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A general and efficient method for the palladium-catalyzed cross-coupling of thiols and secondary phosphines

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Dedicated to Professor Bob Grubbs in recognition of his continuing contributions to organic chemistry and for his mentoring over the years

Abstract—The general and efficient cross-coupling of thiols with aryl halides was developed utilizing $Pd(OAc)_2$/1,1′-bis(diisopropylphosphino)ferrocene as the catalyst. The substrate scope is broad and includes a variety of aryl bromides and chlorides, which can be coupled to aliphatic and aromatic thiols. This catalyst system has the widest substrate scope of any reported to date. The present catalyst system also enables the palladium-catalyzed coupling of secondary phosphines with aryl bromides and chlorides.

1. Introduction

During the past few years, significant progress in palladium-catalyzed methods for the formation of carbon–nitrogen and –oxygen bonds has been achieved.[1] In particular, by the use of bulky and electron-rich monophosphine ligands, not only aryl bromides and iodides but also aryl chlorides can be used as substrates for palladium-catalyzed cross-couplings.[2] In contrast, methods for the analogous formation of carbon–sulfur and –phosphorus bonds have lagged behind. In fact, examples of the coupling of aryl chlorides with sulfur-[3] and phosphorus-based nucleophiles[4] are rare. This may be due to the high coordinating abilities of both the substrates and products. In this paper, we wish to report a general protocol for palladium-catalyzed synthesis of aryl sulfides and tertiary phosphines via cross-coupling protocols. Our method overcomes a number of limitations of previous systems and is the most general system that is available to date.

2. Results and discussion

2.1. Palladium-catalyzed carbon–sulfur bond formation

Despite the early work of Migita,[5] the preparation of aryl sulfides by C–S bond-forming reactions using palladium catalysis has only recently received increased attention. Some success has been realized using bidentate phosphines[6–8] or dialkylphosphine oxides[3] as ligands. These protocols, however, lack generality: electron-rich or sterically-hindered substrates are often problematic.[9] While the nickel-[10] and copper-catalyzed[11] cross-coupling of thiols has been reported, these methods are limited to aryl iodides. Based on our success in related chemistry, we decided to determine whether we could contribute to this area.

In our initial screening experiments, 4-bromoanisole and benzenethiol were used as substrates for discovery of suitable reaction conditions (Fig. 1, series 1). All reagents except for the substrates were stirred together at room temperature for 1 h before the thiol and the aryl bromide were added. If all reaction components were simply mixed together, low conversion to the desired product was observed.[6] As shown, use of DPPF,[6] DPEphos[8] and 1,1′-bis(diisopropylphosphino)ferrocene (DiPPF) as supporting ligand gave the best results. The use of BINAP for this coupling was unsuccessful. This is not unexpected as in previous work on the reaction of aryl triflates with aliphatic thiols using tol-BINAP, the reaction of aromatic thiols were not suitable substrates.[7] We found that inclusion of 10 mol% $PhB(OH)_2$[12] in the reaction mixture with BINAP as ligand allowed the reaction to proceed to full conversion. Thus, it appears that reduction from Pd(II) to Pd(0) is slow when BINAP is used with aromatic thiols. This is consistent with the notion that BINAP is bulkier than DPPF and more rigorously η^2 than DPPF or DPEphos. Our bulky monodentate phosphines were also ineffective under these reaction conditions; inclusion of 10% $PhB(OH)_2$ with these ligands led to ca. 50% yield (GC analysis). Our supposition is that a chelating ligand is necessary to prevent

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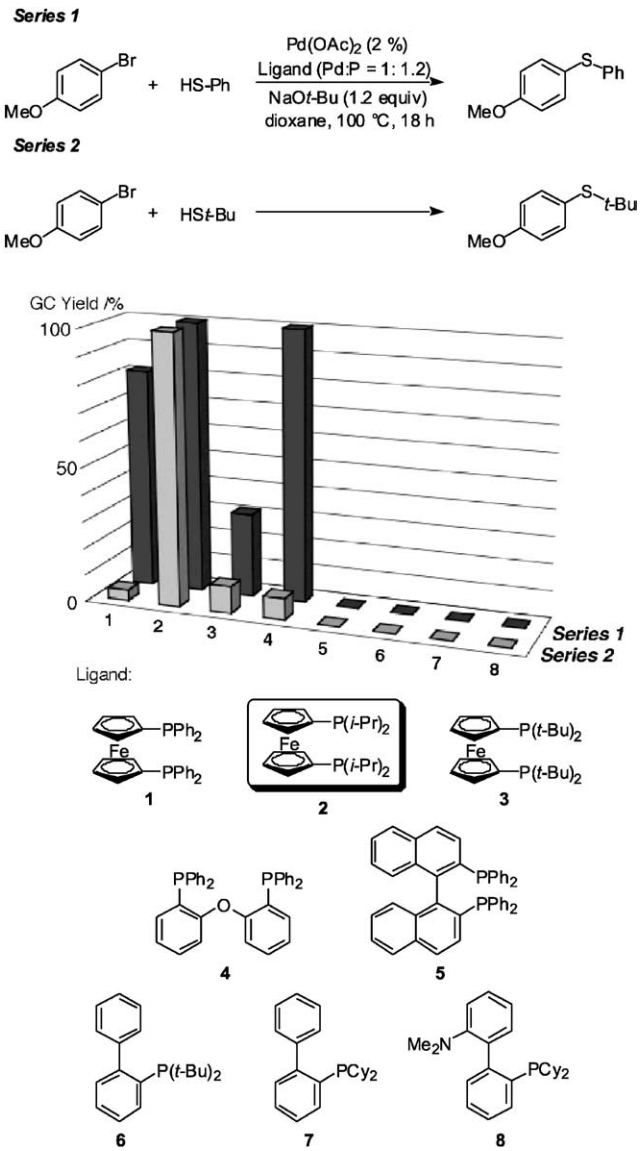


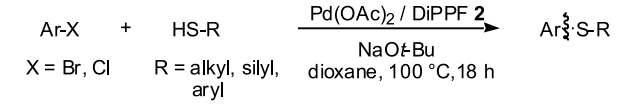
Figure 1. Screen for ligand efficiency in Pd-catalyzed C–S bond-forming reactions. Reaction conditions: ArBr (1.0 mmol), RSH (1.0 mmol), $Pd(OAc)_2$ (2.0 mol%), Ligand (Pd/P=1.0/1.2), *t*-BuONa (1.2 mmol) in dioxane (2 mL) at 60 °C for 18 h.

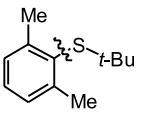
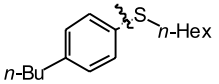
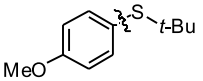
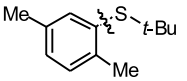
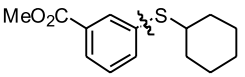
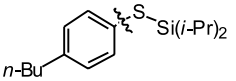
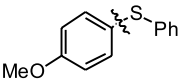
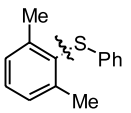
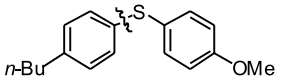
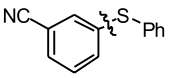
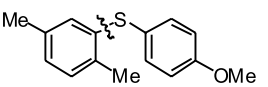
binding of more than one substrate that could lead to catalyst deactivation. It must, however, be of a suitable size or flexibility to allow for reduction of Pd(II) to Pd(0) to occur.

We also examined the reaction of 4-chloroanisole with 2-methyl-2-propanethiol (Fig. 1, series 2). DiPPF proved to be the most effective ligand for the coupling of unactivated aryl chlorides. In this case, DPPF and DPEphos were inefficient, as expected. NaO*t*-Bu proved to be the most generally useful base in these C–S coupling reactions. Tertiary amines were also found to be effective as bases for the reactions of aryl bromides with aliphatic thiols.[6,7] The use of NaO*t*-Bu was essential, however, for the reactions of aromatic thiols.[8] The use of other bases such as Et_3N or Cs_2CO_3 gave no product. Dioxane proved to be the most generally effective solvent, while the use of toluene resulted in slower conversion to product.

The reaction conditions described above were applied to the coupling of a number aryl bromides and chlorides at 100 °C (Table 1). As can be seen, the reactions of both of electron-rich 4-haloanisoles[3,6,7] and di-*ortho*-substituted halides,[8] which were problematic substrates in previous catalyst systems, proceeded in high yield (entries 1, 3, 7 and 8). The present technique tolerated a broad range (in terms of size) of aliphatic thiols, including primary, secondary and tertiary thiols. In addition, commercially available[13] DiPPF provides a general catalyst system for C–S bond formation

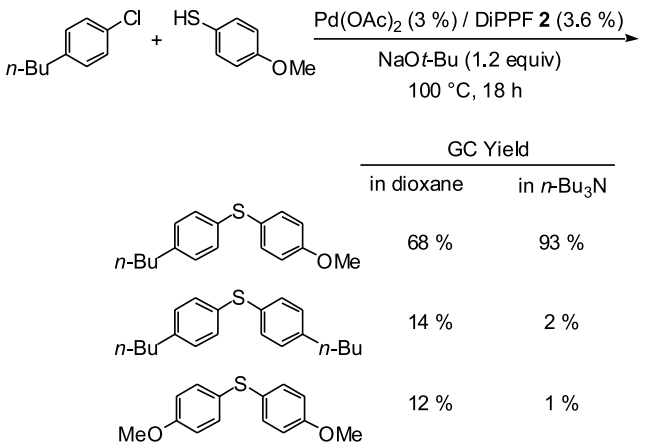
Table 1. Pd-catalyzed C–S bond formation



Entry	Product	X of Ar–X	Yield (%)
1		X=Br	98
2		X=Cl	95
3		X=Cl	99
4		X=Cl	95
5[a]		X=Cl	77
6[b]		X=Cl	85
7		X=Br	93
8		X=Br	95
9[c,d]		X=Cl	89
10		X=Cl	82
11[c,d,e]		X=Cl	91

Reaction conditions: ArX (1.0 mmol), RSH (1.0 mmol), $Pd(OAc)_2$ (2.0 mol%), DiPPF (2.4 mol%), *t*-BuONa (1.2 mmol) in dioxane (2 mL) at 100 °C for 18 h.

[a] 1.02 mmol of *t*-BuONa was used.
[b] The reaction was carried out in toluene (2.0 mL).
[c] In Bu_3N (2.0 mL).
[d] 3.0 mol% of catalyst was used.
[e] At 120 °C.



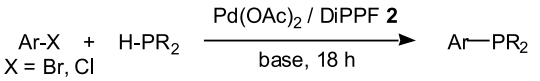
Scheme 1. Coupling of aromatic thiols with aryl chlorides.

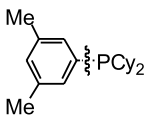
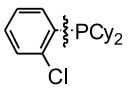
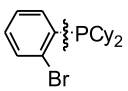
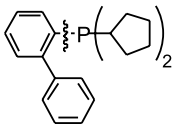
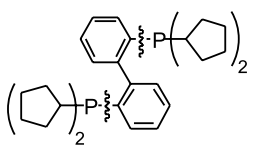
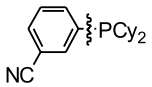
for aryl chlorides substrates, even electron-rich 4-chloroanisole can be processed in excellent yield (entry 3). Several functional groups in the starting aryl halides were tolerated, including a nitrile and a methyl ester (entries 5 and 10). In the case of the methyl ester, it was necessary to use a stoichiometric quantity of base; the use of excess amount of base caused the formation of the *t*-butyl ester as a side product. It was also found that triisopropylsilanethiol, an H_2S surrogate, coupled well under these conditions (entry 6).[14] In contrast to the couplings of aliphatic thiols, the reactions of aryl chlorides with aromatic thiols were initially problematic. Under the standard reaction conditions, the desired product was formed along with symmetrical diarylsulfides. For example, the reaction of 4-*n*-butylchlorobenzene and 4-methoxybenzenethiol in dioxane gave the desired product along with 4-*n*-butylphenyl sulfide and 4-methoxyphenyl sulfide (Scheme 1).[10] Several attempts to alleviate this problem including using lower reaction temperatures, or lower quantities of catalyst, or through the use of toluene as solvent resulted in low conversion to product, although the selectivity of the process was increased. We found, however, aryl–aryl scrambling could be prevented by the use of Bu_3N as a solvent, and the products were obtained in high yields (entries 9 and 10).

2.2. Palladium-catalyzed carbon–phosphorus bond formation

The results presented above suggested to us that bidentate ligands having di(*sec*-alkyl)phosphino groups could be highly efficient as supporting ligands for the coupling of aryl bromides and chlorides in situation in which the nucleophile and/or the product could potentially slow the desired catalytic process. In light of our results in C–S coupling reactions, we proceeded to examine the same catalyst system in carbon–phosphorus bond-forming

Table 2. Pd-catalyzed C–P bond formation



Entry	Product	X of Ar–X	Base	Solvent	Temp. (°C)	Yield (%)
1[a]		X=Br	NaO*t*-Bu	Toluene	80	87
2		X=Br	Cs_2CO_3	Dioxane	80	82
3		X=I	Cs_2CO_3	Dioxane	80	85
4		X=Br	NaO*t*-Bu	Toluene	100	76
5[b]		X=Br	Cs_2CO_3	DMF	120	63
6		X=Cl	Cs_2CO_3	Diglyme	120	75

Reaction condition: ArX (1.0 mmol), R_2PH (1.0 mmol), $Pd(OAc)_2$ (2.0 mol%), DiPPF (2.4 mol%), base (1.2 mmol) in solvent (1 mL) for 18 h.
[a] The reaction was carried out for 6 h.
[b] 0.5 mmol of $ArBr_2$ was used.

reactions (Table 2). The palladium-catalyzed coupling of various phosphorus-based nucleophiles, such as phosphites,[15] phosphine oxides,[16] phosphines,[17] and phosphine–borane complexes,[18] has previously been reported. This has been stimulated by a need to access tertiary phosphines, which are widely used as ligands for transition metal-catalyzed reactions. Secondary phosphines have been employed as coupling partners with transition-metal catalysts based on palladium, nickel[19] or copper complexes.[20] Common protocols, however, have been inefficient for the coupling of aryl bromides,[21] and there has been no report of the coupling of aryl chlorides with secondary phosphines. In addition, previous reports have focused on the reaction of diarylphosphines; the literature on the coupling reactions of dialkylphosphine with aryl halides is sparse.[20a]

The reaction conditions for the C–P coupling was optimized using 5-bromo-*m*-xylene and dicyclohexylphosphine as substrates. Phosphination proceeded in high yield at 80 °C using the $Pd(OAc)_2$/DiPPF catalyst system (Table 2, entry 1). In contrast, DPPF and DtBPF proved ineffective as supporting ligands for this coupling process. NaO*t*-Bu/toluene and Cs_2CO_3/dioxane were found to be effective combinations of base and solvent for C–P coupling reactions, whereas tertiary amines, which were used in the previous studies, were ineffective. The coupling of *ortho*-substituted aryl halides could also be accomplished, although a small amount of reduction product was observed in several reactions (entries 2–5). Chemoselective phosphination of 1,2-dihalobenzenes could be successfully carried out to obtain (2-halophenyl)dialkylbenzenes using Cs_2CO_3 as base (entries 2 and 3). Interestingly, the present reaction was selective for the diphosphination of 2,2′-dibromo-1,1′-biphenyl (entry 5).[22] Although the crude product was contaminated with reduced (2-biphenyl)dicyclopentylphosphine (25% yield), no monophosphinated 2-bromo-2′-dicyclopentylphosphino-1,1′-biphenyl was observed. The coupling of dicyclohexylphosphine with electron-deficient aryl chlorides could be carried out in good yield, although a reaction temperature of 120 °C was required (entry 6). Unfortunately, the reaction of electron-neutral 4-chlorotoluene with dicyclohexylphosphine resulted in only 36% conversion and GC yield of product under these reaction conditions (120 °C). To the best of our knowledge, this is the first example of a palladium-catalyzed cross-coupling reaction of aryl chlorides with secondary phosphines.

3. Conclusion

We have developed a general method for the cross-coupling of thiols with aryl halides using $Pd(OAc)_2$/1,1′-bis(diisopropylphosphino)ferrocene (DiPPF) as the catalyst. The substrate scope is significantly broader than previous methods and includes electron-rich and sterically-hindered aryl halides as well as primary, secondary and tertiary and aromatic thiols. In addition, the present system is efficient for the coupling of thiols with unactivated aryl chlorides. The $Pd(OAc)_2$/DiPPF catalyst system is also effective for the palladium-catalyzed coupling of secondary phosphines with aryl bromides and chlorides.

4. Experimental

4.1. General considerations

$Pd(OAc)_2$ and 1,1′-bis(diisopropylphosphino)ferrocene (DiPPF) were purchased from Strem Chemical Co. and used without further purification. Anhydrous NaO^{t}Bu was purchased from Aldrich and Cs_2CO_3 was purchased from Chemetall; the bulk of the material was stored under nitrogen in a Vacuum Atmospheres glovebox. Small portions (1–2 g) were removed from the glovebox in glass vials, stored in the air, and weighed in the air. Anhydrous dioxane, diglyme, and DMF were purchased from Aldrich in Sure/Seal® bottles and used without further purification. Toluene was purchased from J. T. Baker in CYCLE-TAINER® solvent delivery kegs, which were vigorously purged with argon for 2 h, and further purified by passing the solvent through two packed columns of neutral alumina and copper(II) oxide under argon pressure. All other reagents were purchased from Alfa Aesar or Aldrich or Strem Chemcal Co., and used without further purification. All reactions were carried out under an argon atmosphere in oven-dried glassware. Melting points were obtained on a Mel-Temp capillary melting point apparatus. IR spectra were obtained by placing neat samples directly on the DiComp probe of an ASI REACTIR in situ IR instrument. ^{1}H NMR, ^{13}C NMR and ^{31}P NMR spectra were recorded on a Bruker 400 MHz with chemical shifts reported in ppm relative to the residual deuterated solvent, the internal standard tetramethylsilane, or external 85% H_3PO_4 for ^{31}P. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA. Gas chromatography analyses were performed on a Hewlett Packard 6890 instrument with a FID detector and a Hewlett Packard 25 m×0.2 mm i.d. HP-1 capillary column. Mass spectra (GC-MS) were recorded on a Hewlett Packard model G1800B. Flash chromatography was performed on E.M. Science Kieselgel 60 (230–400 mesh). Yields refer to isolated yields of compounds greater than 95% purity as determined by capillary GC and ^{1}H NMR analysis. Yields reported in Tables 1 and 2 are an average of two independent runs. The procedures described in this section are representative; thus, the yields may differ slightly from those given in Tables. All new compounds were further characterized by elemental analysis.

4.2. General procedure for palladium-catalyzed carbon–sulfur bond formation

$Pd(OAc)_2$ (0.020 mmol), DiPPF (0.024 mmol), NaO^{t}Bu (1.2 mmol) and the aryl halide (1.0 mmol) (if a solid) were added to an oven-dried re-sealable Schlenk tube (Table 1). The tube was evacuated and backfilled with argon (3 cycles) and then charged with dioxane (2.0 mL). The solution was stirred for 1 h at room temperature. Then aryl halide (1.0 mmol) (if a liquid) and the thiol (1.0 mmol) were added by syringe. The Schlenk tube was sealed with a Teflon valve, heated to 100 °C and stirred for 18 h. The reaction mixture was then allowed to reach room temperature. Ether (ca. 3 mL) was added and an aliquot was removed and analyzed by GC. The reaction mixture was then filtered and concentrated. The crude product was purified by flash column chromatography on silica gel to afford the desired thioether.

4.2.1. 2,6-Dimethylphenyl 2-methyl-2-propyl sulfide (entry 1).[23] Following the general procedure, the coupling of 2-bromo-*m*-xylene and 2-methyl-2-propanethiol afforded 191 mg (99% yield) of the title compound as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 9H), 2.58 (s, 6H), 7.12 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 23.3, 31.8, 49.4, 128.1, 128.5, 132.4, 145.4. IR (neat, cm^{-1}) 2962, 1578, 1457, 1362, 1165, 1055. MS (EI) *m/z* (relative intensity) 194 (M^+, 6), 138 (100). Anal. Calcd for $C_{12}H_{18}S$, C: 74.16, H: 9.34. Found C: 74.20, H: 9.41.

4.2.2. 4-Butylphenyl hexyl sulfide (entry 2). Following the general procedure, the coupling of 4-butylchlorobenzene and hexanethiol afforded 236 mg (95% yield) of the title compound as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J=7.0 Hz, 3H), 0.92 (t, J=7.3 Hz, 3H), 1.2–1.7 (m, 12H), 2.57 (t, J=7.6 Hz, 2H), 2.88 (t, J=7.5 Hz, 2H), 7.09 (d, J=8.1 Hz, 2H), 7.25 (d, J=8.1 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 13.9, 13.9, 22.3, 22.5, 28.5, 29.2, 31.4, 33.5, 34.3, 35.1, 128.9, 129.6, 133.5, 140.8. IR (neat, cm^{-1}) 2927, 2858, 1493, 1466, 1092. MS (EI) *m/z* (relative intensity) 250 (M^+, 53), 207 (54), 166 (27), 123 (100). Anal. Calcd for $C_{16}H_{26}S$, C: 76.73, H: 10.46. Found C: 76.73, H: 10.51.

4.2.3. 4-Methoxyphenyl 2-methyl-2-propyl sulfide (entry 3). Following the general procedure, the coupling of 4-chloroanisole and 2-methyl-2-propanethiol afforded 194 mg (99% yield) of the title compound as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 9H), 3.81 (s, 3H), 6.86 (d, J=8.7 Hz, 2H), 7.44 (d, J=8.7 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 31.0, 45.7, 55.5, 114.2, 123.9, 139.1, 160.5. IR (neat, cm^{-1}) 2960, 1590, 1492, 1362, 1285, 1245, 1169, 1102, 1032. MS (EI) *m/z* (relative intensity) 196 (M^+, 11), 140 (100). Anal. Calcd for $C_{11}H_{16}OS$, C: 67.30, H: 8.22. Found C: 66.51, H: 8.27.

4.2.4. 2,5-Dimethylphenyl 2-methyl-2-propyl sulfide (entry 4).[24] Following the general procedure, the coupling of 2-chloro-*p*-xylene and 2-methyl-2-propanethiol afforded 177 mg (91% yield) of the title compound as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 9H), 2.31 (s, 3H), 2.47 (s, 3H), 7.07 (d, J=7.7 Hz, 1H), 7.16 (d, J=7.7 Hz, 1H), 7.35 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 20.9, 21.5, 31.3, 47.3, 129.9, 130.4, 132.0, 135.4, 139.7, 140.8. IR (neat, cm^{-1}) 2962, 1488, 1455, 1362, 1158. MS (EI) *m/z* (relative intensity) 194 (M^+, 11), 138 (100). Anal. Calcd for $C_{12}H_{18}S$, C: 74.16, H: 9.34. Found C: 74.01, H: 9.24.

4.2.5. Methyl 3-(cyclohexylsulfanyl)benzoate (entry 5). Following the general procedure, slightly modified so that a stoichiometric quantity of NaO^{t}Bu (98 mg, 1.02 mmol) was used, the coupling of methyl 3-chlorobenzoate and cyclohexanethiol afforded 263 mg (82% yield) of the title compound as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.2–2.0 (m, 10H), 3.14 (br s, 1H), 3.92 (s, 3H), 7.57 (d, J=7.8 Hz, 1H), 7.88 (d, J=7.8 Hz, 1H), 8.06 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 25.9, 26.2, 33.4, 46.7, 52.5, 127.9, 128.9, 130.9, 132.6, 136.2, 136.3, 166.9. IR (neat, cm^{-1}) 2931, 2854, 1719, 1573, 1436, 1258. MS (EI) *m/z* (relative intensity) 250 (M^+, 22), 168 (100). Anal. Calcd for $C_{14}H_{18}O_2S$, C: 67.16, H: 7.25. Found C: 67.41, H: 7.31.

4.2.6. 4-Butylphenyl triisopropylsilyl sulfide (entry 6). Following the general procedure, slightly modified so that the reaction was carried out in toluene (2 mL), the coupling of 4-butylchlorobenzene and triisopropylsilanethiol afforded 263 mg (82% yield) of the title compound as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J=7.3 Hz, 3H), 1.07 (d, J=7.2 Hz, 18H), 1.1–1.6 (m, 7H), 2.55 (t, J=7.6 Hz, 2H), 7.01 (d, J=8.1 Hz, 2H), 7.39 (d, J=8.1 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 13.1, 13.9, 18.4, 22.2, 33.5, 35.1, 127.7, 128.7, 135.3, 141.6. IR (neat, cm^{-1}) 2944, 2865, 1492, 1461, 1383. MS (EI) *m/z* (relative intensity) 322 (M^+, 17), 279 (100). Anal. Calcd for $C_{19}H_{34}SSi$, C: 70.73, H: 10.62. Found C: 70.51, H: 10.45.

4.2.7. 4-Methoxyphenyl phenyl sulfide (entry 7).[25] Following the general procedure, the coupling of 4-bromoanisole and thiophenol afforded 206 mg (95% yield) of the title compound as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 3.82 (s, 3H), 6.90 (d, J=8.8 Hz, 2H), 7.1–7.3 (m, 5H), 7.42 (d, J=8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 55.7, 115.4, 124.8, 126.2, 128.7, 129.3, 135.7, 139.0, 160.3. IR (neat, cm^{-1}) 3058, 3004, 2941, 2834, 1592, 1492, 1287, 1243, 1171. MS (EI) *m/z* (relative intensity) 216 (M^+, 100), 201 (53). Anal. Calcd for $C_{13}H_{12}OS$, C: 72.19, H: 5.59. Found C: 72.31, H: 5.50.

4.2.8. 2,6-Dimethylphenyl phenyl sulfide (entry 8).[25] Following the general procedure, the coupling of 2-bromo-*m*-xylene and thiophenol afforded 202 mg (94% yield) of the title compound as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 6H), 6.9–7.2 (m, 8H). ^{13}C NMR ($CDCl_3$) δ 22.3, 125.1, 126.1, 128.9, 129.3, 129.7, 131.0, 138.5, 144.3. IR (neat, cm^{-1}) 3058, 2975, 1582, 1476, 1461, 1439, 1376. MS (EI) *m/z* (relative intensity) 214 (M^+, 100), 136 (48). Anal. Calcd for $C_{14}H_{14}S$, C: 78.46, H: 6.58. Found C: 78.34, H: 6.53.

4.2.9. 4-Butylphenyl 4-methoxyphenyl sulfide (entry 9). The coupling reaction of 4-butylchlorobenzene and 4-methoxybenzenethiol was carried out in Bu_3N (2 mL) using $Pd(OAc)_2$ (6.8 mg, 0.030 mmol) and DiPPF (15.0 mg, 0.036 mmol). The reaction mixture was heated to 100 °C, stirred for 18 h, then allowed to reach room temperature. After ether (ca. 6 mL) was added, the resulting mixture was washed with 1 M HCl aq. (3×5 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography to afforded 231 mg (85% yield) of the title compound as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.93 (t, J=7.3 Hz, 3H), 1.3–1.6 (m, 4H), 2.55 (t, J=7.8 Hz, 2H), 3.80 (s, 3H), 6.87 (d, J=8.9 Hz, 2H), 7.06 (d, J=8.3 Hz, 2H), 7.13 (d, J=8.3 Hz, 2H), 7.37 (d, J=8.9 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 13.9, 22.3, 33.5, 35.1, 55.3, 114.9, 125.5, 129.1, 129.2, 134.4, 134.6, 141.1, 159.5. IR (neat, cm^{-1}) 2929, 2858, 1592, 1492, 1287, 1245, 1171. MS (EI) *m/z* (relative intensity) 272 (M^+, 62), 229 (100). Anal. Calcd for $C_{17}H_{20}OS$, C: 74.96, H: 7.40. Found C: 74.67, H: 7.31.

4.2.10. 3-Cyanophenyl phenyl sulfide (entry 10).[26] Following the above procedure, slightly modified so that the reaction was carried out at 100 °C using $Pd(OAc)_2$ (0.020 mmol) and DiPPF (0.024 mmol), the coupling of 3-chlorobenzonitrile and thiophenol afforded 162 mg (77% yield) of the title compound as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.3–7.5 (m). ^{13}C NMR ($CDCl_3$) δ 113.3, 118.2,

128.8, 129.5, 129.5, 129.8, 131.6, 132.2, 132.8, 133.3, 140.0. IR (neat, cm^{-1}) 3060, 2231, 1567, 1474, 1439, 1405. MS (EI) *m/z* (relative intensity) 211 (M^+, 100), 184 (16). Anal. Calcd for $C_{13}H_9NS$, C: 73.90, H: 4.29. Found C: 73.77, H: 4.26.

4.2.11. 2,5-Dimethylphenyl 4-methoxyphenyl sulfide (entry 11). Following the above procedure, slightly modified so that the reaction was carried out at 120 °C, the coupling of 2-chloro-*p*-xylene and 4-methoxybenzenethiol afforded 225 mg (92% yield) of the title compound as a colorless oil. ^1H NMR ($CDCl_3$) δ 2.20 (s, 3H), 2.32 (s, 3H), 3.79 (s, 3H), 6.8–6.9 (m, 4H), 7.06 (d, J=7.6 Hz, 1H), 7.29 (d, J=8.7 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 19.8, 20.9, 55.3, 114.9, 125.1, 127.3, 130.1, 130.4, 133.9, 134.5, 136.1, 136.1, 159.3. IR (neat, cm^{-1}) 2964, 2834, 1592, 1492, 1287, 1243, 1173. MS (EI) *m/z* (relative intensity) 244 (M+, 100), 229 (17), 136 (49). Anal. Calcd for $C_{15}H_{16}OS$, C: 73.73, H: 6.60. Found C: 73.78, H: 6.61.

4.3. General procedure for palladium-catalyzed carbon–phosphorus bond formation

$Pd(OAc)_2$ (4.5 mg, 0.020 mmol), DiPPF (10.0 mg, 0.024 mmol), base (1.2 mmol) and the aryl halide (1.0 mmol) (if a solid) were added to an oven-dried resealable Schlenk tube (Table 2). The Schlenk tube was evacuated and backfilled with argon (3 cycles) and then charged with solvent (1.0 mL). The solution was stirred for 1 h at room temperature. Then aryl halide (1.0 mmol) (if liquid) and the secondary phosphine (1.0 mmol) were added by syringe. The Schlenk tube was sealed with a Teflon valve, heated and stirred for 18 h. The reaction mixture was then allowed to reach room temperature. Ether (ca. 3 mL) was added and the aliquot was analyzed by GC. The reaction mixture was then filtered and concentrated. The crude product was purified by flash column chromatography on silica gel to afford the desired tertiary phosphine.

4.3.1. Dicyclohexyl(3,5-dimethylphenyl)phosphine (entry 1). Following the general procedure, the coupling of 5-bromo-*m*-xylene and dicyclohexylphosphine was carried out in toluene (1 mL) at 80 °C for 6 h using NaO^{t}Bu (115 mg, 1.2 mmol) as a base to afford 255 mg (84% yield) of the title compound as a white solid, mp 77–78 °C. ^1H NMR (C_6D_6) δ 1.0–2.0 (m, 22H), 2.16 (s, 1H), 6.82 (s, 1H), 7.34 (d, J=7.1 Hz, 2H). ^{13}C NMR (C_6D_6) δ 21.7, 27.2, 27.8 (d, J=7 Hz), 27.9 (d, J=12 Hz), 29.8 (d, J=8 Hz), 31.1 (d, J=17 Hz), 33.7 (d, J=14 Hz), 131.3, 133.4 (d, J=20 Hz), 135.9 (d, J=19 Hz), 137.7 (d, J=7 Hz). ^{31}P NMR (C_6D_6) δ 3.62. IR (neat, cm^{-1}) 2921, 2848. MS (EI) *m/z* (relative intensity) 302 (M^+, 26), 247 (23), 220 (95). Anal. Calcd for $C_{20}H_{31}P$, C: 79.43, H: 10.33. Found C: 79.29, H: 10.43.

4.3.2. (2-Chlorophenyl)dicyclohexylphosphine (entry 2). Following the general procedure, the coupling of 2-chlorobromobenzene and dicyclohexylphosphine was carried out in dioxane at 80 °C using Cs_2CO_3 as a base to afford 259 mg (84% yield) of the title compound as a white solid, mp 82–83 °C. ^1H NMR (C_6D_6) δ 1.0–2.0 (m, 22H), 6.82 (t, J=7.6 Hz, 1H), 6.91 (t, J=7.4 Hz, 1H), 7.2–7.4 (m, 2H). ^{13}C NMR (C_6D_6) δ 26.8, 27.5 (d, J=8 Hz), 27.6 (d, J=12 Hz), 29.7 (d, J=7 Hz), 30.9 (d, J=18 Hz), 34.2 (d, J=16 Hz), 126.2, 130.0, 130.4, 134.9, 135.7 (d, J=25 Hz), 142.8 (d, J=26 Hz). ^{31}P NMR (C_6D_6) δ −4.75. IR (neat, cm^{-1}) 2921, 2848, 1418, 1034. MS (EI) *m/z* (relative intensity) 308 (M^+, 10), 273 (100). Anal. Calcd for $C_{18}H_{26}ClP$, C: 70.00, H: 8.49. Found C: 69.85, H: 8.62.

4.3.3. (2-Bromophenyl)dicyclohexylphosphine (entry 3). Following the general procedure, the coupling of 2-bromoiodobenzene and dicyclohexylphosphine was carried out in dioxane (1 mL) at 80 °C for 18 h using Cs_2CO_3 (391 mg, 1.2 mmol) as a base to afford 300 mg (85% yield) of the title compound as a white solid, mp 76–77 °C. ^1H NMR (C_6D_6) δ 1.0–2.0 (m, 22H), 6.73 (t, J=7.7 Hz, 1H), 6.95 (t, J=7.4 Hz, 1H), 7.24 (d, J=7.6 Hz, 1H), 7.49 (dd, J=8.0, 3.1 Hz, 1H). ^{13}C NMR (C_6D_6) δ 27.0, 27.7 (d, J=8 Hz), 27.8 (d, J=12 Hz), 29.9 (d, J=10 Hz), 31.0 (d, J=17 Hz), 35.0 (d, J=17 Hz), 127.0, 130.5, 134.1 (d, J=3 Hz), 134.5 (d, J=30 Hz), 134.9, 138.1 (d, J=23 Hz). ^{31}P NMR (C_6D_6) δ 2.26. IR (neat, cm^{-1}) 2919, 2848, 1019. MS (EI) *m/z* (relative intensity) 354 (M^+, 6), 352 (M^+, 6), 273 (100). Anal. Calcd for $C_{18}H_{26}BrP$, C: 61.20, H: 7.42. Found C: 60.97, H: 7.40.

4.3.4. 2-(Dicyclopentylphosphino)biphenyl (entry 4). Following the general procedure, the coupling of 2-bromobiphenyl and dicyclopentylphosphine was carried out in toluene at 100 °C using NaO^{t}Bu as a base to afford 265 mg (83% yield) of the title compound as a white solid, mp 88–89 °C. ^1H NMR (C_6D_6) δ 1.3–2.2 (m, 18H), 7.2–7.4 (m, 6H), 7.48 (d, J=8.1 Hz, 2H), 7.55 (d, J=8.1 Hz, 1H). ^{13}C NMR (C_6D_6) δ 26.3 (d, J=7 Hz), 27.3 (d, J=8 Hz), 32.0 (d, J=24 Hz), 32.2 (d, J=15 Hz), 40.0 (d, J=14 Hz), 127.2, 127.7, 128.8, 130.7 (d, J=5 Hz), 131.7 (d, J=4 Hz), 132.9 (d, J=3 Hz), 139.1 (d, J=20 Hz), 143.7 (d, J=6 Hz), 150.4 (d, J=28 Hz). ^{31}P NMR (C_6D_6) δ −12.42. IR (neat, cm^{-1}) 2944, 2863, 1463. MS (EI) *m/z* (relative intensity) 321 (M^+, 97), 253 (20), 183 (100). Anal. Calcd for $C_{22}H_{27}P$, C: 81.95, H: 8.44. Found C: 81.90, H: 8.49.

4.3.5. 2,2′-Bis(dicyclopentylphosphino)-1,1′-biphenyl (entry 5). Following the general procedure, the coupling of 2,2′-dibromo-1,1′-biphenyl (0.5 mmol) and dicyclopentylphosphine (1.0 mmol) was carried out in DMF (1 mL) at 120 °C using Cs_2CO_3 (1.2 mmol) as a base. Additional recrystallization from methanol/CH_2Cl_2 was required to provide the analytically pure product, afforded 159 mg (65% yield) of the title compound as a white solid, mp 158–159 °C. ^1H NMR (C_6D_6) δ 1.3–2.2 (m, 36H), 7.3–7.4 (m, 6H), 7.61 (d, J=6.7 Hz, 2H). ^{13}C NMR (C_6D_6) δ 26.1 (t, J=4 Hz), 26.7 (t, J=4 Hz), 26.9 (t, J=3 Hz), 28.1 (t, J=4 Hz), 31.7 (t, J=9 Hz), 32.0 (t, J=7 Hz), 32.4 (t, J=11 Hz), 32.8 (t, J=14 Hz), 37.5 (dd, J=8, 5 Hz), 43.0 (dd, J=8, 5 Hz), 127.4, 127.8, 132.3 (t, J=4 Hz), 132.6, 139.3 (dd, J=10, 6 Hz), 150.1 (t, J=18 Hz). ^{31}P NMR (C_6D_6) δ −13.01. IR (neat, cm^{-1}) 2948, 2863, 1426. Anal. Calcd for $C_{32}H_{44}P$, C: 78.34, H: 9.04. Found C: 78.51, H: 8.99.

4.3.6. 3-(Dicyclohexylphosphino)benzonitrile (entry 6). Following the general procedure, the coupling of 3-chlorobenzonitrile and dicyclohexylphosphine was carried out in diglyme (1 mL) at 120 °C for 18 h using Cs_2CO_3 as a base to afford 210 mg (70% yield) of the title compound as a white solid, mp 77–78 °C. ^1H NMR (C_6D_6) δ 0.9–1.8 (m, 22H),

6.72 (t, J=7.7 Hz, 1H), 7.00 (d, J=7.7 Hz, 1H), 7.36 (t, J=6.5 Hz, 1H), 7.68 (t, J=5.2 Hz, 1H). ^{13}C NMR (C_6D_6) δ 26.9, 27.4 (d, J=7 Hz), 27.6 (d, J=12 Hz), 29.5 (d, J=8 Hz), 30.6 (d, J=17 Hz), 33.1 (d, J=14 Hz), 113.4 (d, J=7 Hz), 119.2, 128.8 (d, J=7 Hz), 132.5, 138.1 (d, J=19 Hz), 138.4 (d, J=26 Hz), 139.3 (d, J=21 Hz). ^{31}P NMR (C_6D_6) δ 4.28. IR (neat, cm^{-1}) 2923, 2850. MS (EI) m/z (relative intensity) 299 (M^+, 19), 244 (17), 217 (79). Anal. Calcd for $C_{19}H_{26}NP$, C: 76.22, H: 8.75. Found C: 75.98, H: 8.70.

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