

A Copper- and Amine-Free Sonogashira Reaction Employing Aminophosphines as Ligands

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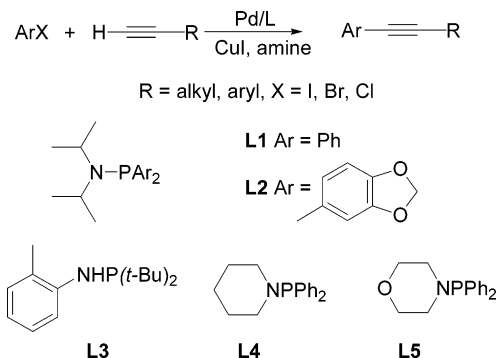
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An efficient Pd-catalyzed Sonogashira coupling reaction was achieved in the absence of a copper salt or amine with an inorganic base and easily prepared, air-stable aminophosphine ligands in commonly used organic solvents; good to excellent yields were obtained. Under optimized reaction conditions, the Sonogashira coupling reaction occurred selectively when an enyne substrate was employed and no Heck reaction product was detected; acetone-masked acetylene and trimethylsilylacetylene can also be efficiently coupled, providing a method to make terminal alkynes.

Introduction

Palladium-catalyzed coupling of terminal alkynes with aryl or alkenyl iodides, which was described for the first time by Sonogashira et al. in 1975, is one of the most straightforward methods for the preparation of aryl-alkynes and conjugated enynes (Scheme 1).¹ Generally, the Sonogashira coupling is carried out in the presence of a catalytic amount of a palladium complex as well as copper iodide in an amine as the solvent to obtain a good yield.² Numerous applications in natural product synthesis have been reported, for example, in the construction of the complex unsaturated framework of the enediyne antibiotics.³ Recently, the use of aryl bromide and aryl chloride has been explored, and good results were achieved.⁴ Muller et al. reported a method to synthesize α,β -unsaturated alkynones by the cross-coupling of aryl chloride with trimethylsilylacetylene.^{4h} In addition to traditional palladium-catalyzed methods, the nickel-catalyzed Sonogashira reaction was also reported.⁵

SCHEME 1



Although an impressive variety of modifications have been reported for this reaction, including phase-transfer reaction conditions⁶ and aqueous,⁷ and solvent-free⁸ versions, a copper cocatalyst is still needed. The copper(I) acetylides formed in situ could undergo oxidative

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(1) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467–4470. (b) Cassar, L. *J. Organomet. Chem.* **1975**, 93, 253–257. (c) Dieck, H. A.; Heck, F. R. *J. Organomet. Chem.* **1975**, 93, 259–263.

(2) For reviews, see: (a) Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 3, pp 521–549. (b) Rossi, R.; Carpita, A.; Bellina, F. *Org. Prep. Proced. Int.* **1995**, 27, 129–169. (c) Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: Chichester, U.K., 1995; pp 168–171. (d) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weinheim, Germany, 1996; pp 582–586. (e) Brandsma, L.; Vasilevsky, S. F.; Verkrujse, H. D. *Application of Transition Metal Catalysts in Organic Synthesis*; Springer: Berlin, 1998; pp 179–225. (f) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; pp 203–229.

(3) (a) Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.* **1991**, 30, 1387–1416. (b) Maier, M. E. *Synlett* **1995**, 13–26. (c) Grissom, J. W.; Gunawardena, G. U.; Kingberg, D.; Huang, D. *Tetrahedron* **1996**, 52, 6453–6518.

(4) For recent examples, see: (a) Choudary, B. M.; Madhi, S.; Chowdari, N. S.; Kantam, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2002**, 124, 14127–14136. (b) Eberhard, M. R.; Wang, Z.; Jensen, C. M. *Chem. Commun.* **2002**, 818–819. (c) Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, 2, 1729–1731. (d) Alami, M.; Crousse, B.; Ferri, F. *J. Organomet. Chem.* **2001**, 624, 114–123. (e) Ansorge, M.; Müller, T. J. J. *J. Organomet. Chem.* **1999**, 585, 174–178. (f) Thorand, S.; Krause, N. *J. Org. Chem.* **1998**, 63, 8551–8553. (g) Köllhofer, A.; Pullmann, T.; Plenio, H. *Angew. Chem., Int. Ed.* **2003**, 42, 1056–1058. (h) Karpov, A. S.; Müller, T. J. J. *Org. Lett.* **2003**, 5, 3451–3454.

(5) Beletskaya, I. P.; Latyshev, G. V.; Tsvetkov, A. V.; Lukashev, N. V. *Tetrahedron Lett.* **2003**, 44, 5011–5013.

(6) Chow, H.-F.; Wan, C.-W.; Low, K.-H.; Yeung, Y.-Y. *J. Org. Chem.* **2001**, 66, 1910–1913.

(7) (a) Bong, D. T.; Ghadiri, M. R. *Org. Lett.* **2001**, 3, 2509–2511. (b) Dibowski, H.; Schmidtchen, F. P. *Tetrahedron Lett.* **1998**, 39, 525–528. (c) Genet, J.-P.; Blart, E.; Savignac, M. *Synlett* **1992**, 715–717. (d) Casalnuovo, A. L.; Calabrese, J. C. *J. Am. Chem. Soc.* **1990**, 112, 4324–4330.

(8) Kabalka, G. W.; Wang, L.; Namboodiri, V.; Pagni, R. M. *Tetrahedron Lett.* **2000**, 41, 5151–5154.

dimerization to give diaryldiacetylenes when they are exposed to air or an oxidant (a reaction known as the Glaser coupling).⁹ These byproducts are generally difficult to separate from the desired products. Furthermore, the copper acetylide is a potential explosive reagent. Some examples of “palladium-only” catalysts have been reported in this cross-coupling reaction.¹⁰

Trivalent aminophosphines that contain one or more P–N bonds have been recently employed as ligands in transition-metal-catalyzed cross-coupling reactions.¹¹ A few reports on the coordination chemistry of aminophosphine compounds revealed that the function of amino groups was more diversified than that of alkoxy groups in phosphites.¹² In mono- and diamino phosphines, alkyl- and/or arylamino groups served as strong electron-donating groups, making the phosphines stronger σ -donor ligands. In our previous work, we found phosphinamides **L1**, **L4**, and **L5** (Scheme 1) were highly efficient ligands in the Suzuki cross-coupling reaction.¹³ We attempted to extend the use of this type of ligand to the Sonogashira reaction. Herein, we report a copper- and amine-free Sonogashira reaction employing aminophosphine ligands.

Results and Discussion

We first chose *p*-bromoanisole (**2a**) and phenylacetylene (**1a**) as substrates and **L1** as ligand to investigate the Sonogashira reaction in the absence of a copper salt.

Treatment of a mixture of **1a** (245 mg, 2.4 mmol), **2a** (374 mg, 2 mmol), Pd(OAc)₂ (11 mg, 0.05 mmol), and **L1** (43 mg, 0.15 mmol) in Et₃N (5 mL) at 65 °C under an inert atmosphere for 8 h produced the desired product

TABLE 1. Effect of Bases in the Sonogashira Cross-Coupling Reaction^a

entry	base	yield ^b (%)	entry	base	yield ^b (%)
1	Et ₃ N	83 ^c	6	Na ₂ CO ₃	25 (88) ^d
2	Et ₃ N	21	7	NaHCO ₃	23
3	pyridine	NR	8	K ₃ PO ₄ ·3H ₂ O	90
4	morpholine	24	9	KOH	NR
5	K ₂ CO ₃	97	10	KF	7

^a All reactions were run with *p*-bromoanisole (374 mg, 2 mmol), phenylacetylene (245 mg, 2.4 mmol), Pd(OAc)₂ (11 mg, 0.05 mmol), and **L1** (43 mg, 0.15 mmol) with the indicated base (6 mmol) in 5 mL of THF at 65 °C for 8 h. ^b Isolated yield. ^c Et₃N was employed as solvent. ^d 30 h.

TABLE 2. Effects of Ligands and Solvents in the Sonogashira Reaction between *p*-Bromoanisole and Phenylacetylene^a

entry	ligand	solvent	3aa yield ^b (%)
1	L1	THF	97
2	L2	THF	91
3	L3	THF	67
4	L4	THF	9
5	L5	THF	11
6	L1	dioxane	80
7	L1	toluene	77
8	L1	DMF	93
9	L1	CH ₃ CN	95

^a All reactions were run with *p*-bromoanisole (374 mg, 2 mmol), phenylacetylene (245 mg, 2.4 mmol), Pd(OAc)₂ (11 mg, 0.05 mmol), K₂CO₃ (828 mg, 6 mmol), and ligand (0.15 mmol) in 5 mL of the indicated solvent at 65 °C for 8 h. ^b Isolated yield.

3aa in 83% yield. This is a promising result, since no copper salt was required. If we can reduce the amount of the base, or realize the reaction in a commonly used organic solvent, the reaction would be more attractive. However, only a 21% yield of product was obtained when the reaction was performed in THF (5 mL) with Et₃N (6 mmol) as the base (Table 1, entries 1 and 2). To improve the efficiency of the reaction in a common organic solvent other than triethylamine, we investigated the effect of the commonly used organic and inorganic bases in THF. The results are summarized in Table 1.

A significant effect of bases was found in the reaction. With a strong base such as KOH, no desired product was isolated (Table 1, entry 9). Morpholine, which is commonly employed to accelerate the Sonogashira reaction, and KF failed to give good yields under this reaction condition (Table 1, entries 4 and 10). K₃PO₄·3H₂O showed high efficiency, giving the product in 90% yield (Table 1, entry 8). However, the best base was K₂CO₃, which provided a 97% yield of the desired product (Table 1, entry 5).

We then turned our attention to ligand and solvent effects. The results are summarized in Table 2.

Both **L1** and **L2** are highly effective ligands in this reaction (Table 2, entries 1 and 2), while other ligands

(9) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, 39, 2632–2657.

(10) Copper-free Sonogashira coupling reactions are not common. See: (a) Böhm, V. P.; Hermann, W. A. *Eur. J. Org. Chem.* **2000**, 3679–3681. (b) Pal, M.; Parasuraman, K.; Gupta, S.; Yaleswarapu, K. R. *Synlett* **2002**, 12, 1976–1982 and references therein. (c) Fu, X.; Zhang, S.; Yin, J.; Schumacher, D. *Tetrahedron Lett.* **2002**, 43, 6673–6676. (d) Alonso, D. A.; Nájera, C.; Pacheco, M. C. *Tetrahedron Lett.* **2002**, 43, 9365–9368. (e) Fukuyama, T.; Shinmen, M.; Nishitani, S.; Sato, M.; Ryu, I. *Org. Lett.* **2002**, 4, 1691–1694 and references therein. (f) Méry, D.; Heuzé, K.; Astruc, D. *Chem. Commun.* **2003**, 1934–1935. (g) Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, 2, 1729–1731. (h) Heuzé, K.; Méry, D.; Gauss, D.; Astruc, D. *Chem. Commun.* **2003**, 2274–2275. (i) Soheili, A.; Albaneze-Walker, J.; Murry, J. A.; Dormer, P. G.; Hughes, D. L. *Org. Lett.* **2003**, 5, 4191–4194. (j) Ma, Y.; Song, C.; Jiang, W.; Wu, Q.; Wang, Y.; Liu, X.; Andrus, M. B. *Org. Lett.* **2003**, 5, 3317–3319. (k) Nájera, C.; Gil-Moltó, J.; Karlström, S.; Falvello, L. R. *Org. Lett.* **2003**, 5, 1451–1454. (l) Alonso, D. A.; Nájera, C.; Pacheco, M. C. *Adv. Synth. Catal.* **2003**, 345, 1146–1158. (m) Buchmeiser, M. R.; Schareina, T.; Kempe, R.; Wurst, K. J. *Organomet. Chem.* **2001**, 634, 39–46. (n) Uozumi, Y.; Kobayashi, Y. *Heterocycles* **2003**, 59, 71–74.

(11) (a) Clarke, M. L.; Cole-Hamilton, D. J.; Woollins, J. D. *J. Chem. Soc., Dalton Trans.* **2001**, 2721–2723. (b) Schareina, T.; Kempe, R. *Angew. Chem., Int. Ed.* **2002**, 41, 1521–1523. (c) Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *Tetrahedron Lett.* **2002**, 43, 8921–8924. (d) Clarke, M. L.; Cole-Hamilton, D. J.; Slawin, A. M. Z.; Woollins, J. D. *Chem. Commun.* **2000**, 2065–2066. (e) Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *J. Org. Chem.* **2003**, 68, 452–459. (f) Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *Org. Lett.* **2003**, 5, 815–818. (g) You, J.; Verkade, J. G. *J. Org. Chem.* **2003**, 68, 8003–8007. (h) Urgaonkar, S.; Xu, J.-H.; Verkade, J. G. *J. Org. Chem.* **2003**, 68, 8416–8423.

(12) (a) Rømming, C.; Songstad, J. *Acta Chem. Scand., Ser. A* **1978**, 32, 689–699. (b) Rømming, C.; Songstad, J. *Acta Chem. Scand., Ser. A* **1979**, 33, 187–197. (c) Rømming, C.; Songstad, J. *Acta Chem. Scand., Ser. A* **1982**, 36, 665–671. (d) Moloy, K. G.; Petersen, J. L. *J. Am. Chem. Soc.* **1995**, 117, 7696–7710. (e) Socol, S. M.; Jacobson, R. A.; Verkade, J. G. *Inorg. Chem.* **1984**, 23, 88–94.

(13) Cheng, J.; Wang, F.; Xu, J.; Pan, Y.; Zhang, Z. *Tetrahedron Lett.* **2003**, 44, 7095–7098.

TABLE 3. Reaction of Aryl Bromides and Phenylacetylene^a

$\text{Ph}-\text{C}\equiv\text{C}-\text{H} + \text{ArBr} \longrightarrow \text{Ph}-\text{C}\equiv\text{C}-\text{Ar}$			
entry	2	3	yield ^b (%)
1	<i>p</i> -bromoanisole (2a)	3aa	97 (91)
2	2a	3aa	92 ^c
3	<i>p</i> -bromotoluene (2b)	3ab	65 (94)
4	bromobenzene (2c)	3ac	78 (95)
5	2,6-dimethylphenyl bromide (2d)	3ad	15 (88)
6	<i>o</i> -bromotoluene (2e)	3ae	86 (99)
7	1-bromonaphthalene (2f)	3af	68 (80)
8	3-bromopyridine (2i)	3ai	(95)

^a All reactions were run with aryl bromide (2 mmol), phenylacetylene (245 mg, 2.4 mmol), Pd(OAc)₂ (11 mg, 0.05 mmol), and **L1** (43 mg, 0.15 mmol) with K₂CO₃ (828 mg, 6 mmol) in 5 mL of THF at 65 °C for 8 h. ^b Isolated yield. The yields in parentheses refer to reaction when **L2** was employed as ligand. ^c Yield obtained at room temperature for 24 h.

are inferior. **L3**, **L4**, and **L5** are workable ligands in the Suzuki–Miyaura cross-coupling reaction;¹³ however, they gave poor yields in the Sonogashira reaction (Table 2, entries 3–5).

The reaction proceeded well in polar solvents, such as THF, dioxane, DMF, and acetonitrile; 97%, 80%, 93%, and 95% isolated yields were obtained, respectively (Table 2, entries 1, 6, 8, and 9). The yields decreased in less polar solvents such as toluene. Simple primary and secondary alcohols are not proper solvents for this reaction, since they would react with the ligands to give alkoxyphosphines.¹⁴

On the basis of these results, we employed the following optimized reaction conditions: 2 mmol of aryl bromide, 2.4 mmol of alkyne, 0.05 mmol of Pd(OAc)₂, 0.15 mmol of **L1**, 6 mmol of K₂CO₃, and 5 mL of THF as solvent. In fact, even if the reaction was performed at rt for 24 h, the product was obtained in an excellent yield (92%) (Table 3, entry 2). However, when *p*-bromotoluene (**2b**) and bromobenzene (**2c**) were employed as substrates, the yields decreased to 65% and 78%, respectively (Table 3, entries 3 and 4). Fortunately, the yields increased to 94% and 95%, respectively, when the ligand **L2** was employed instead of **L1** (Table 3, entries 3 and 4). The results using **L1** and **L2** as ligands are summarized in Table 3. In general, **L2** showed higher efficiency toward the Sonogashira reaction of aryl bromides and phenylacetylene. The reaction is not sensitive to steric hindrance; for **2d** and **2e**, which have *ortho* substituent groups, the coupling reactions were still realized in 88% and 99% yields, respectively (Table 3, entries 5 and 6). When bromonaphthalene (**2f**) was employed as substrate, a good isolated yield could also be obtained (Table 3, entry 7).

If we perform this reaction with aryl bromides and hexyne, no obvious difference is found between **L1** and **L2** (Table 4, entries 2 and 3). Since **L1** is easier to prepare and handle (**L1** is stable in air; no change was detected when it was exposed in air for 3 days), we employed ligand **L1** in the reaction of aryl bromides and other alkynes. The results are summarized in Table 4.

All of the alkyne substrates worked well under the reaction conditions in the absence of Cu and amine. The aryl bromides which contain electron-donating substituents

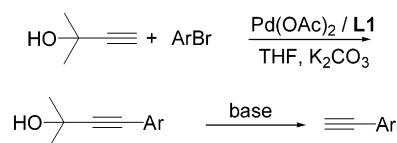
TABLE 4. Sonogashira Reaction between Aryl Bromides and Alkynes^a

entry	alkyne	aryl bromide	product	yield ^b (%)
1	1-hexyne (1b)	2a	3ba	96
2	1b	2b	3bb	93 (94)
3	1b	2c	3bc	86 (91)
4	1b	2d	3bd	88
5	1b	2h	3bh	93 ^c
6	1b	2i	3bi	72
7	1-naphthylacetylene (1c)	2b	3cb	93
8	benzyl propargyl ether (1d)	2c	3dc	96
9	1-cyclohexenylacetylene (1e)	2c	3ec	88
10	1e	2j	3ej	95 ^c
11	benzylacetylene (1f)	2c	3fc	83
12	2-methyl-3-butyne-2-ol (1g)	2a	3ga	86
13	1g	2b	3gb	92
14	1g	2c	3gc	94
15	1g	2f	3gf	78
16	1g	1,4-dibromobenzene (2g)	3gg	88 ^d
17	3-methoxy-3-methyl-1-butyne (1h)	2c	3hc	96
18	trimethylsilylacetylene (1i)	2b	3ib	87
19	1i	2c	3ic	94

^a All reactions were run at 65 °C for 8 h with aryl bromide (2 mmol), alkyne (2.4 mmol), Pd(OAc)₂ (11 mg, 0.05 mmol), and **L1** (43 mg, 0.15 mmol) with K₂CO₃ (828 mg, 6 mmol) in 5 mL of THF.

^b Isolated yield. The yields in parentheses refer to reaction when **L2** was employed as ligand. ^c The reaction was complete in 3 h.

^d 2.4 mol of **1g**/mol of **2g** was used.

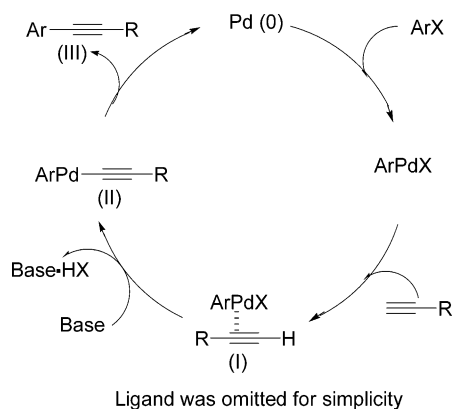
SCHEME 2

uents were considered reluctant to oxidative addition to Pd(0); however, a 96% isolated yield of product **3ba** was obtained for the coupling reaction of hexyne (**1b**) and *p*-bromoanisole (**2a**) (Table 4, entry 1). The *ortho* group in the aryl bromide had hardly any effect in the reaction; the yield reached 88% for **1b** and 2,6-dimethylphenyl bromide (**2d**) (Table 4, entry 4). As the primary alcohol will react with the phosphinamide ligands, prop-2-yn-1-ol is not a proper substrate in the procedure.¹⁴ However, if the hydroxy group was protected with a benzyl group (**1d**), the coupling reaction could be realized with **2c**, providing a 96% isolated yield of **3dc** (Table 4, entry 8). It is worth noting that with unprotected tertiary alcohol 2-methyl-3-butyne-2-ol (**1g**), the coupling reaction may be realized, giving the coupling product in 94% isolated yield. The product could be further converted to the terminal alkyne in the presence of a strong base (Scheme 2).¹⁵ Because **1g** is a large-volume industrial product, the successful coupling of this compound is of great significance; it provides a possible entry to large-scale production of terminal aryl alkynes by the Sonogashira coupling reaction. The commonly used substitute for **1g**, trimethylsilylacetylene, is a good reactant (Table 4, entries 18,19). For substrate **1e**, which possesses both a C=C double bond and a C≡C triple bond, only the Sonogashira

(14) Mukaiyama, T.; Kikuchi, W.; Shintou, T. *Chem. Lett.* **2003**, 32, 300–301.

(15) Havens, S. J.; Hergenrother, P. M. *J. Org. Chem.* **1985**, 50, 1763–1764.

SCHEME 3



cross-coupling product **3ec** was isolated in 88% yield and no Heck reaction product was detected (Table 4, entry 9). As expected, aryl halides with electron-withdrawing groups are more reactive than those with electron-donating groups; when bromoacetone and methyl 2-bromobenzoate were employed, the reaction was complete in 3 h (Table 4, entries 5 and 10).

The mechanism of the reaction is suggested as in Scheme 3. The first step is the oxidative addition of Pd(0) with aryl halide. The application of electron-rich aminophosphine ligands makes this step easier. The second step is the activation of the terminal alkyne. Because no copper salt was employed, and the bases are not strong enough to subtract a proton from the alkyne, a transmetalation step could be excluded. The terminal alkyne C–H bond activation is accomplished by the coordination of the alkyne to the ArPdX complex. Upon coordination, the C–H bond is weakened, and HX is removed from **I** in the presence of a base to form arylalkynylpalladium species **II**, which undergoes reductive elimination to afford the product **III** and regenerates the catalyst. The electron-rich, and bulky, aminophosphine ligands may play key roles in facilitating the reductive elimination step.

In conclusion, we have developed an efficient, copper- and amine-free Sonogashira reaction with easily prepared, air-stable aminophosphines as the ligands. The mild reaction conditions, the obviation of copper salt as cocatalyst and amine as solvent, and the utilization of inorganic base are the most attractive features of the reaction.

Experimental Section

Materials. THF was distilled from sodium–benzophenone prior to use. K_2CO_3 , $K_3PO_4 \cdot 3H_2O$, KF, $Pd(OAc)_2$, KOH, aryl bromides, phenylacetylene, and hexyne were used directly as obtained commercially unless otherwise noted. Other alkynes were prepared according to the literature.

Preparation of Ligands. *Caution: The aminophosphine ligands may be toxic, no MSDS available.* **L1** was prepared according to the literature,¹⁶ while **L2** was prepared according to the process mentioned as follows: Under a nitrogen atmosphere, a 100 mL three-necked flask was charged with 5-bromobenzo[1,3]dioxole (4.0 g, 20 mmol) in dry ether (15 mL) and *n*-BuLi (15 mL, 1.6 M in hexanes, 24 mmol) was added dropwise at $-20^\circ C$ with stirring. The mixture was further

stirred for 1 h at this temperature, and then iPr_2NPdCl_2 (2.0 g, 10 mmol) in dry ether (15 mL) was added dropwise in 2 h. The reaction mixture was stirred overnight. Then the solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography on Al_2O_3 to give **L2** (1.53 g, 43%) as a colorless oil.

Data for L1. White solid. Mp: $69-70^\circ C$. 1H NMR (300 MHz, $CDCl_3$): δ 7.53–7.47 (m, 4H), 7.34–7.30 (m, 6H), 3.39 (m, 2H), 1.08 (d, $J = 6.3$ Hz, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.5 (d, $J = 19.8$ Hz), 132.4 (d, $J = 20.3$ Hz), 127.9, 127.9, 47.4 (d, $J = 8.3$ Hz), 23.8 (d, $J = 7.1$ Hz). ^{31}P NMR (121 MHz, $CDCl_3$): δ 38.2. MS (EI): m/z 285, 270, 242, 228, 194, 183, 108, 100. IR (KBr, cm^{-1}): 3067, 2981, 2965, 1433, 1360, 1178, 1120.

Data for L2. Oil. 1H NMR (300 MHz, $CDCl_3$): δ 7.03–6.97 (m, 2H), 6.82–6.79 (m, 2H), 6.82–6.79 (m, 2H), 5.97 (s, 4H), 3.38 (m, 2H), 1.13 (d, $J = 6.0$ Hz, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.5, 126.7, 126.4, 111.9, 111.6, 108.2, 100.8, 47.1, 23.8. ^{31}P NMR (121 MHz, $CDCl_3$): δ 40.1. MS (EI): m/z (rel intens) 373, 316, 273, 238. HRMS: m/z calcd for $C_{20}H_{24}NO_4P$ 373.1443, found 373.1466. IR (neat, cm^{-1}): 2965, 2893, 1502, 1473, 1413, 1362, 1234, 1042.

General Procedure for Palladium-Catalyzed Copper- and Amine-Free Sonogashira Cross-Coupling Reaction.

Under a nitrogen atmosphere, a Schlenk reaction tube was charged with alkyne substrate **1** (2.4 mmol), aryl bromide **2** (2 mmol), K_2CO_3 (828 mg, 6 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), ligand (0.15 mmol), and THF (5 mL). The reaction tube was purged with N_2 in a dry ice bath. After the mixture was heated at $65^\circ C$ for 8 h, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel to give the product **3**.

Data for Hex-1-ynyl-2,6-dimethylbenzene (3bd). 1H NMR (300 MHz, $CDCl_3$): δ 7.03–7.01 (m, 3H), 2.50 (t, $J = 7.2$ Hz, 2H), 2.54 (s, 6H), 1.62–1.52 (m, 4H), 0.95 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.9, 126.8, 126.5, 123.7, 98.9, 78.1, 31.1, 22.0, 21.1, 19.4, 13.6. MS (EI): m/z (rel intens) 186, 157, 143, 142, 141, 129, 115. HRMS: m/z calcd for $C_{14}H_{18}$ 186.1409, found 186.1396. IR (neat, cm^{-1}): 3022 (m), 2980 (s), 2924 (s), 2874 (m), 2226 (m), 1467 (s), 1378 (m), 769 (s), 734 (m).

Data for 2-Methyl-4-(1'-naphthalen-2-yl)but-3-yn-2-ol (3gf). 1H NMR (300 MHz, $CDCl_3$): δ 8.35–8.31 (m, 1H), 7.85–7.79 (m, 2H), 7.67–7.65 (m, 1H), 7.58–7.50 (m, 2H), 7.42–7.37 (m, 1H), 2.70 (s, br, 1H), 1.76 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.2, 133.0, 130.3, 128.6, 128.2, 126.7, 126.3, 125.9, 125.0, 120.2, 98.8, 80.1, 65.8, 31.6. MS (EI): m/z (rel intens) 210 (M^+ , 67), 209 (28), 195 (98), 165 (24), 152 (33), 86 (28), 84 (41), 43 (100). HRMS: m/z calcd for $C_{15}H_{14}O$ 210.1045, found 210.1029. IR (neat, cm^{-1}): 3368 (s), 3060 (m), 2983 (s), 2248 (m), 1396 (s), 1164 (s), 908 (s), 808 (s), 774 (s), 733 (s).

Data for 1,4-Bis(3-hydroxy-3-methylbut-1-ynyl)benzene (3gg). 1H NMR (300 MHz, CD_3COCD_3): δ 7.35 (s, 4H), 4.53 (s, br, 2H), 1.53 (s, 12H). ^{13}C NMR (75 MHz, CD_3COCD_3): δ 131.6, 123.2, 97.2, 80.6, 64.5, 31.3. MS (EI): m/z (rel intens) 242 (M^+ , 12), 227 (47), 135 (15), 107 (47), 92 (17), 91 (24), 59 (16), 46 (21), 43 (100). HRMS: m/z calcd for $C_{16}H_{18}O_2$ 242.1307, found 242.1329. IR (KBr, cm^{-1}): 3339 (s), 2981 (s), 2983 (s), 1508 (m), 1362 (s), 1273 (s), 1187 (m), 1143 (s), 960 (s), 905 (s), 836 (s), 788 (m).

Deprotection of Acetone-Masked Alkynes.¹⁷ To a solution of **3gf** (2.2 g, 10.5 mmol) in dry toluene (50 mL) was added sodium hydroxide powder (400 mg, 10 mmol). The suspension was refluxed till the starting material was consumed completely (8 h). Brine (15 mL) was added, and the separated toluene layer was dried ($MgSO_4$). The solvent was evaporated under reduced pressure, and the residue was purified by flash

(16) Contreras, R.; Grevy, J. M.; Garcia-Hernandez, Z.; Gueizado-Rodriguez, M.; Wrackmeyer, B. *Heteroat. Chem.* **2001**, *12*, 542–550.

(17) (a) Havens, S. J.; Hergenrother, P. M. *J. Org. Chem.* **1985**, *50*, 1763–1764. (b) Pourjavadi, A.; Marandi, G. B. *J. Chem. Res., Synop.* **2002**, *11*, 552–555. (c) Takalo, H.; Kankare, J.; Häenninen, E. *Acta Chem. Scand., Ser. B* **1988**, *42*, 448–454.

column chromatography on a silica gel to give 1-naphthylacetylene (**4gf**) as a colorless liquid (1.17 g, yield 73%). ^1H NMR (300 MHz, CDCl_3): δ 8.42 (d, $J = 8.1$ Hz, 1H), 7.87 (d, $J = 8.1$ Hz, 2H), 7.80–7.76 (m, 1H), 7.62–7.54 (m, 2H), 7.46–7.42 (m, 1H), 3.52 (s, 1H). ^{13}C NMR (75 MHz, CDCl_3): 133.4, 133.0, 131.2, 129.2, 128.2, 126.9, 126.4, 126.0, 125.0, 119.7, 82.0, 81.7.

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Supporting Information Available: Analytical data and copies of spectra for the ligands and the cross-coupling products (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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