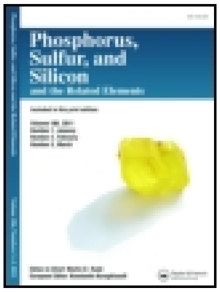

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A MILD AND EFFICIENT CsOH-PROMOTED SYNTHESIS OF DITERTIARY PHOSPHINES

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A MILD AND EFFICIENT CsOH-PROMOTED SYNTHESIS OF DITERTIARY PHOSPHINES

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A mild and efficient method for the synthesis of ditertiary phosphines has been developed. In the presence of cesium hydroxide, molecular sieves, and DMF, various dihalides were coupled with diphenylphosphine at room temperature, and the results have demonstrated that this methodology offers a general synthetic procedure producing a variety of ditertiary phosphines in high yields.

Keywords: Alkylation; cesium hydroxide; ditertiary phosphines; ligand

Ditertiary phosphine ligands have been shown to have excellent metal complexation properties.[1,2] These complexes have a wide variety of uses, serving as antitumor agents,[3] oxygen transfer reagents,[4] catalysts for homogenous hydrogenation,[5] and applications in thin-film electronic device manufacture.[6] In addition, these ligands can be used in the extraction of rare earths, uranium, and transuranium elements.[6] As useful as these complexes are, the starting phosphine chelating agents are notoriously difficult to prepare employing mild reaction conditions. Traditional synthetic methods for ditertiary phosphines involve multistep reactions, free-radical catalysis, or the use of alkali metal phosphides in liquid ammonia, THF, or dioxanes, often at elevated temperatures.[7–9] Moreover, many of these protocols suffer from several disadvantages, such as significant, if not exclusive, oxidation of the phosphine, cumbersome reaction procedures, poor product yields, and the use of phosphorus protecting groups.[10–13] Therefore, we have embarked on the search for a convenient and mild reaction procedure better suited for

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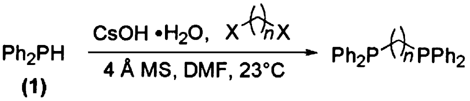
the synthesis of phosphine macrocycles and their congeners. As part of these current investigations, we have discovered a new, mild and efficient way to prepare tertiary phosphines using cesium hydroxide (Scheme 1). Application of this novel method to the facile synthesis of ditertiary phosphines at ambient temperature, while employing easy reaction procedures is reported here.

SCHEME 1 Tertiary phosphine synthesis.

RESULTS AND DISCUSSION

The "cesium effect"[14–16] has been well utilized in the alkylation of amines[17–20] and alcohols,[21–23] but to our knowledge there are no reports regarding the alkylations of phosphines using cesium bases. Given its utility in similar reactions, we decided to explore this methodology in P-alkylation, and its applications toward the synthesis of ditertiary phosphines. At the outset of this study LiOH, NaOH, KOH, CsOH, and RbOH, as well as organic bases including triethylamine (TEA) and 1,8-diazobicycloundec-7-ene (DBU) were screened. The use of cesium hydroxide gave excellent yields, while the other bases failed, giving rise to either no product or poor yields (Scheme 1).[24] Thus, CsOH was determined to be the base of choice. Furthermore, the choice of reaction solvent was also determined to be crucial. Therefore, we examined the reaction in several different solvents. We found that anhydrous DMF was the solvent of choice, although NMP, DMAC, acetonitrile, and DMSO also were screened, but did not give successful results. Moreover, water also proved to be problematic. When dry, powdered, activated 4 Å molecular sieves were added to the reaction vessel to sequester any water, the reaction proceeded smoothly, resulting in high product yields. However, in the absence of molecular sieves, the reaction was sluggish and resulted in the predominant recovery of the starting phosphine. All reactions were performed under a nitrogen atmosphere to prevent oxidation.

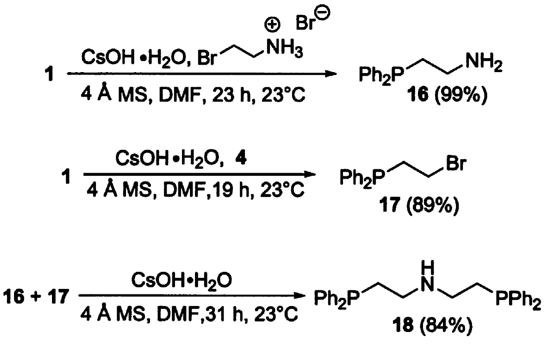
Given our success with P-alkylations using this CsOH procedure,[24] we decided to apply this protocol toward the synthesis of various ditertiary phosphines. Several ditertiary phosphine ligands were prepared using these new conditions (Scheme 2). Diphenylphosphine (2 equiv.)



SCHEME 2 Synthesis of ditertiary phosphines.

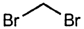
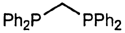
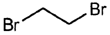
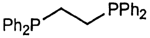
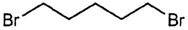
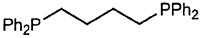
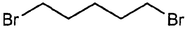
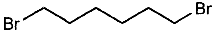
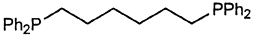
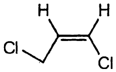
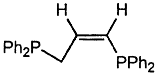
was reacted with various dihalides (1 equiv.) to give the corresponding products (Table I). For example, when diphenylphosphine (**1**) was reacted with dibromomethane (**2**), ditertiary phosphine **3** formed in excellent yield (95%) after 16 h (entry 1). Increasing the length of the carbon chain of the dihalide was also quite successful and resulted in high product yields. For instance, 1,2-dibromoethane (**4**) generated dppe (**5**) in outstanding yield (entry 2). Likewise, 1,3-dibromopropane (**6**) and 1,4-dibromobutane (**8**) also produced the desired phosphine products, 1,3-dppp (**7**) and 1,4-dppb (**9**), respectively in excellent yields (entries 3–4). Similarly, when 1,5-dibromopentane (**10**) and 1,6-dibromohexane (**12**) were used, the reaction time had to be increased to 72 h, and yields were slightly less, though still very good (entries 5–6). To further assess the generality of this protocol, *cis*-1,3-dichloropropene (**14**), a dihalide containing a double bond, also reacted efficiently (entry 7). All of the ligands were formed without appreciable side products under these mild and effective conditions.

To further probe the feasibility of these conditions, we decided to investigate other chelating moieties embedded into these phosphine substrates. Toward this end, we have synthesized a ditertiary phosphine product containing a secondary amine, a P-N-P ligand, as shown in Scheme 3. The product was formed in good yield, and protection of the primary amine proved unnecessary, further emphasizing the high chemoselectivity of the "cesium effect." Both parts of the ligand



SCHEME 3 Synthesis of a P-N-P ligand.

TABLE I Synthesis of Ditertiary Phosphines

Entry	Dihalide		Diphosphine		Reaction time (h)	Yield (%)[a,b]
1		(**2**)		(**3**)	16	95
2		(**4**)		(**5**)	36	78
3		(**6**)		(**7**)	45	83
4		(**8**)		(**9**)	47	87
5		(**10**)		(**11**)	72	63
6		(**12**)		(**13**)	72	69
7		(**14**)		(**15**)	48	91

[a] Refers to yield of isolated product.

[b] All products were identified by comparison of their physical and spectroscopic data with those of authentic samples.

subsequently were formed using the aforementioned protocol, as well as the final coupling. The overall yield for the formation of the P-N-P ligand, **18** was 84%.

In conclusion, we have developed a mild and convenient synthetic method for the synthesis of ditertiary phosphine ligands using a secondary phosphine and a dihalide in the presence of cesium hydroxide, 4 Å molecular sieves and DMF. This new method is simple, effective, and circumvents many of the problems seen using traditional procedures. Furthermore, our mild reaction conditions were compatible with numerous substrates and avoid the use of unnecessary protecting groups.

EXPERIMENTAL

All substrates and solvents were commercially available and used without further purification. All reactions were run under a dry inert atmosphere with scrupulously dried glassware, and molecular sieves were activated by drying in a 120°C oven for 24 h prior to use. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a JEOL 270 MHz NMR spectrometer, using TMS as an internal reference ($\delta = 0.00$ ppm). The appropriate precautions in handling moisture and/or air-sensitive compounds were observed. Elemental analysis was performed by the Materials Characterization Center at Western Kentucky University.

General Procedure for Preparation of Ditertiary Phosphines

Under a dry nitrogen atmosphere, 4 Å powdered molecular sieves (1 g) were added to a flame dried round bottom flask containing anhydrous DMF (12 mL). 2 equiv. of CsOH (2.30 mmol) were added to the flask, and stirred for 10 min. 2 equiv. of Ph_2PH (2.30 mmol) were added, and the dark orange solution was subsequently stirred for 1 h. 1 equiv. of the dihalide (1.15 mmol) was added, and the reaction was stirred for the time listed in Table I for each entry. The progress of the reaction was monitored by TLC. After the completion of the reaction, the product was extracted with methylene chloride (3 × 50 mL) and degassed water made slightly basic with CsOH (20 mL). The organic layers were combined, washed with basic degassed water (5 × 50 mL), and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by recrystallization from benzene afforded the respective products (Table I, entries 1–7).

1-Amino-(2-diphenylphosphino)ethane (16)

Under a dry nitrogen atmosphere, 4 Å powdered molecular sieves (500 mg) were added to a flame dried round bottom flask containing 13 mL of anhydrous DMF. CsOH (2.5 mmol) was added, and the mixture was stirred for 10 min. Ph_2PH (1.15 mmol) was added via syringe, and the reaction was subsequently stirred for 1 h. 2-Bromoethylamine HBr (1.38 mmol) was added, and the reaction was stirred for 23 h until **1** was consumed. The product was extracted with methylene chloride (3 × 50 mL), followed by degassed water made slightly basic with CsOH (20 mL). The methylene chloride layers were combined, washed with the basic degassed water (5 × 50 mL), dried over anhydrous sodium sulfate, decanted, and the solvent was subsequently removed in vacuo. The crude product was purified by flash column chromatography (neutral alumina), using ethyl acetate: methanol (1:1) to afford **16** as a pale yellow oil in 99% yield.

1-Bromo-(2-diphenylphosphino)ethane (17)

Under a nitrogen atmosphere, 4 Å powdered molecular sieves (500 mg) were added to a flame dried round bottom flask containing 6 mL of anhydrous DMF. CsOH (1.15 mmol) was added, and the reaction was stirred for 10 min. Ph_2PH (1.15 mmol) was added, and the reaction was stirred for 1 h. 1,2-Dibromoethane (1.38 mmol) was added dropwise, and the reaction was stirred for 19 h. The product was extracted with methylene chloride (3 × 50 mL), followed by degassed water made slightly basic with CsOH (20 mL). The organic layers were combined, washed with basic degassed water (5 × 50 mL), and dried over anhydrous sodium sulfate. The organic solvent was removed and the crude product was recrystallized from benzene to afford a white crystalline product in 89% yield.

P-N-P Ligand (18)

Under a nitrogen atmosphere, 4 Å powdered molecular sieves (500 mg) were added to a flame dried round bottom flask containing 6 mL anhydrous DMF. CsOH (1.15 mmol) was added, and the reaction was stirred for 10 minutes. 1-Amino-(2-diphenylphosphino)ethane (**16**) (1.15 mmol) was added, and the reaction was stirred for 1 h. 1-Bromo-(2-diphenylphosphino)ethane (**17**) (1.15 mmol) was subsequently added and the reaction was stirred for an additional 31 h. The product was extracted with methylene chloride (3 × 50 mL), followed by degassed water made slightly basic with CsOH (20 mL). The combined organic layers were washed with basic degassed water (5 × 50 mL), dried over anhydrous sodium sulfate, and the solvent was removed in vacuo. The product was recrystallized from benzene to afford **18** an 84% overall yield.

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