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High Atom-Economical One-Pot Synthesis of Secondary Phosphines and Their Borane Complexes Using Recycling Phosphorus Donor Reagent

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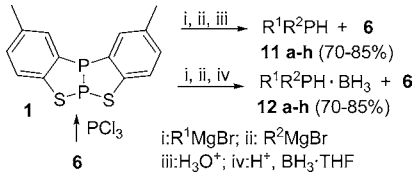
ABSTRACT



A general new method for the one-pot preparation of secondary phosphines 11 and in situ generation of their borane complexes 12 is described. This method consists of the sequential addition, at room temperature, of equivalent amounts of R^1MgBr and R^2MgBr to 1 equiv of the phosphorus atom donor reagent 1. Final treatment with water gives secondary phosphines R^1R^2PH (or the corresponding phosphine–borane complexes if treated with BH_3·THF) and the end product 6, which can be recycled.

Secondary phosphines are useful intermediates in organic synthesis and represent versatile synthons for the preparation of chiral mono- and bidentate phosphinic ligands.[1] However, the synthetic procedures for preparing such secondary phosphines are, as a rule, multistep and laborious with very low overall yields in the case of alkyl asymmetric secondary phosphines. Some indirect methods have been developed for the synthesis of secondary phosphines in which a monochlorophosphine is synthesized and subsequently converted into the desired phosphine by reduction with lithium alanate, sodium borohydride, or sodium.[2] Unfortunately, only a few monochlorophosphines are readily available by reaction of PCl_3 with Grignard reagents: in practice, this synthetic route is easy when the desired phosphines contain aryl groups but becomes more complicated when they contain only alkyl groups, and further difficulties are encountered when the phosphines contain two different alkyl groups.

Another factor complicating the synthesis of secondary phosphines is their very high air sensitivity, which makes them very difficult to handle and leads to the need for special equipment and experience that may not be available in every laboratory. To overcome this problem, secondary phosphines are often transformed into the corresponding phosphine−borane complexes, which are air-insensitive, present particular and very interesting reactivities, and are smoothly cleaved. In the past decade, there has been considerable interest in the preparation and controlled reactivity of phosphine−borane complexes, in particular, those involving secondary phosphines. Various applications for these complexes have been identified, including their use in carbonyl additions,[3] alkylation,[3,4] hydrophosphination,[5] and conjugate

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addition processes,[6] as well as in metal-mediated couplings.[7] Two recent reviews[8] highlight the importance of protecting secondary phosphines in the synthesis of chiral phosphine ligands as well as the expanded range of controlled synthetic possibilities available with phosphine−borane complexes in comparison to the parent phosphines. Secondary phosphine−boranes are generally obtained by one of the following procedures: reaction of the parent free phosphine with BH_3·THF or BH_3·SMe_2 complexes;[9] directly from parent phosphine oxides by in situ reduction with $LiAlH_4$ in the presence of $NaBH_4$ and $CeCl_3$;[10] or by reacting parent phosphine oxides with a large excess of BH_3·SMe_2 together with a small amount of water.[11] Recently, a general synthesis of phosphine−borane complexes from parent-free phosphines and $NaBH_4$/acetic acid has also been reported.[12]

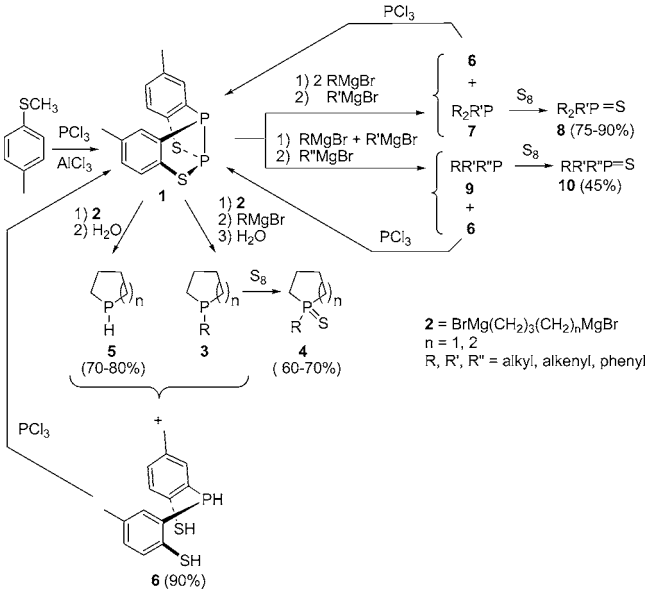
In this paper, we report a very efficient and general one-pot synthesis of symmetrical and asymmetrical secondary phosphines and the possible in situ conversion into their borane complexes in high yields, under mild conditions. Importantly, the proposed procedure completely avoids the need to handle obnoxious and air-sensitive secondary phosphines and involves the recycling of the byproduct **6** into the starting reagent **1**.

Recently, we reported[13] a new procedure for synthesizing the tertiary cyclic phosphines **3** and their sulfides **4**. This synthesis uses a reagent that we developed,[14] the benzothiadiphosphole **1**, which is easily obtained by treatment of *p*-methylthioanisole with PCl_3 and $AlCl_3$ (Scheme 1). In particular, the simultaneous or the sequential addition of equimolar amounts of a bis(Grignard reagent) **2** (n = 1, 2) and a mono-Grignard reagent RMgBr (R = alkyl, phenyl, alkenyl) to 1 equiv of **1** gives tertiary cyclic phosphines **3** and, after addition of elemental sulfur, affords the sulfides **4** in good yields at room temperature (Scheme 1).

We additionally reported[15] a very efficient and atom-economic new method for the one-pot preparation of secondary cyclic phosphines **5** (five- and six-membered) in 70−80% yields, as shown in Scheme 1.

The reaction pathways underlying these synthetic procedures were tentatively explained in terms of the intervention of hypervalent phosphorus intermediates.[16]

Scheme 1



More recently, we studied[17] the reaction between reagent **1** and mono-Grignard reagents. The symmetric tertiary phosphines **7** (R = R′ and R ≠ R′), or their corresponding sulfides **8**, were obtained in very high yield, and the asymmetric tertiary **9**, or their sulfides **10**, were obtained in 45% yield by addition of equimolar amounts of different Grignard reagents to a solution of **1** in two steps, as depicted in Scheme 1.The yields obtained are very close to the maximum value dictated by statistical factors.[17]

These findings prompted us to examine whether a similar one-pot procedure, employing the same phosphorus atom donor reagent **1**, could be used to synthesize symmetric and asymmetric diaryl-, arylalkyl-, and dialkylphosphines and their borane complexes.

The simultaneous addition, at room temperature, of equivalent amounts of the Grignard reagents R^1MgBr and R^2MgBr to a solution of benzothiadiphosphole (**1**) gave, after quenching with acidic water,[18a] symmetrical or asymmetrical secondary phosphines **11** and compound **6** (Scheme 2). The intermediate of this reaction might be a hypervalent phosphorus species such as **A**, as reported elsewhere.[17] The proposed synthesis affords symmetrical secondary phosphines ($R^1 = R^2$) in high yield (80−85%) and asymmetrical secondary phosphines ($R^1 \neq R^2$) in yields close to the maximum value of 50% imposed by statistical factors.[17] To overcome this statistical limit and to obtain the highest yields of asymmetric secondary phosphines, we carried out the reaction with sequential addition[18a] of the two different RMgBr reagents. We found that, with this procedure, asymmetric secondary phosphines were obtained in 70−75% yields. It is worth noting that the yields obtained using this procedure are, to our knowledge, the best obtained to date

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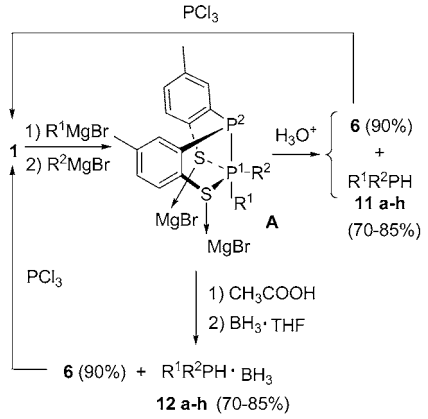
Scheme 2



	a	b	c	d	e	f	g	h
R^1	Et	*n*-Bu	*n*-Pent	Ph	Me	Et	*n*-Bu	Et
R^2	Et	*n*-Bu	*n*-Pent	Ph	Ph	Ph	Ph	*n*-Hex

for the synthesis of secondary asymmetrical phosphines in a one-pot procedure.

Then, this method represents a general protocol for the synthesis of a large number of secondary phosphines without remarkable limitations due to steric effects.[19] This generality arises because the method starts from phosphorus atom donor **1** and easily available Grignard reagents and overcomes the limitations typical of the classical syntheses of secondary phosphines, which involve multistep syntheses and are limited by the availability of commercial sources of the organic phosphorus compounds that are used as starting reagents.

The growing interest in the protection of secondary phosphines as phosphine−borane complexes prompted us to investigate whether the borane complexes of secondary phosphines could be obtained using our one-pot procedure without separation of free phosphine precursor. We found that treatment of the reaction mixture containing intermediates such as **A** with acetic acid followed by in situ addition of BH_3·THF complex (or BH_3·Me_2S or $NaBH_4$/acetic acid) did indeed afford phosphine−borane complexes **12**[18b] in high yields. Unexpectedly, we found that the secondary phosphine **6** was not complexed; this is of fundamental importance because it enabled easy recycling of **6** by treatment with PCl_3, which afforded the starting reagent **1**. It is noteworthy that reported syntheses[8b,11,12] of phosphine−borane complexes require, as starting material, the isolation of free phosphines or their derivatives. Our method represents the first reported procedure for synthesizing secondary phosphine−boranes that does not require isolation of any phosphine derivatives as precursors. In our procedure, the three borane sources can be used without distinction. However, it should be noted that secondary dialkylphosphines were easily and quantitatively tranformed into their BH_3 complexes by simple addition of 1 equiv of BH_3·THF to the reaction mixture, whereas in the case of phosphines bearing phenyl groups, the complexation was slower and possibly incomplete because of the instability in the BH_3·THF solution. This latter limitation was easily overcome by adding further amounts of BH_3·THF solution in successive steps until the reaction was complete. This reaction is clean and does not use BH_3·Me_2S, which has a strong odor that is difficult to eradicate, nor does it use the $NaBH_4$/AcOH system, which requires removal of residue salts.

In conclusion, here we have reported a new approach to the synthesis, in high yields, of secondary phosphines and their borane complexes using an almost identical, but independent, procedure. In addition, using this one-pot procedure to obtain phosphine−borane complexes, free compound **6** was recovered and recycled to starting reagent **1**, making the whole process highly atom-economic and environmentally friendly.

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(18) (a) P**reparation of phosphines 11a−h. Typical Procedure A.** Solutions of the two Grignard reagents (R^1MgBr, 1.0 mmol, and R^2MgBr, 1.0 mmol) were sequentially added (1−2 min between the addition of the first and the second Grignard reagent) to a solution of benzothiadiphosphole (**1**) (1.0 mmol) in anhydrous THF and under an argon atmosphere (when $R^1 = R^2$ the addition of 2 equiv of the Grignard reagent is in one step). After about 20−30 min, the solvent was partially evaporated and the reaction mixture was treated with degassed acidic (HCl) aqueous solution. Extraction with CH_2Cl_2 gave a mixture of phosphines and of the residue **6**. An easy separation of these compounds was carried out by treating the organic solution with degassed aqueous NaOH; in this way, the sodium salt of compound **6** is dissolved in the aqueous solution, whereas the organic one contains the phosphines **11** which were immediately purified by bulb-to-bulb distillation. Compound **6**[15] was recovered (90%) from the basic aqueous layer by acidification and extraction with dichloromethane, purified by distillation, and stored under argon. By simple treatment of a dry solution of compound **6** with an equimolar amount of PCl_3 the starting reagent **1** was regenerated in almost pure form so that it can be reused without further purification. (b) **Preparation of Phosphine Boranes 12a−h. Typical Procedure B.** Solutions of the two Grignard reagents (R^1MgBr, 1.0 mmol, and R^2MgBr, 1.0 mmol) were sequentially added (1−2 min between the addition of the first and the second Grignard reagent) to a solution of benzothiadiphosphole (**1**) (1.0 mmol) in anhydrous THF and under an argon atmosphere (when $R^1 = R^2$ the addition of 2 equiv of the Grignard reagent is in one step). After 20−30 min, the reaction mixture was treated with glacial acetic acid (2−3 mmol) and stirred for 5 min. The flask was immersed in an ice bath, BH_3−THF complex (1.5−3.0 mmol) was added, and the reaction mixture was allowed to stand for 2−4 h. The ice bath was removed, and the solvent was partially removed. The reaction mixture was treated with degassed acidic (HCl) aqueous solution. Extraction under argon atmosphere with CH_2Cl_2 gave a mixture of phosphine borane **12** and of the residue **6**. An easy separation of these compounds was carried out by treating, under argon atmosphere, the organic solution with degassed aqueous NaOH; in this way, the sodium salt of compound **6** was dissolved in the aqueous solution, whereas the organic solution contained the phosphine borane complex **12**, which was purified by chromatography on silica gel (*n*-hexane/EtOAc 95/5). Compound **6** was recovered as reported above.[15]

(19) As suggested by a reviewer, we have tested the possibility of obtaining other crowded *sec*-phosphines. As first results, we report that isopropyl(phenyl)phosphine and bis(2-methylphenyl)phosphine are obtained in good yields. Characterization data of these compounds are in agreement with those reported in the literature: Busacca, C. A.; Lorenz, J. C.; Grinberg, N.; Haddad, N.; Hrapchak, M.; Latli, B.; Lee, H.; Sabila, P.; Saha, A.; Sarvestani, M.; Shen, S.; Varsolona, R.; Wei, X.; Senanayake, C. H. *Org. Lett*. **2005**, *7*, 4277−4280. Work is in progress to evaluate limitations using other bulky groups.

Supporting Information Available: General experimental details, characterization data of compounds **11a**−**h** and **12a**−**h**, and copies of ^{1}H, ^{13}C, and ^{31}P NMR spectra for new compounds and for those whose reported data are uncomplete. This material is available free of charge via the Internet at http://pubs.acs.org.

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