An Improved Synthesis of Functionalized Biphenyl-Based Phosphine Ligands

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Functionalized dicyclohexyl- and di-*tert*-butylphosphinobiphenyl ligands are prepared by the reaction of arylmagnesium halides with benzyne, followed by the addition of a chlorodialkylphosphine. This one-pot procedure is considerably less expensive and time-consuming than the method used previously to prepare such ligands. The cost of introducing the dicyclohexylphosphine group can be decreased by preparing chlorodicyclohexylphosphine from PCl_3 and cyclohexylmagnesium chloride, and using the reagent without further purification. The new method is significant, as a variety of ligands can be produced in useful amounts by a procedure that is simple, with starting materials that are relatively inexpensive, and, in most cases, without chromatographic purification.

We recently reported that aminophosphine **1**, when combined with a source of Pd, gives an exceptional catalyst for the amination[1] and Suzuki coupling[2] reactions of aryl chlorides and bromides.[3,4] The catalyst based on **1** could transform aryl bromides or an activated aryl chloride to arylamines at room temperature, and it was the first catalyst that was useful for the amination reactions of electron-rich aryl chlorides. The activity of the catalyst for Suzuki coupling reactions was also unprecedented: even electron-rich aryl chlorides and aryl bromides could be coupled with arylboronic acid derivatives at room temperature.[3,5] Preliminary experiments further indicated that **1** would be a useful ligand for Pd-catalyzed formation of α-aryl ketones.[3,6,7] For the first time, an aryl chloride was used in a ketone arylation reaction, and an aryl bromide could be coupled with a ketone at room temperature.[3]

Although the Pd-catalyst derived from **1** was, at the time of publication, the most active catalyst for amination and Suzuki reactions, its usefulness was limited because four steps were required to prepare it (Scheme 1).[3] Accordingly, efforts were focused on the synthesis of ligands that would function as efficiently as **1**, but would be more readily available. Thus, the discovery that Pd-catalysts based on ligands **3** and **4** are also highly active in Suzuki[8,9] and amination[8,10] reactions was of considerable importance, since these can be prepared in one step from 2-bromobiphenyl and are now commercially available.[11] The scope of substrates that can be coupled by Pd-catalysts that employ **3** and **4** is large, and in many instances, the utility of these ligands equals or is superior to that of **1**.[8−10] For example, in amination and Suzuki coupling reactions that are conducted at room temperature, catalysts from ligand **4** are more active than those based on **1**.[8−10] However, **1** cannot be substituted by **3** or **4** for every substrate combination. Thus, for Suzuki

(1) For reviews on Pd-catalyzed amination, see (a) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125. (b) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (c) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805.

(2) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; Ch. 2.

(3) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722.

(4) For other reports on the amination reactions of aryl chlorides, see (a) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617. (b) Yamamoto, M.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 2367. (c) Reddy, N. P.; Tanaka, M. *Tetrahedron Lett.* **1997**, *38*, 4807. (d) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369. (e) Bei, X.; Guram, A. S.; Turner, H. W.; Weinberg, W. H. *Tetrahedron Lett.* **1999**, *40*, 1237. (f) Bei, X.; Uno, T.; Norris, J.; Turner, H. W.; Weinberg, W. H.; Guram, A. S.; Peterson, J. L. *Organometallics* **1999**, *18*, 1840. (g) Riermeier, T. H.; Zapf, A.; Beller, M. *Top. Catal.* **1997**, *4*, 301, and references therein. (h) Huang, J.; Grasa, G.; Nolan, S. P. *Org. Lett.* **1999**, *1*, 1307. For a recent report of room-temperature Pd-catalyzed amination reactions of aryl bromides and aryl chlorides using $P(t\text{-}Bu)_3$, see (i) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575.

(5) For other reports on the Suzuki reactions of aryl chlorides, see (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387. (b) Beller, M.; Fischer, H.; Herrmann, W. A.; Öfele, K.; Brossmer, C. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1848. (c) Herrmann, W. A.; Reisinger, C.-P.; Spiegler, M. J. *J. Organomet. Chem.* **1998**, *557*, 93. (d) Weskamp, T.; Böhm, V. P. W.; Herrmann, W. A. *J. Organomet. Chem.* **1999**, *585*, 348. (e) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804. (f) Zhang, C.; Trudell, M. L. *Tetrahedron Lett.* **2000**, *41*, 595. (g) Shen, W. *Tetrahedron Lett.* **1997**, *38*, 5575. (h) Firooznia, F.; Gude, C.; Chan, K.; Satoh, Y. *Tetrahedron Lett.* **1998**, *39*, 3985. (i) Bei, X.; Turner, H. W.; Weinberg, H.; Guram, A. S.; Peterson, J. L. *J. Org. Chem.* **1999**, *64*, 6797. (j) Bei, X.; Crevier, T.; Guram, A. S.; Jandeleit, B.; Powers, T. S.; Turner, H. W.; Uno, T.; Weinberg, W. H. *Tetrahedron Lett.* **1999**, *40*, 3855. (k) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.

(6) For earlier reports on the Pd-catalyzed intermolecular α-arylation of ketones, see (a) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108. (b) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382. (c) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1740. (d) Hou, D.; Mas, J. L. U.S. Patent, 4992591, 1991. *Chem. Abstr.* **1991**, *115*, 28927z. For more recent reports, see ref 12, and (e) Satoh, T.; Inoh, J.-i.; Kawamura, Y.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2239. (f) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473.

(7) For the asymmetric Pd-catalyzed α-arylation of ketones, see (a) Åhman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918. For the Pd-catalyzed asymmetric α-vinylation of ketones, see (b) Chieffi, A.; Kamikawa, K.; Åhman, J.; Buchwald, S. L., submitted.

(8) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413.

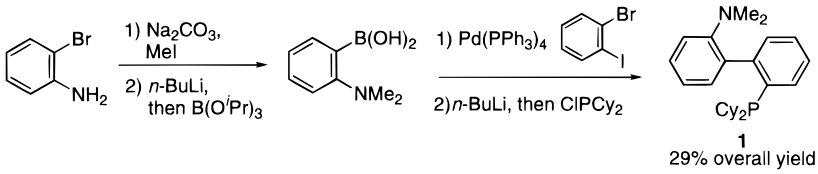
(9) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550.

(10) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.

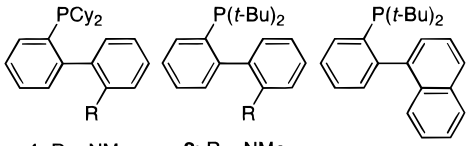
(11) Ligands **1**, **3**, and **4** are commercially available from Strem Chemical Co.

10.1021/jo000691h CCC: $19.00
Published on Web 08/02/2000

Scheme 1



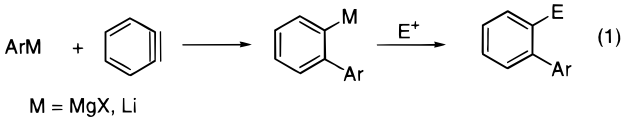
reactions of some sterically hindered substrates, and for the catalytic *N*-arylation of acyclic dialkylamines, catalysts derived from **3** or **4** are less useful than those from **1**.[8−10] In these cases, catalysts based on **5** and **7** function similarly to the catalysts from **1**.[8−10] For the α-arylation of ketones, the most active catalysts that have been reported to date are obtained when **1**, **5**, or **7** is combined with $Pd(OAc)_2$.[12] While these catalysts are selective for a broad range of substrates, in most cases, catalysts based on either **3** or **4** were less useful.[12] Our group has also shown that the *N*-arylation of indoles can be accomplished with the Pd-catalysts derived from **1**, **3**, **4**, **8**, **9** and from a related ligand with a binaphthyl core.[13,14] It is necessary to have access to all of these phosphines in order to effectively couple a large number of functionalized aryl halides and indoles, as the selection of the optimal ligand is dependent on the substrates that are reacted. Similarly, for the Pd-catalyzed formation of diaryl ethers, several biphenyl-derived ligands, including **2** and **4**, must be employed in order to effectively couple a range of aryl halides and phenols.[15,16]



1: R = NMe_2 **2**: R = NMe_2 **9**
3: R = H **4**: R = H
5: R = Me **6**: R = Me
7: R = *i*-Pr **8**: R = *i*-Pr

Phosphines **2** and **5**−**9** were originally synthesized by methods analogous to that used to prepare **1** (Scheme 1),[8−10,12,13,15] and although the syntheses of **5**−**9** were shorter than those of **1** or **2**, their utility was still compromised by the requirement of two- to three-step preparations. Thus, a concise route to ligands **1**, **2**, and **5**−**9** was necessary. Ideally, the syntheses would require only one reaction vessel, use precursors that are inexpensive, and be amenable to application on a large scale. Furthermore, it would be advantageous if the method could be applied to the synthesis of new biphenyl-based phosphine ligands, since, as is noted above, subtle changes of the structure of the ligands can dramatically alter their reactivity.

The need to improve the syntheses of these ligands prompted us to survey the known procedures for biphenyl synthesis. One of the oldest methods is to generate benzyne in the presence of an arylmagnesium halide or an aryllithum;[17] *cine*-addition of the organometallic species to benzyne produces an *ortho*-metalated biphenyl derivative, which can subsequently react with an electrophile (eq 1).[18] We hypothesized that, if a dialkylchlorophosphine were used the electrophile, the reaction depicted in eq 1 would be well suited for the preparation of biphenyl-based phosphine ligands, as the precursors for benzyne and the required aryl Grignard or aryllithium reagents are inexpensive. We report here the realization of this possibility: a one-pot process that utilizes arylmagnesium reagents and benzyne that is prepared in situ from 1-bromo-2-chlorobenzene and magnesium. The method is applied to the synthesis of phosphine ligands **1**, **2**, and **5**−**9**, and to the preparation of a number of new, structurally related ligands. Although the yields for these reactions are modest (18−59%), 11 of the 13 phosphines that are synthesized can be purified without chromatography, and therefore substantial quantities of these ligands can be obtained with little time, cost, or effort. Furthermore, it is shown that chlorodicyclohexylphosphine can be made from PCl_3 and cyclohexylmagnesium chloride and used without purification to prepare **1** and **5** in a yield similar to that obtained with pure (and more costly) chlorodicyclohexylphosphine.

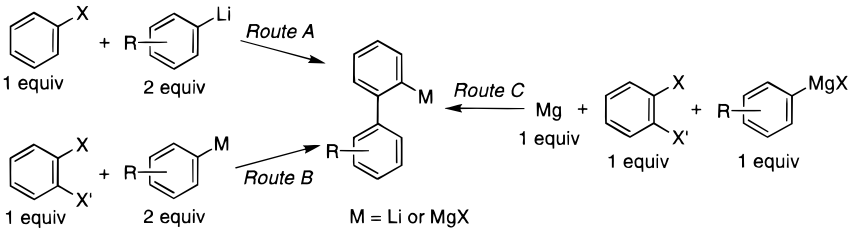


Results and Discussion

Three strategies for the synthesis of biaryls via a benzyne intermediate were considered (Scheme 2). A well-precedented method is to generate benzyne by dehydrohalogenation of an aryl halide, followed by addition of an aryllithium (Scheme 2, route A).[17b,18,19] Alternatively, benzyne can be prepared by metal−halogen exchange of an *o*-dihalobenzene with an aryllithium or arylmagnesium halide, followed by the addi-

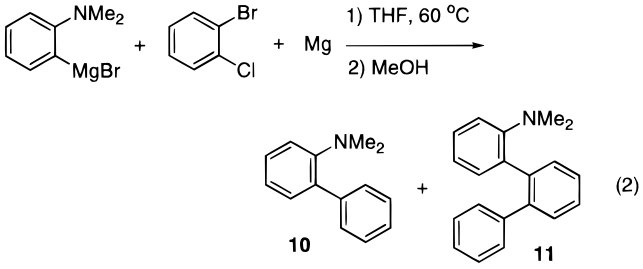
(12) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360.
(13) Old, D. W.; Harris, M. C.; Buchwald, S. L. *Org. Lett.*, in press.
(14) For other reports on the Pd-catalyzed formation of *N*-aryl indoles, see ref 4i, and Mann, G.; Hartwig, J. F.; Driver, M. S.; Fernández-Rivas, C. *J. Am. Chem. Soc.* **1998**, *120*, 827.
(15) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369.
(16) For an additional report on the Pd-catalyzed formation of diaryl ethers, see: Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224.
(17) The formation of biphenyls from arylmetals and benzyne dates back to experiments that were conducted in a retort by Fittig: (a) Fittig, R. *Ann.* **1864**, *132*, 202. For a discussion of the history of benzyne chemistry, see pp 1−8 of (b) Hoffmann, R. W. *Dehydrobenzene and Cycloalkynes*; Academic Press: New York, 1967.
(18) For reviews, see Ch 2 of ref 17b and (a) Sharp, J. T. In *Comprehensive Organic Chemistry*; Barton, D., Ollis, W. D., Stoddart, J. F., Eds., Pergamon Press: Oxford, 1979; Vol. 1, p 455. (b) Gilchrist, T. L. In *The Chemistry of Functional Groups*; Patai, S., Rappoport, Z., Eds., Wiley: Chichester, 1983, Suppl. C, part 1, Chapter 11. (c) Grundmann, C. In *Methoden der Organischen. Chemie (Houben-Weyl)*; Müller, E., Bayer, O., Ed., Thieme: Stuttgart, New York, 1981, Board 5/2b, pp 613−515. (d) Kessar, S. V. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds., Pergamon Press: Oxford, 1991; Vol. 4, Chapter 2.3. (e) Huisgen, R.; Sauer, J. *Angew. Chem.* **1960**, *72*, 91.
(19) (a) Wittig, G.; Pieper, G.; Fuhrmann, G. *Chem. Ber.* **1940**, *73*, 1193. (b) Wittig, G.; Merkle, W. *Chem. Ber.* **1942**, *75*, 1491. (c) Huisgen, R.; Rist, H. *Liebigs Ann. Chem.* **1955**, *594*, 137. (d) Wittig, G.; Pohmer, L. *Chem. Ber.* **1956**, *89*, 1334.

Scheme 2



tion of a second equivalent of the organometal (Scheme 2, route B).[17b,18] [20] Both of these approaches require at least 2 equiv of an organometallic reagent,[21] and in order for the latter method to work efficiently with aryl Grignard reagents, it is necessary to use an expensive *o*-iodohalobenzene derivative.[20e] A more economical way to prepare biphenyls would be to combine equal amounts of magnesium, an aryl Grignard reagent, and an *o*-dihalobenzene (Scheme 2, route C). Unexpectedly, we could find only one example of such a reaction—that of 2-fluorophenylmagnesium bromide with benzyne generated from the same reagent—and it occurred in low yield.[24] Also surprising is that the combination of magnesium and 2-bromochlorobenzene is almost never used to generate benzyne, despite the frequent use of more expensive 2-bromofluorobenzene for this purpose.[25] The probable reason is that, in an early study on the reactivity of benzyne with furan, Wittig and Pohmer suggested that 2-chlorophenylmagnesium bromide decomposes only slowly to benzyne in refluxing THF.[26] However, more recent studies by Hart showed that derivatives of 2-chlorophenylmagnesium bromide (formed by metal−halogen exchange) do form benzyne derivatives in refluxing THF, and that products from subsequent addition of a Grignard reagent to the benzyne can be prepared.[27] In the present work, we show that the combination of an arylmagnesium halide, 2-bromochlorobenzene, and magnesium does indeed provide an inexpensive route to derivatives of *o*-biphenylmagnesium halides and that these can be converted into a series of phosphine ligands in useful yields.

Initially, experiments were conducted so that the synthesis of ligand **1** could be optimized (eq 2). Thus,



magnesium (2 equiv), 2-bromo-*N*,*N*-dimethylaniline (1 equiv), and an internal standard were heated in THF at 60 °C until formation of the Grignard reagent was complete. 2-Bromochlorobenzene was then added, and heating at 60 °C was continued. After 1, 2, 3, and 4 h, aliquots were taken from the reaction mixture, quenched with methanol, and analyzed by GC/MS and GC. The major product of the reaction was **10**, and it was formed in highest yield (66%) after 2 h. At this time, the yield of chlorobenzene was determined to be <2%, indicating that consumption of 2-chlorophenylmagnesium bromide was almost complete. After 3 and 4 h, the yield of **10** was measured to be 55% and 56%, respectively. The major byproduct of this reaction was determined by GC/MS to be a terphenyl derivative, presumably **11**, which could arise from the addition of 2-(2-dimethylaminophenyl)phenylmagnesium bromide to benzyne.[28] After 2 h, the ratio of **10**:**11** was determined to be 11:1. In a similar experiment, in which 1.2 equiv of 2-dimethylaminophenylmagnesium bromide were used, **10** was produced in 76% yield, and only a relatively small amount of **11** was formed (the ratio of **10**: **11** was 25:1). Again, the yield of **10** was lower if the reaction time was increased. Thus, in subsequent experiments, the arylmagnesium halide and 2-chlorobromobenzene were used in a 1.2:1 ratio, and reactions were allowed to proceed for 2 h.

At this time, we found that 2-chloro-*N*,*N*-dimethylaniline is commercially available, and it was therefore used instead of 2-bromo-*N*,*N*-dimethylaniline in subsequent experiments. The Grignard reagent of 2-chloro-*N*,*N*-dimethylaniline was formed using 1,2-dibromoethane to activate the magnesium.[29] Phosphine ligand **1** was obtained in 50% yield when 2-bromochlorobenzene was added to magnesium and the Grignard reagent and subsequently allowed to react with $CuCl$[30] and $ClPCy_2$ (Table 1, entry 1). It is notable that, in a single 250 mL round-bottom flask and without the need for chromatog-

(20) (a) Wittig, G.; Fuhrmann, G. *Chem. Ber.* **1940**, *73*, 1197. (b) Hellwinkel, D. *Chem. Ber.* **1966**, *99*, 3642. (c) Hellwinkel, D.; Knabe, B. *Chem. Ber.* **1971**, *104*, 1761. (d) Hellwinkel, D.; Reiff, G.; Nykodym, V. *Liebigs Ann. Chem.* **1977**, 1013. (e) Hart, H.; Harada, K.; Du, C.-J. F. *J. Org. Chem.* **1985**, *50*, 3104.

(21) For routes A and B of Scheme 2, the organometallic reagent that is the nucleophile is also used for the dehydrohalogenation or for the metal halogen exchange.[17b,18] However, it is also possible to use inexpensive organometallic reagents such as *n*-BuLi[22] or vinylmagnesium bromide[23] for the metal−halogen exchange reaction, with subsequent capture of benzyne by an aryllithium or arylmagnesium halide, respectively. The use of vinylmagnesium bromide is of significant value when the arylmagnesium halides are expensive.[23]

(22) Gilman, H.; Gorsich, R. D. *J. Am. Chem. Soc.* **1956**, *78*, 2217.

(23) (a) Vinod, T.; Hart, H. *J. Org. Chem.* **1990**, *55*, 881. (b) Grewal, R. S.; Hart, H.; Vinod, T. *J. Org. Chem.* **1992**, *57*, 2721. (c) Hart, H.; Rajakumar, P. *Tetrahedron* **1995**, *51*, 1313.

(24) Bartle, K. D.; Heaney, H.; Jones, D. W.; Lees, P. *Tetrahedron* **1965**, *21*, 3289.

(25) See Ch 1 of ref 17b. For a specific example, see Wittig, G. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 964.

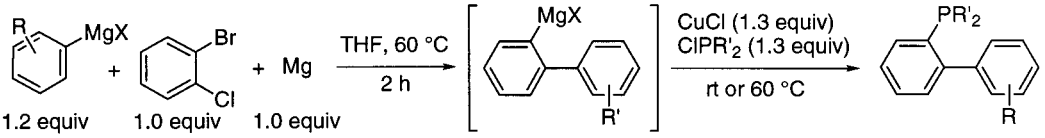
(26) Wittig and Pohmer compared the reactions of *o*-fluorophenylmagnesium bromide and *o*-chlorophenylmagnesium bromide with furan in refluxing THF. After 1 h and treatment with 5 N HCl, the former reaction produced α-naphthol in 54% yield and gave no fluorobenzene; the latter reaction gave α-naphthol in 11% yield and chlorobenzene in 55% yield. After 5 weeks, 1,4-dihydronaphthalene-1,4-endoxide was isolated in 40% yield from the latter reaction. See ref 19d.

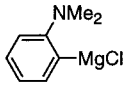
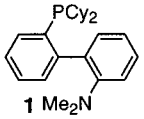
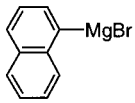
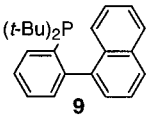
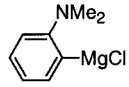
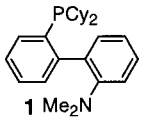
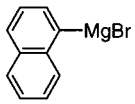
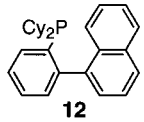
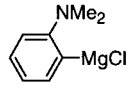
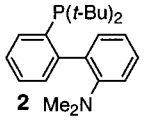
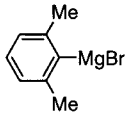
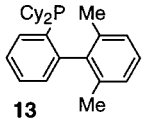
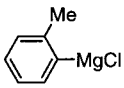
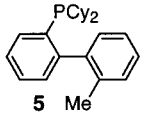
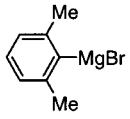
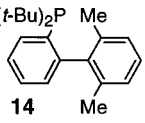
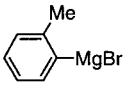
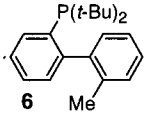
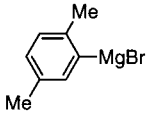
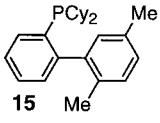
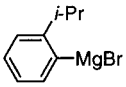
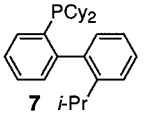
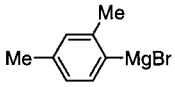
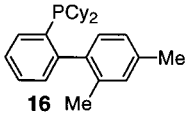
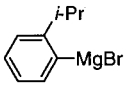
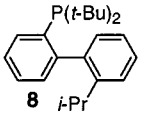
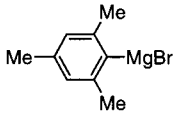
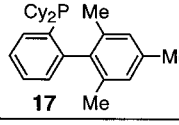
(27) (a) Du, C.-J. F.; Hart, H.; Ng, K.-K. D. *J. Org. Chem.* **1986**, *51*, 3162. (b) Ghosh, T.; Hart, H. *J. Org. Chem.* **1988**, *53*, 3555. (c) Saednya, A.; Hart, H. *Synthesis* **1996**, 1455.

(28) The formation of terphenyls from the reaction of 2 equiv of benzyne with 1 equiv of an arylmetal is well-known. For examples, see refs 22, 24, and Wittig, G.; Hellwinkel, D. *Chem. Ber.* **1964**, *97*, 769.

(29) Lai, Y.-H. *Synthesis* **1981**, 585.

Table 1. Synthesis of Electron-rich Phosphine Ligands with Biphenyl Backbones[a]

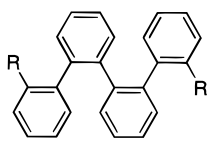


Entry	ArMgX	ClPR'$_2$	Product	Yield (%)	Entry	ArMgX	ClPR'$_2$	Product	Yield (%)
1		$ClPCy_2$	 **1** Me_2N	53[b]	8		$ClP(t\text{-}Bu)_2$	 **9**	31
2		$ClPCy_2$	 **1** Me_2N	52[c,d]	9		$ClPCy_2$	 **12**	36
3		$ClP(t\text{-}Bu)_2$	 **2** Me_2N	23	10		$ClPCy_2$	 **13**	53
4		$ClPCy_2$	 **5** Me	58[d]	11		$ClP(t\text{-}Bu)_2$	 **14**	18
5		$ClP(t\text{-}Bu)_2$	 **6** Me	48	12		$ClPCy_2$	 **15** Me	49
6		$ClPCy_2$	 **7** *i*-Pr	49	13		$ClPCy_2$	 **16** Me	38
7		$ClP(t\text{-}Bu)_2$	 **8** *i*-Pr	29	14		$ClPCy_2$	 **17** Me	53

[a] Yields are based on the use of 2-bromochlorobenzene as the limiting reagent. Reactions with $ClPCy_2$ were conducted at room temperature. Those with $ClP(t\text{-}Bu)_2$ were conducted at 60 °C. [b] 50 mmol scale using 1.2 equiv of $ClPCy_2$. [c] 1.3 equiv of arylmagnesium chloride were used. [d] $ClPCy_2$ was prepared from PCl_3 and cyclohexylmagnesium chloride and used without further purification.

raphy, 9.8 g of ligand **1** was prepared. Since the development of this protocol, ligand **1** has become commercially available.[11] To make the synthesis of **1** even less costly, we prepared chlorodicyclohexylphosphine from cyclohexylmagnesium chloride and PCl_3, both of which are inexpensive. Without further purification, the crude $ClPCy_2$ was employed, and the yield of the reaction was similar (52%) to that obtained when pure $ClPCy_2$ is used (Table 1, entry 2).

The conditions that were used to make **1** could be applied to the synthesis of a variety of phosphine ligands (Table 1). As for synthesis of **1**, unpurified chlorodicyclohexylphosphine was used to prepare **5**, and the material was obtained in 58% yield (Table 1, entry 4). 2-Di-*tert*-butylphosphinobiphenyl derivatives can also be prepared by the method introduced here (Table 1, entries 3, 5, 7, 8, and 11). A temperature of 60 °C is needed for the reaction with di-*tert*-butylchlorophosphine to be efficient, whereas the reactions with chlorodicyclohexylphosphine proceeded smoothly at room temperature. In the preparations of the di-*tert*-butylphosphino derivatives, quaterphenyl byproducts were detected by GC/MS. Although full characterization was not pursued, it is likely that these byproducts have structure **18**, and are formed by



18

(30) Ligand **4** is obtained in highyield when Cu(I)Cl is added to the reaction of biphenyl-2-ylmagnesium bromide and di-*tert*-butylchlorophosphine. Much lower yields are obtained when CuCl is omitted.[15]

the homocoupling reaction of the biphenyl-2-ylmagnesium halides. Consequently, when $ClP(t\text{-}Bu)_2$ was used, the yields were lower than those obtained with $ClPCy_2$. Nonetheless, the scope of the method is quite broad, and even phosphines that are very sterically encumbered can be obtained in useful yields (Table 1, entries 10, 11, and 14). Of importance is that only one reaction vessel is required for each of the preparations described in Table 1 and that chromatography is required only for the purification of **9** and **14**; the other 11 ligands can be obtained in pure form by crystallization. Because the synthesis of the ligands is so straightforward, any of the protocols that utilize them is considerably more practical than before. Furthermore, since the scope of the method introduced here is broad, it should be valuable for the design and rapid synthesis of new ligands, and consequently, for the development and optimization of Pd-catalyzed processes.

Conclusions

Functionalized dialkylphosphinobiphenyl ligands were prepared by the addition of arylmagnesium halides to benzyne, followed by reaction with dialkylchlorophosphines. This one-pot method is significantly less expensive and time-consuming than the route used previously to access such ligands. For the synthesis of phosphines **1** and **5**, it is shown that the cost of synthesis can be reduced further by preparing $ClPCy_2$ from PCl_3 and cyclohexylmagnesium chloride and by using the reagent without further purification.

Experimental Section

General Considerations. All of reactions were carried out under an argon atmosphere in glassware that had been dried in an oven and cooled under argon. Elemental analyses were performed by Atlantic Microlabs Inc, Norcross, GA. Toluene was distilled under nitrogen from molten sodium. THF was distilled under argon from sodium benzophenone ketyl. Aryl halides were purchased from commercial sources and were used without further purification. 2-Chloro-*N*,*N*-dimethylaniline (95.5% chemical purity; the impurity was characterized by GC/MS as 2-chloro-*N*-methylaniline) was purchased from Karl Industries Inc (Aurora, OH) and was used without further purification. Magnesium turnings were purchased from Mallinckrodt. Di-*tert*-butylchlorophosphine was purchased from either Aldrich Chemical Co. or Strem Chemicals, Inc. Copper(I) chloride and chlorodicyclohexylphosphine were purchased from Strem Chemicals, Inc. Phosphorus trichloride was purchased from EM Science and was distilled before use. Yields of Table 1 refer to isolated yields (based on 1-bromo-2-chlorobenzene) of compounds estimated to be ≥97% pure as determined by ^{1}H NMR, ^{31}P NMR, GC, and elemental analysis.

2-Dicyclohexylphosphino-2′-dimethylaminobiphenyl (1)[3] (Table 1, entry 1). An oven-dried 250 mL round-bottomed flask equipped with a magnetic stirbar, a rubber septum, and a reflux condenser was charged with magnesium turnings (2.92 g, 120 mmol), 2-chloro-*N*,*N*-dimethylaniline (9.3 g, 58 mmol), and THF (100 mL). The mixture was heated to reflux, and 1,2-dibromoethane (0.62 mL, 10 mmol) was added dropwise via syringe over 1.5 h.[31] The mixture was refluxed for an additional 28 h and then cooled to 60 °C. 2-Bromochlorobenzene (5.84 mL, 50.0 mmol) was added dropwise over 10 min, and the resulting mixture was heated for 2 h in an oil bath at 60 °C and subsequently cooled to room temperature. The septum was removed and anhydrous copper(I) chloride (6.43 g, 65.0 mmol) was added. The septum was then replaced, and the flask was purged with argon for 5 min. A solution of $ClPCy_2$ (14.0 g, 60.0 mmol) in THF (20 mL) was added dropwise via syringe, and the mixture was stirred at ambient temperature for 9 h. The resulting suspension was poured into a flask containing hexane:EtOAc (1:1, 700 mL), 30% aqueous NH_4OH (500 mL), and brine (500 mL). The mixture was stirred at room temperature for 10 min and transferred to a separatory funnel. The layers were separated, and the organic phase was sequentially washed with 30% aqueous NH_4OH (100 mL × 3) and brine (100 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. To the residual solid was added EtOAc:MeOH (1:6, 175 mL), and the resulting suspension was stirred and cooled in an ice bath for 0.5 h. The solid was collected by filtration, and the damp solid was slurried with 1:6 EtOAc:MeOH (70 mL) in an ice bath for 1 h. Filtration, washing with cold MeOH (20 mL), and drying in vacuo gave 9.77 g (50% yield) of the title compound as a white solid. A similar experiment that was carried out on a 5.00 mmol scale gave 1.08 g (55%) of the title compound. Mp: 116−118 °C (lit.[3] 110 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, 1H, J = 6.9 Hz), 7.42−7.24 (m, 4H), 7.08−6.93 (m, 3H), 2.44 (s, 6H), 2.10−1.93 (m, 1H), 1.97−0.68 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.4 (d, J_{CP} = 1.9 Hz), 149.6 (d, J_{CP} = 30.7 Hz), 135.9 (d, J_{CP} = 5.4 Hz), 135.3 (d, J_{CP} = 20.1 Hz), 132.8 (d, J_{CP} = 3.8 Hz), 132.4, 130.5 (d, J_{CP} = 6.3 Hz), 128.6, 128.2, 125.9, 120.8, 117.3, 43.4, 36.8 (d, J_{CP} = 15.7 Hz), 33.5 (d, J_{CP} = 14.2 Hz), 31.0 (d, J_{CP} = 15.8 Hz), 30.7 (d, J_{CP} = 19.8 Hz), 29.9 (d, J_{CP} = 13.0 Hz), 28.6 (d, J_{CP} = 4.5 Hz), 27.8 (d, J_{CP} = 15.2 Hz), 27.8, 27.7, 27.5 (d, J_{CP} = 11.5 Hz), 26.9, 26.6; ^{31}P NMR (121 MHz, $CDCl_3$) δ −8.7; IR (neat, cm^{-1}) 2923, 2850, 2821, 2771, 1495, 1443, 1426, 947.

Synthesis of 1 Using Unpurified Chlorodicyclohexylphosphine (Table 1, Entry 2). An oven-dried 50 mL Schlenk tube was capped with a rubber septum, evacuated, backfilled with argon, and then charged with PCl_3 (0.65 mL, 7.5 mmol) and diethyl ether (15 mL). The solution was cooled to −40 °C and cyclohexylmagnesium chloride in diethyl ether [prepared from cyclohexyl chloride (2.0 mL, 17 mmol) and magnesium turnings (0.39 g, 16 mmol) in diethyl ether (8 mL)] was added dropwise over 15 min. During the addition, a white solid ($MgCl_2$) precipitated. The mixture was warmed to 0 °C over 2 h, and the solid material was removed with a Schlenk filter and washed with diethyl ether (5 mL) under an argon atmosphere. The filtrate and washing were combined and concentrated in vacuo to give a colorless oil that was diluted with THF (5 mL) and used directly in the reaction described below.

A 25 mL Schlenk tube was charged with magnesium turnings (304 mg, 12.5 mmol) and capped with a rubber septum. 2-Chloro-*N*,*N*-dimethylaniline (1.06 g, 6.50 mmol), and THF (10 mL) were then added via syringe, and the mixture was heated to reflux. At this point, 1,2-dibromoethane (86 μL, 1.0 mmol) was added dropwise via syringe over 1 h,[31] and the mixture was refluxed for 40 h, and subsequently cooled to 60 °C. 2-Bromochlorobenzene (584 μL, 5.00 mmol) was added dropwise, and the resulting mixture was heated for 2 h in an oil bath at 60 °C. The mixture was then cooled to room temperature, the septum was removed, and anhydrous copper(I) chloride (0.50 g, 5.0 mmol) was added. The septum was then replaced and the tube purged with argon for 1 min. The solution of unpurified $ClPCy_2$ in THF was added dropwise with a syringe, and the mixture was stirred overnight at ambient temperature. The resulting suspension was poured into a flask containing hexane:EtOAc (1:1, 50 mL), 30% aqueous NH_4OH (50 mL), and brine (25 mL). The mixture was stirred at room temperature for 5 min and transferred to a separatory funnel. The layers were separated and organic phase was sequentially washed with 30% aqueous NH_4OH (25

(31) The formation of 2-dimethylaminophenylmagnesium chloride was monitored by taking aliquots from the reaction mixture, quenching them with methanol, and analyzing them by GC. The preparation of 2-dimethylaminophenylmagnesium chloride was most efficient when dibromoethane was added to the 2-chloro-*N*,*N*-dimethylaniline and magnesium dropwise over the course of 1−1.5 h. The formation of the Grignard reagent was more sluggish when the dibromoethane was added in one portion to the 2-chloro-*N*,*N*-dimethylaniline and magnesium, or when the dibromoethane was added to the magnesium prior to the addition of 2-chloro-*N*,*N*-dimethylaniline.

mL × 3) and brine (25 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. To the residual oil was added EtOAc:MeOH (1:6, 17.5 mL) and the resulting suspension was stirred in an ice/water bath for 1 h. Filtration, washing with cold EtOAc:MeOH (1:6, 3 mL), and drying in vacuo gave 1.03 g (52% yield) of the title compound. An identical experiment gave 1.02 g (52%).

2-Di-*tert*-butylphosphino-2′-dimethylaminobiphenyl (2) (Table 1, Entry 3).[15] A 25 mL Schlenk tube was charged with magnesium turnings (304 mg, 12.5 mmol) and capped with a rubber septum. 2-Chloro-*N*,*N*-dimethylaniline (gross 0.93 g, ca. 6.0 mmol), and THF (10 mL) were sequentially added via syringe, and the reaction mixture was heated to reflux. At this point,1,2-dibromoethane (86 μL, 1.0 mmol) was added dropwise over 10 min.[31] The mixture was allowed to reflux for an additional 48 h, and was then cooled to 60 °C. 2-Bromochlorobenzene (584 μL, 5.00 mmol) was added dropwise, and the resulting mixture was stirred for 2 h in an oil bath at 60 °C and subsequently cooled to room temperature. The septum was removed and anhydrous copper(I) chloride (0.64 g, 6.5 mmol) was added. The septum was then replaced and the tube purged with argon for 1 min. Di-*tert*-butylchlorophosphine (1.1 mL, 6.0 mmol) was added via syringe, and the mixture was stirred at 60 °C for 15 h. After cooling to room temperature, the resulting suspension was poured into a flask that contained hexane:EtOAc (1:1, 80 mL), 30% aqueous NH_4OH (50 mL), and brine (50 mL). The mixture was stirred at room temperature for 5 min and transferred to a separatory funnel. The layers were separated and the organic phase was sequentially washed with 30% aqueous NH_4OH (20 mL × 3) and brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. The residual oil was crystallized from cold MeOH (5 mL). White crystals of **2** were collected by filtration, washed with a small amount of cold MeOH (3 mL), and dried in vacuo to give 0.356 g (21%) of the title compound. A similar experiment on a 25.0 mmol scale gave 2.07 g (24%). Mp: 111−113 °C (lit.[15] 116−117 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80−7.75 (m, 1H), 7.40−7.20 (m, 4H), 7.00−6.90 (m, 3H), 2.44 (s, 6H), 1.26 (d, 9H, J_{HP} = 11.3 Hz), 0.90 (d, 9H, J_{HP} = 33.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.6 (d, J_{CP} = 2.4 Hz), 150.1 (d, J_{CP} = 33.7 Hz), 137.2 (d, J_{CP} = 7.6 Hz), 136.9 (d, J_{CP} = 15.2 Hz), 135.6 (d, J_{CP} = 3.2 Hz), 132.9, 131.1 (d, J_{CP} = 7.1 Hz), 128.8 (d, J_{CP} = 1.2 Hz), 128.0, 125.3, 121.0, 117.6, 43.5, 33.5 (d, J_{CP} = 24.3 Hz), 31.7 (d, J_{CP} = 16.1 Hz), 31.6 (d, J_{CP} = 27.8 Hz), 30.2 (d, J_{CP} = 15.2 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 25.6; IR (neat, cm^{-1}) 2954, 2861, 1495, 1472, 1457, 1360, 1054, 947.

2-Dicyclohexylphosphino-2′-methylbiphenyl (5) (Table 1, entry 4).[9] A 50 mL Schlenk tube was capped with a rubber septum and sequentially charged with PCl_3 (0.65 mL, 7.5 mmol) and diethyl ether (15 mL). The solution was cooled to −40 °C, and a 2.0 M solution of cyclohexylmagnesium chloride in diethyl ether (7.5 mL, 15 mmol, purchased from Aldrich Chemical Co.) was added dropwise over 15 min. The mixture was warmed to 0 °C over 2 h, and then the $MgCl_2$ that had precipitated was removed with a Schlenk filter and washed with diethyl ether (5 mL) under an atmosphere of argon. The filtrate was used directly in the reaction described below.

A 25 mL Schlenk tube was charged with magnesium turnings (280 mg, 11.5 mmol) and capped with a rubber septum. 2-Chlorotoluene (0.70 g, 6.0 mmol) and THF (10 mL) were sequentially added, and the mixture was heated to reflux. At this point, 1,2-dibromoethane (43 μL, 0.5 mmol) was added dropwise, and the mixture was refluxed for 15 h, and cooled to 60 °C. 2-Bromochlorobenzene (584 μL, 5.00 mmol) was then added dropwise, and the resulting mixture was heated in an oil bath at 60 °C for 2 h and subsequently cooled to room temperature. The septum was removed, anhydrous copper(I) chloride (0.64 g, 6.5 mmol) was added, and the tube was purged with argon for 1 min. The solution of crude $ClPCy_2$ in diethyl ether was then added dropwise via syringe, and the mixture was stirred for 2 h at ambient temperature. The resulting suspension was poured into a flask containing hexane:EtOAc (1:1, 50 mL), 30% aqueous NH_4OH (50 mL), and brine (25 mL). The mixture was stirred at room temperature for 5 min and transferred to a separatory funnel. The layers were separated, and the organic phase was sequentially washed with 30% aqueous NH_4OH (25 mL × 2) and brine (25 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. To the residual oil was added EtOAc:MeOH (1:4, 10 mL), and the resulting suspension was stirred and cooled in an ice bath for 1 h. Filtration, washing with cold EtOAc:MeOH (1:4, 3 mL), and drying in vacuo gave 1.07 g (59%) of the title compound, a white solid. An identical experiment gave 1.04 g (57%). Mp: 109−111 °C (lit.[9] 107−109 °C): ^{1}H NMR (300 MHz, acetone-d_6) δ 7.70−7.62 (m, 1H), 7.46−7.34 (m, 2H), 7.28−7.10 (m, 4H), 7.0 (d, 1H, J = 7.2 Hz), 2.04 (s, 3H), 2.00 (m, 1H), 1.82−1.52 (m, 11H), 1.40−0.90 (m, 10H); ^{13}C NMR (75 MHz, acetone-d_6) δ 150.5 (d, J_{CP} = 31.2 Hz), 143.4 (d, J_{CP} = 6.3 Hz), 136.2 (d, J_{CP} = 1.6 Hz), 135.4 (d, J_{CP} = 20.9 Hz), 133.5 (d, J_{CP} = 3.0 Hz), 131.6 (d, J_{CP} = 2.6 Hz), 130.7 (d, J_{CP} = 5.7 Hz), 130.0, 129.2, 127.7, 127.3, 125.3, 36.5 (d, J_{CP} = 16.7 Hz), 33.9 (d, J_{CP} = 14.0 Hz), 31.7 (d, J_{CP} = 15.5 Hz), 31.1 (d, J_{CP} = 17.3 Hz), 30.9 (d, J_{CP} = 11.3 Hz), 30.0 (d, J_{CP} = 6.3 Hz), 28.2 (d, J_{CP} = 3.9 Hz), 28.1 (d, J_{CP} = 1.3 Hz), 27.7, 27.6 (d, J_{CP} = 3.1 Hz), 27.3, 27.2 (d, J_{CP} = 1.0 Hz), 21.1 (d, J_{CP} = 5.6 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ −11.1; IR (neat, cm^{-1}) 2927, 2910, 2844, 1463, 1443, 849.

General Procedure: Synthesis of Ligands Starting from Aryl Bromides. A Schlenk tube was charged with magnesium turnings (11.5 mmol) and capped with a rubber septum. THF (10 mL) and the aryl bromide (6.00 mmol) were sequentially added via syringe, and the mixture was heated in an oil bath at 60 °C for 2 h. At this point, 2-bromochlorobenzene (5.00 mmol) was added dropwise, and the resulting mixture was heated at 60 °C for 2 h and subsequently cooled to room temperature. The septum was removed and anhydrous copper(I) chloride (6.5 mmol) was added. The septum was then replaced, and the tube was purged with argon for 1 min. A solution of $ClPCy_2$ (6.5 mmol) in THF or neat $ClP(t\text{-}Bu)_2$ (6.5 mmol) was added dropwise via syringe. Reactions with $ClPCy_2$ were conducted at ambient temperature, and those with $ClP(t\text{-}Bu)_2$ were heated at 60 °C. The reactions were stopped after 1−17 h, when judged complete by GC analysis. The reaction was worked up by one of the two methods below:

Workup Method A. The resulting suspension was poured into a flask containing hexane:EtOAc (1:1, 50 mL) and 30% aqueous NH_4OH (50 mL). The mixture was stirred at room temperature for 5 min and transferred to a separatory funnel. The layers were separated, and the organic phase was washed with 30% aqueous NH_4OH (25 mL × 2) and brine (25 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. The resulting residue was further purified as specified.

Workup Method B. Solvent A (hexane or 10:1 hexane:THF) was added to the reaction mixture, and the resulting suspension was cooled in an ice/water bath for 0.5 h, filtered, and washed with solvent B (hexane or 4:1 hexane:THF). The filtered solid was then subjected to workup A.

2-Di-*tert*-butylphosphino-2′-methylbiphenyl (6) (Table 1, entry 5).[12] This reaction was conducted on a 3.00 mmol scale according to the general procedure using workup method A. The reaction of the biphenylylmagnesium halide, CuCl, and chlorophosphine was stopped after 12 h. Crystallization from MeOH (5 mL) in an ice/water bath gave 0.429 g (46% yield) of the title compound as a white solid. A similar experiment on a 25 mmol scale gave 3.90 g (50%). Mp: 91−92 °C (lit.[12] 86−87 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90−7.84 (m, 1H), 7.36−7.07 (m, 7H), 2.11 (s, 3H), 1.16 (d, 9H, J_{HP} = 11.5 Hz), 1.15 (d, 9H, J_{HP} = 11.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.3 (d, J_{CP} = 33.0 Hz), 142.8 (d, J_{CP} = 6.8 Hz), 136.2 (d, J_{CP} = 27.6 Hz), 135.6 (d, J_{CP} = 2.9 Hz), 135.4 (d, J_{CP} = 1.4 Hz), 131.7 (d, J_{CP} = 3.2 Hz), 130.9 (d, J_{CP} = 6.6 Hz), 129.6, 128.4, 127.1, 125.8, 124.3, 33.4 (d, J_{CP} = 24.2 Hz), 32.6 (d, J_{CP} = 25.2 Hz), 31.4 (d, J_{CP} = 15.4 Hz), 31.1 (d, J_{CP} = 14.8 Hz), 21.1 (d, J_{CP} = 2.9 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 20.7; IR (neat, cm^{-1}) 2981, 2960, 2890, 2861, 1468, 1459, 1360, 1171.

2-Dicyclohexylphosphino-2′-isopropylbiphenyl (7) (Table 1, entry 6).[9] The general procedure on a 25.0 mmol scale using workup method B (solvent A = hexane; solvent B = 4:1 hexane:THF) was followed. The reaction of the biphenylylmagnesium halide, CuCl, and chlorophosphine was stopped

after 22 h. Crystallization from 1:4 EtOAc:MeOH (25 mL) in an ice/bath gave 4.65 g (47%) of the title compound, a white crystalline solid. An identical experiment gave 4.99 g (51%) of the title compound. Mp: 111−113 °C (lit.[9] 104 °C): ^{1}H NMR (300 MHz, acetone-d_6) δ 7.67−7.63 (m, 1H), 7.42−7.25 (m, 4H), 7.20−7.10 (m, 2H), 7.00−6.96 (m, 1H); 2.70 (septet, 1H, J = 6.6 Hz); 1.86−1.50 (m, 12H), 1.40−0.82 (m, 10H), 1.24 (d, 3H, J = 6.9 Hz), 0.98 (d, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.8 (d, J_{CP} = 31.1 Hz), 146.3, 141.2 (d, J_{CP} = 6.7 Hz), 134.9 (d, J_{CP} = 18.9 Hz), 132.4 (d, J_{CP} = 3.2 Hz), 131.0 (d, J_{CP} = 2.2 Hz), 130.5 (d, J_{CP} = 6.0 Hz), 128.0, 127.8, 126.4, 124.9, 124.4, 35,9 (d, J_{CP} = 15.3 Hz), 34.0 (d, J_{CP} = 13.7 Hz), 31.1 (d, J_{CP} = 15.3 Hz), 30.4 (d, J_{CP} = 17.6 Hz), 30.2 (d, J_{CP} = 1.9 Hz), 29.9 (d, J_{CP} = 12.5 Hz), 29.1 (d, J_{CP} = 5.4 Hz), 27.8 (d, J_{CP} = 7.5 Hz), 27.7, 27.5, 27.4 (d, J_{CP} = 18.6 Hz), 26.7 (d, J_{CP} = 7.4 Hz), 25.6, 22.9 (d, J_{CP} = 1.7 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ −12.7; IR (neat, cm^{-1}) 2960, 2923, 2844, 1463, 1447, 1003, 849, 756.

2-Di-*tert*-butylphosphino-2′-isopropylbiphenyl (8) (Table 1, entry 7).[13] This reaction was conducted on a 2.00 mmol scale according to the general procedure and workup method B (solvent A = 10:1 hexane: THF; solvent B = hexane). The reaction of the biphenylylmagnesium halide, CuCl, and chlorophosphine was stopped after 17 h. Crystallization from cold MeOH (4 mL) gave 0.200 g (29%) of the title compound as a white solid. Mp: 92−94 °C (lit.[13] 98.5−99.5 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88−7.84 (m, 1H), 7.38−7.28 (m, 4H), 7.21−7.00 (m, 3H), 2.73 (septet, 1H, J = 6.8 Hz), 1.23 (d, 3H, J = 6.8 Hz), 1.18 (d, 9H, J_{HP} = 11.7 Hz), 1.12 (d, 9H, J_{HP} = 11.4 Hz), 1.04 (d, 3H, J = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.3 (d, J_{CP} = 34.6 Hz), 146.2 (d, J_{CP} = 1.2 Hz), 141.7 (d, J_{CP} = 6.6 Hz), 136.3 (d, J_{CP} = 27.6 Hz), 135.5 (d, J_{CP} = 2.9 Hz), 131.6 (d, J_{CP} = 2.4 Hz), 131.2 (d, J_{CP} = 6.4 Hz), 128.2 (d, J_{CP} = 1.2 Hz), 127.5, 125.8, 125.0, 124.2, 33.5 (d, J_{CP} = 24.2 Hz), 32.7 (d, J_{CP} = 25.4 Hz), 31.5 (d, J_{CP} = 15.4 Hz), 30.9 (d, J_{CP} = 14.5 Hz), 30.2, 26.0, 23.1; ^{31}P NMR (121 MHz, $CDCl_3$) δ 20.1; IR (neat, cm^{-1}) 2973, 2956, 2889, 2860, 1472, 1459, 1441, 1362.

1-(2-Di-*tert*-butylphosphinophenyl)naphthalene (9) (Table 1, entry 8).[13] This reaction was carried out on a 2.00 mmol scale according to the general procedure and workup method B (solvent A = 10:1 hexane:THF; solvent B = hexane). The reaction of the biphenylylmagnesium halide, CuCl, and chlorophosphine was stopped after 15 h. Purification by chromatography on silica gel (eluent: 20:1 hexane:EtOAc) followed by crystallization from cold MeOH (3 mL) and recrystallization from MeOH (4 mL) in an ice/water bath gave 0.219 mg (31% yield) of the title compound, a white solid. Mp: 110−111 °C (lit.[13] 107−108 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00−7.94 (m, 1H), 7.87−7.81 (m, 2H), 7.49−7.24 (m, 8H), 1.16 (d, 9H, J_{HP} = 11.5 Hz), 1.05 (d, 9H, J_{HP} = 10.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1 (d, J_{CP} = 34.6 Hz), 141.3 (d, J_{CP} = 7.1 Hz), 137.4 (d, J_{CP} = 27.6 Hz), 135.6 (d, J_{CP} = 2.9 Hz), 133.4, 132.8, 132.7, 131.6 (d, J_{CP} = 6.3 Hz), 128.5 (d, J_{CP} = 3.3 Hz), 128.3 (d, J_{CP} = 1.2 Hz), 128.2, 127.4 (d, J_{CP} = 2.9 Hz), 126.2, 125.4, 125.2, 124.6, 33.2 (d, J_{CP} = 24.5 Hz), 32.3 (d, J_{CP} = 25.1 Hz), 31.4 (d, J_{CP} = 15.5 Hz), 30.1 (d, J_{CP} = 14.9 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 20.3; IR (neat, cm^{-1}) 2962, 2943, 2892, 2861, 1470, 1391, 1362, 1173.

1-(2-Dicyclohexylphosphinophenyl)naphthalene (12) (Table 1, entry 9). The reaction was conducted on a 25.0 mmol scale according to the general procedure and workup method A. The reaction of the biphenylylmagnesium halide, CuCl, and chlorophosphine was stopped after 15 h. The residue was dissolved in 15 mL of ethyl acetate, and the solution was cooled in an ice bath and stirred vigorously. Methanol was then added dropwise until the solution became cloudy. Stirring was continued as several milliliters of methanol were added dropwise over the course of several hours. After a substantial number of white crystals had formed, additional methanol (the total volume was 150 mL) was added, and stirring was continued for 1 h. The solid was filtered and then slurried with methanol:ethyl acetate (12:1, 32 mL). The suspension was cooled in an ice bath and stirred for 1 h. The white solid was then filtered and dried in vacuo. The yield of the title compound was 3.42 g (34%). A similar experiment on a 5.00 mmol scale gave 0.746 g (37% yield) of the title compound. Mp: 111−113 °C: ^{1}H NMR (300 MHz, acetone-d_6) δ 7.92 (d, 1H, J = 9.3 Hz), 7.89 (d, 1H, J = 9.3 Hz), 7.78−7.74 (m, 1H), 7.54−7.43 (m, 4H), 7.40−7.24 (m, 4H), 2.04−1.90 (m, 1H), 1.74−1.52 (m, 10H), 1.30−0.82 (m, 11H); ^{13}C NMR (75 MHz, acetone-d_6) δ 149.2 (d, J_{CP} = 31.4 Hz), 141.6 (d, J_{CP} = 6.7 Hz), 136.9 (d, J_{CP} = 21.5 Hz), 134.2, 133.6 (2 resonances), 131.5 (d, J_{CP} = 5.6 Hz), 129.1 (d, J_{CP} = 1.1 Hz), 128.9 (d, J_{CP} = 2.9 Hz), 128.7, 128.0, 127.8, 127.6 (d, J_{CP} = 1.2 Hz), 126.3, 126.1, 125.4, 36.2 (d, J_{CP} = 16.4 Hz), 34.3 (d, J_{CP} = 14.4 Hz), 31.8 (d, J_{CP} = 16.8 Hz), 31.1 (d, J_{CP} = 18.5 Hz), 30.7 (d, J_{CP} = 12.2 Hz), 30.0 (d, J_{CP} = 6.7 Hz), 28.1 (d, J_{CP} = 3.5 Hz), 28.0 (d, J_{CP} = 2.1 Hz), 27.8, 27.7, 27.5, 27.3 (d, J_{CP} = 0.9 Hz), 27.2 (d, J_{CP} = 1.1 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ −11.1; IR (neat, cm^{-1}) 2921, 2846, 1507, 1443, 1393, 849, 799, 778. Anal. Calcd for $C_{28}H_{33}P$: C, 83.96; H, 8.30. Found: C, 83.75; H, 8.26.

2-Dicyclohexylphosphino-2′,6′-dimethylbiphenyl (13) (Table 1, entry 10). The general procedure on a 5.00 mmol scale using workup method A was followed. The reaction of the biphenylylmagnesium halide, CuCl, and chlorophosphine was stopped after 15 h. The residue was dissolved in 1 mL of ethyl acetate, and the solution was cooled in an ice bath and stirred vigorously. Methanol was then added dropwise until the solution became cloudy. Stirring was continued as additional methanol was added dropwise over the course of several hours. After a substantial number of white crystals had formed, additional methanol (the total volume was 20 mL) was added, and stirring was continued for 1 h. The solid was filtered and then slurried with methanol:ethyl acetate (4:1, 5 mL). The suspension was cooled in an ice bath and stirred for 1 h. The white solid was then filtered and dried in vacuo. The yield of the title compound was 0.982 g (52% yield). A similar experiment on a 25.0 mmol scale gave 4.98 g (53%) of the title compound. Mp: 90−92 °C: ^{1}H NMR (300 MHz, acetone-d_6) δ 7.67−7.60 (m, 1H), 7.45−7.34 (m, 2H), 7.15−7.02 (m, 4H), 1.99 (s, 6H), 1.85−1.55 (m, 12H). 1.30−1.00 (m, 10H); ^{13}C NMR (75 MHz, acetone-d_6)) δ 149.3 (d, J_{CP} = 30.7 Hz), 143.2 (d, J_{CP} = 5.9 Hz), 137.2 (d, J_{CP} = 7.7 Hz), 137.1 (d, J_{CP} = 10.8 Hz), 134.2 (d, J_{CP} = 2.7 Hz). 131.8 (d, J_{CP} = 6.0 Hz), 130.2, 128.6, 128.5, 128.1, 35.6 (d, J_{CP} = 15.8 Hz), 32.4 (d, J_{CP} = 13.9 Hz), 31.3 (d, J_{CP} = 13.9 Hz), 29.0 (d, J_{CP} = 8.9 Hz), 28.9 (d, J_{CP} = 8.6 Hz), 28.1 (d, J_{CP} = 4.4 Hz); ^{31}P NMR (121 MHz, acetone-d_6) δ −7.3; IR (neat, cm^{-1}) 2937, 2917, 2850, 1459, 1443, 996, 851, 764, 741. Anal. Calcd for $C_{26}H_{35}P$: C, 82.50; H, 9.32. Found: C, 82.68; H, 9.25.

2-Di-*tert*-butylphosphino-2′,6′-dimethylbiphenyl (14) (Table 1, entry 11). The general procedure on a 5.00 mmol scale using workup method A was followed. The reaction of the biphenylylmagnesium halide, CuCl, and chlorophosphine was stopped after 15 h. Purification by chromatography on silica gel (eluting first with hexane and then 20:1 hexane:EtOAc), followed by crystallization from cold methanol (5 mL) gave 0.293 g (18% yield) of the title compound, a white solid. Mp: 86−88 °C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86−7.82 (m, 1H), 7.38−7.27 (m, 2H), 7.17−7.02 (m, 4H), 2.06 (s, 6H), 1.15 (d, 18H, J_{HP} = 11.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.9 (d, J_{CP} = 33.0 Hz), 142.0 (d, J_{CP} = 5.4 Hz), 136.6 (d, J_{CP} = 30.0 Hz), 136.2 (d, J_{CP} = 1.8 Hz), 136.1 (d, J_{CP} = 1.4 Hz), 131.3 (d, J_{CP} = 6.9 Hz), 128.6 (d, J_{CP} = 1.2 Hz), 127.1, 127.0, 125.7, 32.9 (d, J_{CP} = 24.7 Hz), 31.2 (d, J_{CP} = 14.9 Hz), 22.4 (d, J_{CP} = 4.5 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 25.0; IR (neat, cm^{-1}) 2993, 2983, 2956, 2890, 2861, 1474, 1457, 1362. Anal. Calcd for $C_{22}H_{31}P$: C, 80.94; H, 9.57. Found: C, 80.76; H, 9.56.

2-Dicyclohexylphosphino-2′,5′-dimethylbiphenyl (15) (Table 1, entry 12). This reaction was conducted on a 2.00 mmol scale according to the general procedure and workup method A. The reaction of the biphenylylmagnesium halide, CuCl, and chlorophosphine was stopped after 1.5 h. Two crystallizations from 8 mL portions of cold EtOAc:MeOH (1:3, 8 mL) gave 0.373 g (49% yield) of the title compound, a white solid. Mp: 93−95 °C: ^{1}H NMR (300 MHz, acetone-d_6) δ 7.66−7.58 (m, 1H), 7.42−7.34 (m, 2H), 7.16−6.98 (m, 3H), 6.86 (s, 1H), 2.29 (s, 3H), 1.98 (s, 3H), 1.80−0.90 (m, 22H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0 (d, J_{CP} = 31.5 Hz), 142.4 (d, J_{CP} = 6.7 Hz), 134.5 (d, J_{CP} = 18.5 Hz), 133.7, 132.6, 132.5, 131.6,

130.0 (d, J_{CP} = 5.8 Hz), 129.3, 128.3, 128.0, 126.3, 35.6 (d, J_{CP} = 15.2 Hz), 33.4 (d, J_{CP} = 13.5 Hz), 31.0 (d, J_{CP} = 15.1 Hz), 30.2 (d, J_{CP} = 17.4 Hz), 30.1 (d, J_{CP} = 11.5 Hz), 29.1 (d, J_{CP} = 5.1 Hz), 27.8 (d, J_{CP} = 11.6 Hz), 27.7 (d, J_{CP} = 5.8 Hz), 27.4, 27.3, 26.6 (2 resonances), 21.2, 20.4 (d, J_{CP} = 4.8 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ −10.6; IR (neat, cm^{-1}) 2931, 2921, 2846, 1465, 1445, 1119, 886, 807. Anal. Calcd for $C_{26}H_{35}P$: C, 82.50; H, 9.32. Found: C, 82.40; H, 9.19.

2-Dicyclohexylphosphino-2′,4′-dimethylbiphenyl (16) (Table 1, entry 13). This reaction was carried out on a 1.00 mmol scale according to the general procedure and workup method A. Crystallization from cold EtOAc:MeOH (1:4, 5 mL) and recrystallization from cold EtOAc:MeOH (1:8, 4.5 mL) in a freezer gave 0.145 g (38% yield) of the title compound, a white solid. Mp: 112−114 °C: ^{1}H NMR (300 MHz, acetone-d_6) δ 7.65−7.60 (m, 1H), 7.41−7.34 (m, 2H), 7.14−7.07 (m, 1H), 7.02−6.90 (m, 3H), 2.32 (s, 3H), 2.00 (s, 3H), 1.80−0.90 (m, 22H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9 (d, J_{CP} = 30.1 Hz), 139.6, 136.6, 135.3, 134.5 (d, J_{CP} = 19.6 Hz), 132.6, 130.7, 130.3 (2 resonances), 128.3, 126.3, 125.4, 35.5 (d, J_{CP} = 15.1 Hz), 33.4 (d, J_{CP} = 13.6 Hz), 31.0 (d, J_{CP} = 14.6 Hz), 30.2, 30.0, 29.8, 28.9 (d, J_{CP} = 4.3 Hz), 27.9, 27.7, 27.4 (d, J_{CP} = 9.8 Hz), 26.7, 26.6, 21.5, 20.9 (d, J_{CP} = 8.4 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ −11.3; IR (neat, cm^{-1}) 2916, 2844, 1461, 1445, 1003, 849, 816, 764. Anal. Calcd for $C_{26}H_{35}P$: C, 82.50; H, 9.32. Found: C, 82.46; H, 9.25.

2-Dicyclohexylphosphino-2′,4′,6′-trimethylbiphenyl (17) (Table 1, entry 14). This reaction was conducted on a 2.00 mmol scale according to the general procedure and workup method A. Crystallization from EtOAc (3 mL), filtration, and drying in vacuo gave 436 mg (53%) of **17**, a white crystalline solid that contained ca. 6% EtOAc by weight. Heating at 80 °C under vacuum for 24 h failed to remove the solvent. Mp: 124−126 °C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60−7.50 (br m, 1H), 7.40−7.28 (br m, 2H), 7.10−7.04 (br m, 1H), 6.90 (s, 2H). 2.31 (s, 3H), 1.97 (s, 6H), 1.84−1.53 (m, 12H), 1.32−1.00 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.2 (d, J_{CP} = 30.6 Hz), 138.7, 136.5, 135.7 (d, J_{CP} = 1.7 Hz), 135.4 (d, J_{CP} = 18.3 Hz), 132.6, 130.7(d, J_{CP} = 4.4 Hz), 128.5, 128.0, 126.2, 34.2 (d, J_{CP} = 14.9 Hz), 30.5 (d, J_{CP} = 12.1 Hz), 29.8 (d, J_{CP} = 13.7 Hz), 27.8 (d, J_{CP} = 4.8 Hz), 27.7 (d, J_{CP} = 6.0 Hz), 26.7, 21.6 (d, J_{CP} = 4.0 Hz), 21.5; ^{31}P NMR (121 MHz, $CDCl_3$) δ −8.9; IR (neat, cm^{-1}) 2916, 2846, 1445, 1001, 847, 766, 748, 739. Anal. Calcd for $C_{27}H_{37}P$·0.28EtOAc: C, 80.95; H, 9.48. Found: C, 81.07; H, 9.44.

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