(28) Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 6040–6044.
(29) Lee, J. C.; Song, I.; Park, J. Y. *Synth. Commun.* **2002**, *32*, 2209–2213.
(30) Demizu, Y.; Shiigi, H.; Oda, T.; Matsumura, Y.; Onomura, O. *Tetrahedron Lett.* **2007**, *49*, 48–52.
(31) Sonda, S.; Kawahara, T.; Murozono, T.; Sato, N.; Asano, K.; Haga, K. *Bioorg. Med. Chem.* **2003**, *11*, 4225–4234.

colorless crystals (0.84 mmol, 84%). ^{1}H NMR: δ 1.84−1.94 (m, 4H), 2.97 (t, J = 6.8 Hz, 2H), 3.43 (t, J = 6.6 Hz, 1H), 3.56 (t, J = 6.3 Hz, 1H), 7.41−7.47 (m, 2H), 7.52−7.57 (m, 1H), 7.92−7.96 (m, 2H). ^{13}C NMR: δ 22.0, 23.2, 32.6, 33.9, 37.9, 45.3, 128.5, 129.1, 133.6, 137.3, 200.0.

Propiophenone, 74.[17] Purification by flash chromatography (hexanes/ethyl acetate 10:1) gave 131.5 mg of a colorless oil (0.98 mmol, 98%). ^{1}H NMR: δ 1.20 (t, J = 7.1 Hz, 3H), 2.95 (q, J = 7.1 Hz, 2H), 7.38−7.44 (m, 2H), 7.48−7.54 (m, 1H), 7.92−7.96 (m, 2H). ^{13}C NMR: δ 8.6, 32.1, 128.3, 128.9, 133.2, 137.3, 201.0.

General Procedure for the POPd-Catalyzed Cross-Coupling of Aryl Halides and Vinylzinc Chloride. Anhydrous $ZnCl_2$ (2.2 mmol) and 4.0 mL of anhydrous *N*-methylpyrrolidone (NMP) were placed in a 50 mL round-bottom flask under nitrogen. Then, vinylmagnesium bromide (1.0 M solution in THF; 2.0 mL, 2.0 mmol) was added dropwise to the colorless solution. The resulting mixture was heated to 60 °C and purged with nitrogen for 20 min to remove THF. The mixture was cooled to room temperature and stirred for 1 h. After addition of the aryl halide (1.0 mmol) and POPd7 (0.05 mmol) in NMP (1.0 mL), the reaction mixture was heated to 50 °C. Upon completion, the reaction mixture was cooled to 25 °C, quenched with water, extracted with diethyl ether and dried over anhydrous $MgSO_4$. The solvents were removed under vacuum and the crude products were purified by flash chromatography on silica gel as described below.

2-Methylstyrene, 76.[32] Purification by flash chromatography (hexanes) gave 107.5 mg of a colorless oil (0.91 mmol, 91%). ^{1}H NMR: δ 2.33 (s, 3H), 5.27 (dd, J = 11.0 Hz, 1.2 Hz, 1H), 5.62 (dd, J = 17.5 Hz, 1.2 Hz, 1H), 6.93 (dd, J = 17.5 Hz, 11.0 Hz, 1H), 7.13−7.17 (m, 3H), 7.44−7.47 (m, 1H). ^{13}C NMR: δ 20.3, 115.8, 126.0, 126.8, 128.3, 130.9, 135.5, 136.0, 137.5.

1-Methyl-2-(2-methylprop-1-enyl)benzene, 78.[33] Purification by flash chromatography (hexanes) gave 134.5 mg of a colorless oil (0.92 mmol, 92%). ^{1}H NMR: δ 1.69 (d, J = 1.0 Hz, 3H), 1.89 (d, J = 1.4 Hz, 3H), 2.22 (s, 3H), 6.21 (dd, J = 1.4 Hz, 1.0 Hz, 1H), 7.09−7.173 (m, 4H). ^{13}C NMR: δ 19.9, 20.6, 124.8, 125.9, 126.9, 130.1, 130.3, 135.6, 137.0, 138.6.

Ethyl 3-vinylbenzoate, 80.[34] Purification by flash chromatography (hexanes/ethyl acetate 10:1) gave 144.5 mg of a colorless oil (0.82 mmol, 82%). ^{1}H NMR: δ 1.38 (t, J = 7.1 Hz, 3H), 4.36 (q, J = 7.1 Hz, 2H), 5.29 (dd, J = 11.0 Hz, 1.2 Hz, 1H), 5.80 (dd, J = 17.5 Hz, 1.2 Hz, 1H), 6.72 (dd, J = 17.5 Hz, 11.0 Hz, 1H), 7.32−7.39 (m, 1H), 7.52−7.56 (m, 1H), 7.90−7.93 (m, 1H), 8.02−8.07 (m, 1H). ^{13}C NMR: δ 14.8, 61.4, 115.5, 127.8, 129.0, 129.3, 130.0, 130.8, 131.3, 136.5, 138.3, 166.9.

3-Vinylacetophenone, 81.[35] Purification by flash chromatography (hexanes/ethyl acetate 10:1) gave 134.0 mg of a colorless oil (0.93 mmol, 93%). ^{1}H NMR: δ 2.60 (s, 3H), 5.33 (dd, J = 11.0 Hz, 1.2 Hz, 1H), 5.82 (dd, J = 17.5 Hz, 1.2 Hz, 1H), 6.75 (dd, J = 17.5 Hz, 11.0 Hz, 1H), 7.38−7.44 (m, 1H), 7.57−7.62 (m, 1H), 7.81−7.84 (m, 1H), 7.97 (t, J = 1.7 Hz, 1H). ^{13}C NMR: δ 27.3, 115.9, 126.6, 128.3, 129.4, 131.2, 136.6, 138.0, 138.6, 198.7.

2-Vinylbenzonitrile, 83.[22] Purification by flash chromatography (hexanes/ethyl acetate 10:1) gave 115.0 mg of a colorless oil (0.89 mmol, 89%). ^{1}H NMR: δ 5.51 (d, J = 11.0 Hz, 1H), 5.93 (d, J = 17.5 Hz, 1H), 7.04 (dd, J = 17.5 Hz, 11.0 Hz, 1H), 7.29−7.35 (m, 1H), 7.51−7.67 (m, 3H). ^{13}C NMR: δ 111.4, 118.2, 119.4, 125.8, 128.4, 133.2, 133.3, 140.9.

General Procedure for the POPd-Catalyzed Cross-Coupling of Aryl Halides and Alkylzinc Chloride. Phenylethylmagnesium bromide was prepared from (2-bromoethyl)benzene (2.0 mmol) and magnesium (3.0 mmol) in 1.0 mL of anhydrous tetrahydofuran. Anhydrous $ZnCl_2$ (2.2 mmol) and 3.0 mL of anhydrous *N*-methylpyrrolidinone (NMP) were placed in a 50 mL round-bottom flask under nitrogen. Then, the Grignard reagent (2.0 M solution in THF; 1.0 mL, 2.0 mmol) was added dropwise to the colorless solution. The resulting mixture was heated to 60 °C and purged with nitrogen for 20 min to remove THF. The mixture was cooled to room temperature and stirred for 1 h. After addition of the aryl halide (1.0 mmol) and POPd7 (0.05 mmol) in NMP (1.0 mL), the reaction mixture was stirred at room temperature. Upon completion, the reaction mixture was quenched with water, extracted with diethyl ether, and dried over anhydrous $MgSO_4$. The solvents were removed under vacuum, and the crude products were purified by flash chromatography on silica gel as described below.

1-Phenylethylnaphthalene, 86.[36] Purification by flash chromatography (hexanes) gave 190.5 mg of a colorless oil (0.82 mmol, 82%). ^{1}H NMR: δ 3.02 (t, J = 7.1 Hz, 2H), 3.34 (t, J = 7.1 Hz, 2H), 7.18−7.49 (m, 9H), 7.69 (d, J = 8.3 Hz, 1H), 7.80−7.84 (m, 1H), 8.06 (d, J = 8.3 Hz, 1H). ^{13}C NMR: δ 35.7, 37.7, 124.3, 126.1, 126.2, 126.5, 126.6, 126.7, 127.4, 129.1, 129.5, 132.4, 134.5, 138.4, 142.6.

Butylbenzene, 89.[37] Purification by flash chromatography (hexanes) gave 116.8 mg of a colorless oil (0.87 mmol, 87%). ^{1}H NMR: δ 0.91 (t, J = 7.1 Hz, 3H), 1.27−1.40 (m, 2H), 1.53−1.63 (m, 2H), 2.58 (t, J = 7.8 Hz, 3H), 7.10−7.26 (m, 5H)h. ^{13}C NMR: δ 14.4, 22.8, 34.2, 36.2, 126.0, 128.7, 128.8, 143.3.

1-Butylnaphthalene, 90.[23] Purification by flash chromatography (hexanes) gave 145.6 mg of a colorless oil (0.79 mmol, 79%). ^{1}H NMR: δ 0.91 (t, J = 7.1 Hz, 3H), 1.27−1.40 (m, 2H), 1.53−1.63 (m, 2H), 2.58 (t, J = 7.8 Hz, 3H), 7.23−7.46 (m, 4H), 7.63 (d, J = 8.3 Hz, 1H), 7.74−7.79 (m, 1H), 7.99 (d, J = 8.3 Hz, 1H). ^{13}C NMR: δ 14.7, 23.6, 33.5, 33.7, 124.6, 126.0, 126.2, 126.3, 126.5, 126.7, 127.1, 128.5, 129.4, 132.6, 134.6, 139.6.

2-Phenylethylbenzonitrile, 91.[38] Purification by flash chromatography (hexanes/ethyl acetate 10:1) gave 167.9 mg of colorless crystals (0.81 mmol, 81%). ^{1}H NMR: δ 2.90−2.96 (m, 2H), 3.07−3.14 (m, 2H), 7.15−7.29 (m, 7H), 7.69 (d, J = 8.3 Hz, 1H), 7.40−7.46 (m, 1H), 7.56 (dd, J = 8.3 Hz, 1.2 Hz, 1H). ^{13}C NMR: δ 37.2, 37.6, 112.8, 118.5, 126.8, 127.2, 128.9 129.0, 130.2, 133.2, 133.3, 141.0, 145.9

Synthesis of Phosphinous Acids L1−L9. *tert*-Butyl(phenylethyl)phosphine Oxide, L1. Phenylethylmagnesium bromide was prepared from (2-bromoethyl)benzene (3.0 mmol) and magnesium (3.5 mmol) in 1.5 mL of anhydrous tetrahydofuran. The Grignard reagent (2.0 M solution in THF; 1.5 mL, 3.0 mmol) was added dropwise to a solution of *t*-BuPCl$_2$ in THF (2 M, 1 mL, 2.0 mmol) under nitrogen. After the addition was complete, the mixture was heated to reflux for 3 h, cooled to 0 °C, quenched with water, extracted with diethyl ether, and dried over anhydrous $MgSO_4$. Then, the solvents were removed under vacuum to yield a yellow oil. Purification by flash chromatography (hexanes/ethyl acetate/methanol = 90:10:2) gave 281.7 mg of colorless crystals (1.34 mmol, 67%). ^{1}H NMR: δ 1.18 (d, J = 16.5 Hz, 9H), 1.90−2.09 (m, 2H), 2.93−3.18 (m, 2H), 6.44 (dd, J_{P-H} = 440.4 Hz, 7.5 Hz, 1H), 7.19−7.34 (m, 5H). ^{13}C NMR: δ 24.1, 26.3 (d, J = 58.6 Hz), 28.9, 31.4 (d, J = 67.1 Hz), 126.9, 128.6, 129.1, 141.0 (d, J = 12.0 Hz). ^{31}P NMR: δ 49.8 (s). Anal. Calcd for $C_{12}H_{19}OP$: C, 68.55; H, 9.11. Found: C, 68.21; H, 8.78.

Bis(2,4-dimethoxyphenyl)phosphine Oxide, L2. 2,4-Dimethoxyphenylmagnesium bromide was prepared from 1-bromo-2,4-dimethoxybenzene (5.0 mmol) and magnesium (6.0 mmol) in 2.5 mL of anhydrous tetrahydofuran. The Grignard reagent (2.0 M solution in THF; 2.5 mL, 5.0 mmol) was added dropwise to a solution of P(OEt)$_3$ in THF (2 M, 1 mL, 2.0 mmol) under nitrogen. After the addition was complete, the mixture was heated to reflux for 2 days, cooled to 0 °C, quenched with 3 M HCl solution,

(32) Ramgopal, S.; Ramesh, K.; Chakradhar, A.; Reddy, N. M.; Rajanna, K. C. *Tetrahedron Lett.* **2007**, *48*, 4043–4045.
(33) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719–2724.
(34) Cuisiat, S.; Bourdiol, N.; Lacharme, V.; Newman-Tancredi, A.; Colpaert, F.; Vacher, B. *J. Med. Chem.* **2007**, *50*, 865–876.
(35) Molander, G. A.; Brown, A. R. *J. Org. Chem.* **2006**, *71*, 9681–9686.
(36) Luo, X.; Zhang, H.; Duan, H.; Liu, Q.; Zhu, L.; Zhang, T.; Lei, A. *Org. Lett.* **2007**, *9*, 4571–4574.
(37) Aycock, D. F. *Org. Process Res. Dev.* **2007**, *11*, 156–159.
(38) Husemoen, G.; Olsson, R.; Andersson, C.; Harvey, S. C.; Hansen, H. C. *J. Comb. Chem.* **2003**, *5*, 606–609.

extracted with diethyl ether, and dried over anhydrous $MgSO_4$. Then, the solvents were removed under vacuum to give a yellow oil. Purification by flash chromatography (hexanes/ethyl acetate/methanol 70:30:5) gave 470.5 mg of colorless crystals (1.46 mmol, 73%). ^{1}H NMR: δ 3.72 (s, 6H), 3.85 (s, 6H), 6.46 (m, 2H), 6.53 (d, J = 8.3 Hz, 2H), 7.53 (m, 1H), 8.13 (d, J_{P-H} = 510.1 Hz, 1H). ^{13}C NMR: δ 55.6, 55.8, 98.4, 105.3, 111.4 (d, J = 110.6 Hz), 135.2, 162.5, 164.8. ^{31}P NMR: δ 7.78 (s). Anal. Calcd for $C_{16}H_{19}O_5P$: C, 59.63; H, 5.94. Found: C, 59.29; H, 5.87.

***tert*-Butyl(1-naphthyl)phosphine Oxide, L3.** A solution of $P(OEt)_3$ (2 M, 1 mL, 2.0 mmol) in THF was added at 0 °C to 1-naphthylmagnesium bromide prepared from 1-bromonaphthalene (200 mg, 0.97mmol) and magnesium (48 mg, 2.0 mmol). The mixture was heated to reflux for 2 days, cooled to 0 °C, quenched with 3 M HCl solution, extracted with methylene chloride, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give ethyl 1-naphthylphosphinate in 65% yield (132 g, 0.61mmol). The phosphinate ester was used without further purification. It was dissolved in anhydrous THF and added dropwise to a 1 M solution of *tert*-butylmagnesium chloride (0.9 mL, 0.9 mmol) at −10 °C. The reaction mixture was then heated to reflux for 24 h. After the mixture was cooled to 0 °C, 1 mL of 1 M HCl was added dropwise. The solution was then stirred vigorously with diethyl ether for 5 min and extracted with ether. The combined organic layers were dried over $MgSO_4$ and concentrated. Purification by flash chromatography (ethyl acetate/methylene chloride 1:0.5) gave 86 mg of a colorless oil (0.36 mmol, 60%). ^{1}H NMR: δ 1.19 (d, J = 6.4 Hz, 9H), 7.46 (d, J_{P-H} = 302.1 Hz, 1H), 7.27−7.37 (m, 3H), 7.73 (dd, J = 5.4, 8.3 Hz, 1H), 7.90 (d, J = 6.0 Hz, 1H), 8.03 (d, J = 6.3 Hz, 1H), 8.72 (d, J = 6.3 Hz, 1H). ^{13}C NMR: δ 24.3, 33.7 (d, J = 68.1 Hz), 124.5, 124.9 (d, J = 14.2 Hz), 126.1 (d, J = 86.3 Hz), 127.1, 127.5, 129.0, 132.1, 132.2, 133.4 (d, J = 7.5 Hz), 133.9 (d, J = 7.5 Hz). ^{31}P NMR: δ 53.8 (s). Anal. Calcd for $C_{14}H_{17}OP$: C, 72.40; H, 7.38. Found: C, 72.12; H, 7.33.

***tert*-Butyl(2,6-diisopropoxyphenyl)phosphine Oxide, L4.** In a 50 mL three-neck round-bottom flask was added dropwise 2.7 mL of *sec*-butyllithium solution (1.6 M in hexane, 4.4 mmol) to a solution of 1,3-diisopropoxybenzene in THF (2 M, 2.0 mL, 4.0 mmol) under nitrogen at 0 °C. The mixture was stirred at 0 °C for 1 h, and a solution of *t*-$BuPCl_2$ in THF (2 M, 1 mL, 2.0 mmol) was added dropwise. After the addition was complete, the mixture was heated to reflux overnight, cooled to 0 °C, quenched with water, extracted with diethyl ether, and dried over anhydrous $MgSO_4$. After removal of the solvents, a yellow oil was obtained. Purification by flash chromatography (hexanes/ethyl acetate/methanol 40:60:10) gave 381.9 mg of colorless crystals (1.28 mmol, 64%). ^{1}H NMR: δ 1.20 (d, J = 16.8 Hz, 9H), 1.33- 1.42(m, 12H), 4.61 (m, 2H), 6.49 (dd, J = 8.7 Hz, 3.9 Hz, 2H), 7.33 (t, J = 8.7 Hz, 1H), 7.56 (d, J_{P-H} = 484.5 Hz, 1H). ^{13}C NMR: δ 22.2, 25.1, 33.7 (d, J = 75.0 Hz), 70.8, 105.2, 107.5 (d, J = 87.1 Hz), 134.3, 161.8. ^{31}P NMR: δ 33.2(s). Anal. Calcd. for $C_{16}H_{27}O_3P$: C, 64.41; H, 9.12. Found: C, 64.05; H, 9.04.

***tert*-Butyl(2-biphenyl)phosphine Oxide, L5.** A solution of $P(OEt)_3$ (2 M, 1 mL, 2.0 mmol) in THF was added at 0 °C to 2-bromobiphenyl (200 mg, 0.86 mmol) and magnesium (41 mg, 1.7 mmol), and the mixture was heated to reflux for 2 days. After being cooled to 0 °C, the mixture was quenched with 3 M HCl solution, extracted with methylene chloride, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give ethyl 2-biphenylphosphinate in 60% yield (127 g, 0.52 mmol). The phosphonite ester was dissolved in anhydrous THF and added dropwise to a 1 M solution of *tert*-butylmagnesium chloride (0.8 mL, 0.8 mmols) at −10 °C. The resulting reaction mixture was heated to reflux for 24 h. Then, the it was cooled to 0 °C and 1 mL of 1 M HCl was added dropwise. The solution was stirred vigorously with diethyl ether for 5 min and extracted with ether. The resulting organic layer was dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/methylene chloride 1:1) gave 94.0 mg of a colorless yellow oil (0.36 mmol, 70%). ^{1}H NMR: δ 0.95 (d, J = 13.2 Hz, 9H), 7.05 (d, J_{P-H} = 353.1 Hz, 1H), 7.30−7.44 (m, 6H), 7.49 (dd, J = 5.7, 8.5 Hz, 1H), 7.58 (d, J = 5.7, 8.5 Hz, 1H), 7.98 (dd, J = 0.9, 8.1 Hz, 1H). ^{13}C NMR: δ 23.9, 33.8 (d, J = 82.5 Hz), 127.2, 127.6 (d, J = 12.8 Hz), 128.2 (d, J = 18.2 Hz), 128.5, 130.2, 131.1, 132.0, 132.7, 140.1, 145.9. ^{31}P NMR: δ 40.5 (s). Anal. Calcd for $C_{16}H_{19}OP$: C, 74.40; H, 7.41. Found: C, 74.21; H, 7.49.

***tert*-Butyl(2,4-dimethoxyphenyl)phosphine Oxide, L6.** 2,4-Dimethoxyphenylmagnesium bromide was prepared from 1-bromo-2,4-dimethoxybenzene (3.0 mmol) and magnesium (3.5 mmol) in 1.5 mL of anhydrous tetrahydofuran. The Grignard reagent (2.0 M solution in THF; 1.5 mL, 3.0 mmol) was added dropwise to a solution of *t*-$BuPCl_2$ in THF (2 M, 1 mL, 2.0 mmol) under nitrogen. After the addition was complete, the mixture was heated to reflux for 3 h, cooled to 0 °C, quenched with water, extracted with diethyl ether, and dried over anhydrous $MgSO_4$. Then, the solvents were removed under vacuum to afford a yellow oil. Purification by flash chromatography (hexanes/ethyl acetate/methanol 80:20:2) gave 310.1 mg of colorless crystals (1.28 mmol, 64%). ^{1}H NMR: δ 1.14 (d, J = 16.8 Hz, 9H), 3.82 (s, 3H), 3.85 (s, 3H), 6.46 (d, J = 8.3 Hz, 1H), 6.60 (d, J = 8.3 Hz, 1H), 7.26 (d, J_{P-H} = 472.4 Hz, 1H), 7.64 (m, 1H). ^{13}C NMR: δ 24.1, 33.0 (d, J = 71.5 Hz), 55.6, 55.8, 98.5, 105.7, 109.5 (d, J = 96.6 Hz), 135.2, 162.5,164.9 (d, J = 2.4 Hz). ^{31}P NMR: δ 37.1 (s). Anal. Calcd for $C_{12}H_{19}O_3P$: C, 59.50; H, 7.91. Found: C, 59.07; H, 7.94.

***tert*-Butyl(2,4,6-trimethoxyphenyl)phosphine Oxide, L7.** In a 50 mL three-neck round-bottom flask was added dropwise 2.7 mL of *sec*-butyllithium solution (1.6 M in hexane, 4.4 mmol) to a solution of 1,3,5-trimethoxybenzene in THF (2 M, 2.0 mL, 4.0 mmol) under nitrogen at 0 °C. The mixture was stirred at 0 °C for 1 h. Then, a solution of *t*-$BuPCl_2$ in THF (2 M, 1 mL, 2.0 mmol) was added dropwise to the mixture. After the addition was complete, the mixture was heated to reflux overnight, cooled to 0 °C, quenched with water, extracted with diethyl ether, and dried over anhydrous $MgSO_4$. After removal of the solvents, a yellow oil was obtained. Purification by flash chromatography (hexanes/ethyl acetate/methanol 70:30:10) gave 190.6 mg of colorless crystals (0.70 mmol, 35%). ^{1}H NMR: δ 1.18 (d, J = 17.1 Hz, 9H), 3.82 (s, 6H), 3.84 (m, 3H), 6.10 (d, J = 3.6 Hz, 2H), 7.44 (d, J_{P-H} = 483.9 Hz, 1H). ^{13}C NMR: δ 24.9, 33.6 (d, J = 73.0 Hz), 55.8, 56.2, 91.2, 98.3 (d, J = 91.6 Hz), 164.7, 165.6. ^{31}P NMR: δ 32.7(s). Anal. Calcd for $C_{13}H_{21}O_4P$: C, 57.35; H, 7.77. Found: C, 57.09; H, 7.64.

***tert*-Butyl(2′,6′-dimethoxy-2-biphenyl)phosphine Oxide, L8.** A solution of *tert*-butyllithium (1.6 mmol, 1.0 mL) in THF was added dropwise to a solution of 1,3-dimethoxybenzene (200 mg, 1.4 mmol) in 5 mL of anhydrous THF at room temperature. After the mixture was stirred for 3 h, 1,2-dibromobenzene (276 mg, 1.0 mmol) dissolved in 1 mL of THF was added dropwise, and the mixture was stirred overnight. Then, it was quenched with 1 mL of water and extracted with chloroform. The combined organic layers were dried over $MgSO_4$, and the solvents were removed in vacuo to afford 2-bromo-2′,6′-dimethoxybiphenyl in 95% yield (270 mg, 0.95 mmol). To a solution of biphenyl in THF was added *tert*-butyllithium (1.4 mmol, 0.9 mL) and the reactioin was stirred at −78 °C for 3 h. Then, a solution of *t*-$BuPCl_2$ in THF (2 M, 0.5 mL, 1.0 mmol) was added dropwise, and the mixture was heated to reflux overnight. After the mixture was cooled to 0 °C, it was quenched with water, extracted with methylene chloride, and dried over anhydrous $MgSO_4$. The solvents were removed to give a yellow oil. Purification by flash chromatography (ethyl acetate) gave 255 mg of colorless crystals (0.80 mmol, 85%). ^{1}H NMR: δ 0.95 (d, J = 12.1 Hz, 9H), 3.71 (d, J = 27.6 Hz, 6H), 6.60 (d, J = 6.0 Hz, 1H), 6.66 (d, J = 6.0 Hz, 1H), 7.33 (dd, J = 5.7, 8.5 Hz, 1H), 7.46 (d, J = 8.5 Hz, 1H), 7.56 (dd, J = 6.0 Hz, 9.0 Hz, 1H), 7.95 (d, J = 6.0 Hz, 1H), 7.98 (d, J = 5.7, 9.0 Hz, 1H). ^{13}C NMR: δ 23.2, 32.2 (d, J = 60.0 Hz), 55.6 (d, J = 45.0 Hz), 103.8 (d, J = 45.0 Hz), 116.5, 118.5 (d, J = 38.3 Hz), 129.1 (d, J = 67.5 Hz), 130.0, 131.3 (d, J = 1.5 Hz), 131.8, 103.5 (d, J = 15.0 Hz),131.9 (d, J = 1.5 Hz), 137.1 (d, J = 6.7 Hz),156.6, 157.6. ^{31}P NMR: δ

20.7 (s). Anal. Calcd for $C_{18}H_{23}O_3P$: C, 67.91; H, 7.28. Found: C, 67.92; H, 7.54.

***tert*-Butyl(ferrocene)phosphine Oxide, L9.** In a 50 mL three-neck round-bottom flask was added dropwise 2.7 mL of a *t*ert-butyllithium solution (1.6 M in hexane, 4.4 mmol) to a solution of ferrocene in THF (2 M, 2.0 mL, 4.0 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h, and a solution of *t*-$BuPCl_2$ in THF (2 M, 1 mL, 2.0 mmol) was added dropwise. After the addition was complete, the mixture was heated to reflux overnight, cooled to 0 °C, quenched with water, extracted with diethyl ether, and dried over anhydrous $MgSO_4$. The solvents were removed under vacuum to yield a yellow oil. Purification by flash chromatography (hexanes/ethyl acetate/methanol 70:30:10) gave 371.4 mg of a brown solid (1.28 mmol, 64%). ^{1}H NMR: δ 1.10 (d, J = 16.8 Hz, 9H), 4.44 (s, 5H), 4.30−4.64 (m, 4H), 6.89 (d, J_{P-H} = 453.9 Hz, 1H). ^{13}C NMR: δ 24.0, 32.6 (d, J = 71.1 Hz), 67.6(d, J = 110.1 Hz), 70.31, 71.2 (d, J = 37.5 Hz), 72.2 (d, J = 33.1 Hz). ^{31}P NMR: δ 47.9(s). Anal. Calcd for $C_{14}H_{19}FeOP$: C, 57.96; H, 6.60. Found: C, 57.54; H, 6.69.

Acknowledgment. We thank Combiphos Catalysts, Inc. (www.combiphos.com) for a generous supply of palladium−phosphinous acid complexes.

Supporting Information Available: NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801445Y