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Air-Stable Phosphine Sulfide Ligand Precursors for Nickel-Catalyzed Cross-Coupling Reactions of Unactivated Aryl Chlorides with Aryl Grignard Reagents

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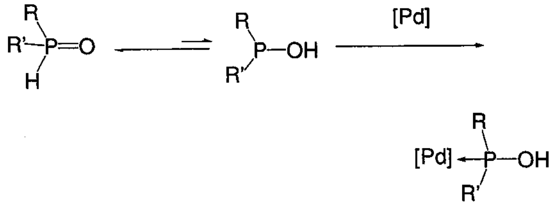
Summary: The air-stable phosphine sulfide [(^{t}Bu)$_2$P(S)H] serves as a ligand precursor for the efficient nickel-catalyzed cross-coupling reactions of a variety of unactivated aryl chlorides with aryl Grignard reagents (Kumada−Tamao−Corriu reaction) at room temperature to yield the corresponding biaryls with isolated product yields ranging from 79 to 97%.

Carbon−carbon bond-forming processes are of fundamental importance in organic synthesis, and the efficient cross-coupling reactions of aryl halides and arylmagnesium halides are extremely versatile and powerful approaches for the construction of a variety of biaryl compounds.[1] Recently, a number of promising catalytic systems spurred innovation in new and efficient catalysts for using both more readily available and less expensive aryl chlorides as starting materials.[2,3] As part of our ongoing efforts to apply combinatorial approaches for the discovery of new materials and catalysts,[4,5] we reported the discovery of air-stable phosphine oxide [$R_2P(O)H$] ligand precursors, for a variety of transition-metal-catalyzed cross-coupling reactions of unactivated aryl chlorides.[6] All these reactions proceeded via novel metal−phosphinous acid compounds,[7] which can be deprotonated in the presence of base to generate anionic species as catalysts for Cl−C bond activation of aryl chlorides (eq 1).



(1)

These results pose an interesting situation for the analogous phosphine sulfides [$R_2P(S)H$]: that the tautomerization results in phosphinothious acid ($R_2P{-}SH$). Herein, we report our preliminary results on the first phosphine sulfide that replacement of the phosphine oxides with air-stable phosphine sulfides provides a new-type ligand precursor for the C−C bond-forming reactions of aryl chlorides with aryl Grignard reagents in high yields at ambient temperature.

The ligand precursor used for cross-coupling reactions was straightforwardly synthesized by reaction of (t-Bu)$_2$PH with S_8 in benzene[8] and characterized by X-ray crystallography (see the Supporting Information for full details), and an ORTEP view is shown in Figure 1.[9]

The precatalysts were generated in situ by treating Ni(COD)$_2$ with phosphine sulfides [(t-Bu)$_2$PS(H)] in THF at room temperature. The catalytic cross-coupling reactions were carried out in organic solvents (e.g. THF,

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(6) (a) Li, G. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1513−1516. (b) Li, G. Y.; Zheng, G.; Noonan, A. F. *J. Org. Chem.* **2001**, *66* (25), 8677−8681. (c) Li, G. Y. *J. Organomet. Chem.* (Special Issue on Cross-Coupling Reaction), in press.

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(9) Crystallographic data for di-*tert*-butylphosphine sulfide: orthorhombic, $Pna2_1$, $a = 15.7278(16)$ Å, $b = 8.6445(9)$ Å, $c = 7.7953(8)$ Å, $V = 1059.84(19)$ Å^3, $Z = 4$, $T = -100$ °C, formula weight 178.26, density 1.117 mg/m^3, μ(Mo Kα) = 0.40 mm^{-1}, data collected using a Bruker Smart 1K CCD system (Mo Kα radiation), with SAINT integration and SADABS correction applied, structure solved by direct methods and refined using full-matrix least squares on F^2 (SHELXTL), 2247 unique data with $5.18° < 2\theta < 56.58°$, 101 parameters, R indices (all data) $R1 = 0.026$, $wR2 = 0.064$, GOF = 1.04, refined Flack parameter −0.07-(8), maximum difference peak and hole 0.196 and −0.151 e/Å^3. All of the methyl hydrogen atoms have been idealized using a riding model. H1 is fully refined.

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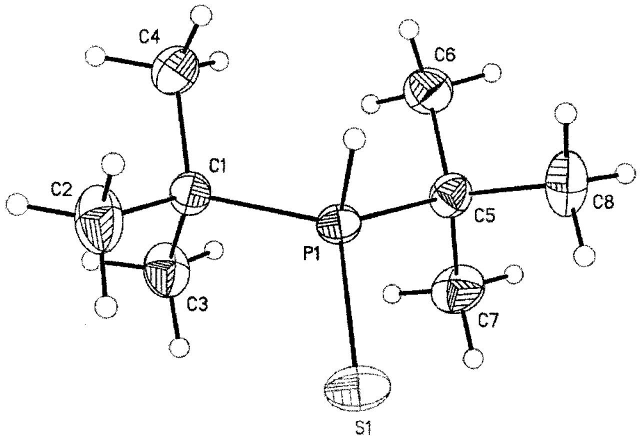
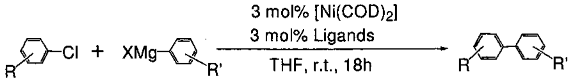
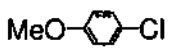
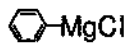
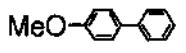
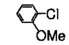
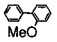
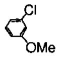
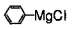
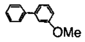
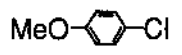
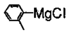
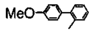
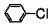
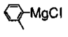
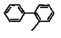
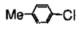
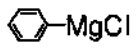
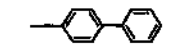
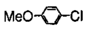
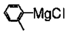
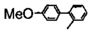
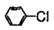
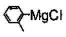
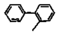


Figure 1. ORTEP view (50% probability) of di-*tert*-butylphosphine sulfide. Selected interatomic distances (Å) and angles (deg) are as follows: P(1)−C(1) = 1.8599(15), P(1)−C(5) = 1.8601(15), P(1)−S(1) = 1.9666(6); C(1)−P(1)−C(5) = 116.21(7), C(1)−P(1)−S(1) = 113.12(5), C(5)−P(1)−S(1) = 112.03(5), C(4)−C(1)−P(1) = 112.25(10), C(3)−C(1)−P(1) = 111.23(10), C(2)−C(1)−P(1) = 105.17(11), C(6)−C(5)−P(1) = 112.11(10), C(7)−C(5)−P(1) = 110.77(11), C(8)−C(5)−P(1) = 104.63(11).

Table 1. Nickel/Phosphine SulfIde Catalyzed Cross-Coupling Results of Aryl Chlorides with RMgX[a]



Entry	Aryl Halide	Aryl Grignard Reagent	Ligand	Product	Yield (%) (Isolated)
1			$(t\text{-Bu})_2P(S)H$		**96**
2			$(t\text{-Bu})_2P(S)H$		**89**
3			$(t\text{-Bu})_2P(S)H$		**82**
4			$(t\text{-Bu})_2P(S)H$		**79**
5			$(t\text{-Bu})_2P(S)H$		**80**
6			$(t\text{-Bu})_2P(S)H$		**97**
7			$(t\text{-Bu})_2P(O)H$		**93**[6]
8			$(t\text{-Bu})_2P(O)H$		**96**[6]

[a] General reaction conditions (not optimized): 1.0 equiv of aryl chloride, 1.5 equiv of RMgX, THF, room temperature. Grignard reagents and aryl chlorides were used as received.

Et_2O, dioxane) under anhydrous/anaerobic conditions (catalyst loading 3 mol %). Isolated yields in Table 1 refer to products isolated by column chromatography. Known products were identified by comparison with literature data and/or with those of authentic samples. New compounds were characterized by 1-D and 2-D ^1H/^{13}C NMR, HRMS, or elemental analysis.[10]

It can be seen that $Ni(COD)_2/RR'P(S)H$ precatalysts were capable of catalyzing the cross-coupling reactions of a variety of aryl chlorides and aryl Grignard reagents at room temperature to yield the desired biaryls in high isolated yields. Entries 1−4 illustrate that a variety of electron-rich chloroanisoles could be coupled with aryl Grignard reagents quantitatively. Entries 2 and 3 demonstrate that the more sterically demanding and electron-rich substrates 2-chloroanisole and 3-chloroanisole were both coupled with phenyl Grignard reagents to yield 2-phenylanisole (entry 2) and 3-phenylanisole (entry 3). Entries 4 and 5 illustrate that bulky Grignard reagents are effective coupling groups with aryl chlorides, yielding 4-(2-tolyl)anisole and 2-phenyltoluene.

A number of aspects of the present phosphine sulfide ligand precursors are noteworthy and offer both informative parallels and contrasts to the corresponding phosphine ligands[2a] and phosphinous acid ligands[5,6] in the cross-coupling reactions of aryl chlorides. The present process is capable of using air-stable phosphine sulfides [RR′P(S)H] as ligand precursors for Ni-catalyzed cross-coupling reactions of aryl chlorides and Grignard reagents (Kumada−Tamao−Corriu coupling reaction) at room temperature, and all the cross-coupling results are comparable with those from the corresponding phosphinous acid ligands under the same reaction conditions (entries 7 and 8). It was well-known in many cases that organic sulfur compounds strongly bind to the transition metals through M−S bonds, thus poisoning them and making catalytic reactions ineffective.[11] However, the phosphinothious acid ($R_2P{-}SH$) derived from tautomerization of phosphine sulfides can be tolerated in the present catalytic processes.

In conclusion, we have shown for the first time that air-stable phosphine sulfides (RR′P(S)H) are ideal ligand precursors for the activation of C−Cl bonds of unactivated aryl chlorides in the presence of bases and that such processes can be incorporated into efficient catalytic cycles for C−C bond-forming processes. Of note are the efficiency for unactivated aryl chlorides and the simplicity, low cost, air stability, and ready accessibility for these ligand precursors. Additional applications of these air-stable phosphine sulfide ligand precursors for catalysis are currently under investigation.

Acknowledgment. We thank Dr. Paul J. Fagan and Dr. Patricia L. Watson for helpful discussions.

Supporting Information Available: Tables of atomic coordinates, anisotropic thermal parameters, and crystal data and data collection and refinement details and text giving details of the syntheses of compounds noted in this paper and characterization data. Ordering information is given on any current masthead page.

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(10) Typical experimental procedure: in the drybox, 54.0 mg (0.303 mm) of $(Me_3C)_2PH(S)$, 83.4 mg (0.303 mm) of $Ni(COD)_2$, and 10.0 mL of THF were loaded into a reactor (20 mL) equipped with a magnetic stir bar. The resulting mixture was stirred at room temperature over a period of 10 min. After addition of 1.43 g (10.0 mm) of 4-chloroanisole, the resulting mixture was stirred for 5 min until the catalytic reaction was initiated by dropwise addition of 7.5 mL (15.0 mm, 2.0 M in THF) of phenylmagnesium chloride at room temperature over a period of 5 min. The resulting mixture was stirred at room temperature for 18 h before the reaction was quenched with 50 mL of H_2O and extracted with 400 mL of diethyl ether. The organic extracts were washed with H_2O (2 × 50 mL) and brine (50 mL), dried over $MgSO_4$, and filtered, and the ether and THF removed from the filtrate by rotary evaporation. The resulting residue was chromatographed on silica gel using hexane as eluant. The eluate was concentrated by rotary evaporation followed by high vacuum to yield 1.77 g (96% yield) of 4-phenylanisole. It was >95% pure by ^1H NMR and GC/MS. ^1H NMR (500 MHz, $CDCl_3$): δ 7.45 (m, 4H), 7.32 (m, 2H), 7.21 (m, 1H), 6.88 (d, J = 8.72 Hz, 2H), 3.74 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 140.8, 133.8, 128.7, 128.1, 126.7, 126.6, 114.2, 55.3 ppm. HRMS: calcd for $C_{13}H_{12}O$, 185.0966; found, 185.0968. Anal. Calcd for $C_{13}H_{12}O$: C, 84.75; H, 6.57; O, 8.68. Found: C, 84.81; H, 6.65; O, 8.62.

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