

## Conference paper

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# A clean and simple method for deprotection of phosphines from borane complexes

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**Abstract:** Simple, efficient, clean, and stereospecific protocols of protection of phosphorus atom with borane and deprotection from the borane complexes of the tertiary phosphines in mild conditions are reported. The proposed protection/deprotection reactions tolerate a range of functional groups and lead to pure products with excellent yield with no need for application of chromatographic or crystallisation purification procedures. For the first time mechanisms of the reactions of phosphine protection and deprotection have been studied based on experimental kinetic data as well as quantumchemical calculations, which allows designing reaction conditions suitable for a given substrate.

**Keywords:** chiral phosphines; ICGC-6; phosphine boranes; protection and deprotection reactions; quantum-chemical DFT calculations; reaction mechanism elucidation.

## Introduction

Catalytic reactions, especially enantioselective ones, are widely recognised as an environmentally beneficial alternative to well defined classical industrial synthetic approaches based on utilisation of stoichiometric amounts of highly reactive organic substrates. They are also frequently considered as greener methods [1–3]. The transition metal-catalysed reactions constitute the core of modern synthetic tools used in the synthesis of fine organic compounds, pharmaceuticals, functional materials, and plant protective chemicals [4–8]. These reactions are mediated by certain transition metal complexes with organic ligands bearing coordinating heteroatoms such as N, O, P, and S at lower oxidation stages. The selection of the most appropriate ligand depends on the reaction type, and in many cases, transition metal complexes of phosphines are superior. The phosphine ligand based complexes are widely applied in cross-coupling reactions [5, 6, 9–11], in asymmetric hydrogenation [12–16], hydrocarboxylation [17, 18], and many other crucially important processes [19, 20]. In many cases, the syntheses of appropriate phosphines are complicated by their sensitivity to air exposure. Thus, protection of the phosphorus atom during the ligand synthesis is a common practice. Phosphine-borane complexes are regarded as a convenient alternative to free phosphines [21–24]. Borane protection is

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easily introduced with several complementary methods [25–32]. It is also considered to be easy to remove from the phosphorus(III) atom. Only in very rare cases can the phosphine borane complexes be directly used in the syntheses of catalysts [33]. Nevertheless, in general, deprotection of phosphines is required and it is based on only two reactions: (a) less electron-rich phosphines can be liberated in reaction with the excess of strongly basic amines, such as TMEDA, morpholine, diethylamine, or DABCO, run at elevated temperature; (b) more inert P–B bonds of electron-rich phosphines can be efficiently cleaved by treatment with strong acids such as  $\text{MeSO}_3\text{H}$ ,  $\text{CF}_3\text{SO}_3\text{H}$ , or  $\text{HBF}_4$  [24, 34, 35]. Both methods require a post reaction workup and impose significant limitation on the nature of substituents which the phosphines possess. Thus, a new efficient method of deprotection of phosphine from borane complexes is still pursued.

## Experimental

General all reagents were purchased from Sigma-Aldrich, Strem, TCI, and Alfa Aesar chemical companies and used without further purification. Analytical thin-layer chromatography (TLC) was performed using silica gel 60  $\text{F}_{254}$  precoated plates (0.25 mm thickness) with a fluorescent indicator. Visualisation of TLC plates was performed by means of UV light and either  $\text{KMnO}_4$  or  $\text{I}_2$  stains. NMR spectra were recorded on Bruker Avance 500 MHz spectrometers, and chemical shifts are reported in ppm, and calibrated to residual solvent peaks at 7.27 ppm and 77.00 ppm for  $^1\text{H}$  and  $^{13}\text{C}$  in  $\text{CDCl}_3$  or internal reference compounds ( $\text{H}_3\text{PO}_4$  capillary). The following abbreviations are used in reporting the NMR data: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Coupling constants ( $J$ ) are in Hz. Spectra are reported as follows: chemical shift (d, ppm), multiplicity, integration, coupling constants (Hz). Products were purified by flash chromatography on silica gel 60 (230–400 mesh) using a BUCHI MPLC chromatograph. MS spectra were recorded on a Shimadzu LCMS ITTOF spectrometer. Commercially unavailable compounds were obtained by known literature procedures. The additional experimental procedures, spectral and physical data of presented compounds as well as mol2 files of the calculated critical structures are available in ESI.

### General procedure for synthesis of phosphine borane complexes

1.0 M solution of borane in THF (2 mL or 4 mL for diphosphines) was added to an evacuation-degassed and argon-refilled solution of phosphine (1 mmol) in dry THF (2 mL). The mixture was heated to 40 °C and stirred for 0.5 or 1 h. After that time, the reaction was cooled down to r.t. and the solvent was removed in vacuum to afford a crude product. The solid products were simply washed with a minimal amount of dry degassed cyclohexane. The liquid and hexane-soluble boranes were purified by flash column chromatography.

### General procedure for deprotection of phosphine borane complexes with trimethylphosphine

The phosphine borane complex (0.5 mmol) and 2 mL of CPME (cyclopentyl methyl ether) were placed in a Schlenk tube. Then an amount of chromatographic silica gel 60 equal to borane mass was added, and the reactor was evacuated and refilled with argon. The 1.0 M solution of trimethylphosphine in toluene (1.5 mL and 3 mL for diphosphine borane complexes) was added under an argon atmosphere, and the mixture was heated at 100 °C for 12 h. The mixture was cooled down to r. t. After that, the  $^{31}\text{P}$  NMR analysis of the reaction mixture indicated the complete conversion of the starting complexes. The solvents were removed by a rotary evaporator. The trace amounts of volatile impurities were removed during an additional 16 h evacuation of the obtained crude products under 5 torr pressure. The resulting products did not need further purification.

## Kinetic measurements

The starting reaction mixtures were prepared in a Schlenk-type reactor charged with a dicyclohexylphenylphosphine borane complex (576 mg, 2 mmol) and 5.5 mL of toluene; the reactor was evacuated and refilled with argon and 2 mL of a 1 M solution of trimethylphosphine in toluene was added. One milliliter of the obtained solution was introduced into an argon-filled NMR tube, which contained an internal standard capillary. The tube was next sealed with a PTFE screw and placed into oil bath preheated up to the required temperature (80, 95, 110 °C). Progress of the reactions was monitored by means of  $^{31}\text{P}$  NMR spectroscopy. The conversion of  $\text{Cy}_2\text{PhPBH}_3$  was determined at 1 h periods. Since the initial concentrations of the reactants were known, the areas of NMR signals were correlated to the instantaneous concentration ( $c$ ) of the reactants. Next, on the basis of plots  $1/c$  vs. reaction time, second order rate constants were calculated using standard equations [36]. Finally, on the basis of the rate constants measured at different temperatures, the activation enthalpy ( $\Delta H^\ddagger$ ) and activation entropy ( $\Delta S^\ddagger$ ) were calculated using the Eyring equation in the form:

$$k = (k_{\text{B}} \cdot T / h) \cdot \exp(\Delta S^\ddagger / R) \cdot \exp(-\Delta H^\ddagger / R \cdot T) = (k_{\text{B}} \cdot T / h) \cdot \exp(\Delta G^\ddagger / R \cdot T) \quad (1)$$

where  $\Delta G^\ddagger$  is the Gibbs energy of activation,  $k_{\text{B}}$  is Boltzmann's constant,  $h$  is Planck's constant,  $\Delta S^\ddagger$  is the entropy of activation, and  $\Delta H^\ddagger$  is the enthalpy of activation.

## Quantumchemical calculations

The calculations reported in this paper were performed both on the "Prometheus" cluster in the CYFRONET regional computational centre in Cracow and on a personal desktop PC (Intel® Core™ I7 – 3930 K CPU @ 3.20 GHz, 16 GB RAM). Hybrid functional B3LYP with the 6 – 31 + G(d) basis set included in the GAUSSIAN 09 [37] package and Spartan 10 [38] were used. In particular, optimizations of the stable structures were performed with the Berny algorithm, whereas the transition states were calculated using the QST2 procedure followed by the TS method. Stationary points were characterised by frequency calculations. All reactants and products had positive Hessian matrices. All transition states showed only one negative eigenvalue in their diagonalized Hessian matrices, and their associated eigenvectors were confirmed to correspond to the motion along the reaction coordinate under consideration. For all reactions, intrinsic reaction coordinate (IRC) calculations were performed to connect previously computed transition structures (TS) with suitable minima. For the calculations of the solvent effect (GAUSSIAN 09 package) on the reaction paths, the polarizable continuum model (PCM) [39] in which the cavity is created via a series of overlapping spheres was used.

## Results and discussion

In continuation of our studies in the field of synthesis and application of tertiary phosphine ligands [40–48], herein we present a new method of deprotection of phosphines from corresponding borane complexes. The main aim of our studies is to present a simple and inexpensive synthetic approach leading to sensitive target phosphines with high purities and high yields with no need to apply post reaction purification. To achieve this challenge, we decided to use the simplest exchange reaction of low molecular weight volatile nucleophile with phosphine boranes. Low molecular weight amines are not nucleophilic enough to shift the equilibrium of the reactions with phosphine boranes in the direction of products. Phosphines are more reactive and the reaction between small trialkyl phosphines and phosphine borane complexes has been assessed. In analogy to the reaction of phosphine with amine boranes, it is reasonable that an exchange of the  $\text{BH}_3$  group is possible in a mixture of free phosphine and a phosphine borane complex (Scheme 1).

Nevertheless, for the synthesis of phosphines, this possibility has not been explored yet. We decided to use this equilibrium-driven reaction to have direct access to unprotected phosphines.



**Scheme 1:** The exchange reaction between phosphine and phosphine boranes.

The trimethylphosphine was chosen as a reagent of choice to be used for the deprotection of phosphines. It has low molecular weight (76.08 g/mol), low boiling point (38 °C), small size, and marginal steric hindrance at an electron-rich phosphorus atom. In addition, it is commercially available in individual form and in a solution. According to the MSDS data, the environmental and toxicological threats of trimethylphosphine are not critically high [49]. Moreover, its strong stench is a good indicator of possible contamination. Upon rapid oxidation when exposed on air, a trace contamination with trimethylphosphine is self-converted to a much safer trimethylphosphine oxide. On the other hand, borane complex of dicyclohexylphenylphosphine (obtained in high yield according to the classical approach) [50, 51] was selected as a model partner for the reaction with trimethylphosphine because of its high basicity and significant steric hindrance, which are known to complicate the deprotection of the phosphorus site.

In the preliminary experiments run in a toluene solution at 80 and 110 °C, an exchange reaction between the model borane **1** and trimethylphosphine **2**, used in an equimolar ratio, was observed (Scheme 2). The progress of the reaction was monitored by means of  $^{31}\text{P}$  NMR spectroscopy; the spectra were recorded in the presence of an internal standard – a capillary with a solution of phosphoric acid in deuterium oxide.

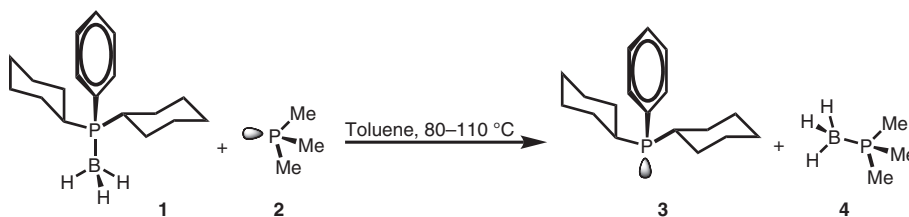
The reaction approaches the equilibrium at conversion of **1** = 32% in less than 5 h at 110 °C. It allows calculating the Gibbs free energy of the reaction ( $\Delta G = -0.52$  kcal/mol) based on the equation:

$$\Delta G = (-R \cdot T) / \ln K \quad (2)$$

where  $K$  is the equilibrium constant, and it is equal to 1.97 at 110 °C

At the same time, the mechanism of this reaction remains unknown. It has been postulated that the reaction may proceed via a dissociation stage [24], but no mechanistic studies of this issue have ever been published.

According to a few previous reports, the exchange reaction of phosphine boranes with amines [52], as well as the reaction of amine boranes with phosphines [53, 54] has the  $\text{S}_{\text{N}}2$ -like mechanism. Some other nucleophilic substitution reactions at the tetrahedral boron atom are also known [55, 56]. To elucidate the mechanism of the reaction studied herein, series kinetic experiments were performed at the temperatures of 80, 95, and 110 °C, molar ratio of **1**:**2** = 1:1, and initial concentration of **1** = 0.25 M (Table 1, Fig. 1). To obtain reliable results, all kinetic experiments were conducted under an argon atmosphere in sealed NMR tubes. Additionally, to exclude possible oxidation and evaporation effects, which may influence the quantitative results, the initial reaction mixtures were prepared under an argon atmosphere in Schlenk-type reactors. The progress of the reactions was monitored by means of  $^{31}\text{P}$  NMR spectroscopy with a  $\text{H}_3\text{PO}_4$  capillary used as an internal standard. The corresponding signals in the  $^{31}\text{P}$  NMR spectra appear as follows ( $\delta$ , ppm): **1** at 27.0 ÷ 27.7 (m), **2** at -62.6 (s), **3** at 1.9 (s), internal standard at 0 (s), and **4** at -1.3 ÷ -2.5 (m,  $J_{\text{P-B}} = 59.7$  Hz). Since the signal of **2** appears very far from the other signals, its accurate integration was problematic; similarly, the integration of borane **4** was not especially accurate because in the  $^{31}\text{P}$  NMR spectra **4** appears as a wide



**Scheme 2:** Model reaction between **1** and **2**.

**Table 1:** Relative intensity of the signals in the  $^{31}\text{P}$  NMR spectra of the reaction mixture.

T (h)	Integration of $^{31}\text{P}$ signals <sup>a</sup>								
	1			3			4		
	80 °C	95 °C	110 °C	80 °C	95 °C	110 °C	80 °C	95 °C	110 °C
0	87.66	88.19	85.60	0	0	0	0	0	0
1	79.50	57.38	41.47	7.31	23.26	37.81	5.05	16.97	26.95
2	70.97	44.39	34.37	13.81	33.34	43.19	9.69	24.03	31.04
3	65.33	37.30	32.47	18.32	36.82	42.60	13.48	26.98	31.60
5	56.51	29.95	32.28	25.38	37.55	42.92	18.44	27.00	32.19
7	50.64	25.95	32.44	30.60	36.55	43.18	21.63	26.37	32.10
9	46.97	23.31	32.46	33.90	34.55	43.36	25.37	24.96	32.02
12	42.60	22.20	32.48	37.30	33.68	43.18	27.91	24.33	31.83

Conditions: initial molar ratio of **1:2** = 1:1 and initial concentration of **1** = 0.25 M. <sup>a</sup>Integration of the internal standard capillary was assigned as 100.

multiple of four separate signals. For this reason, the kinetic calculation was based on the signal of starting borane **1**. In the same time, in the control experiment, left at 20 °C for 2 days, we did not observe progress of the reaction.

The linear dependence in the coordinate  $1/c$  vs time with the acute angle slope clearly indicates the second order of the reaction. The reaction rate constants calculated on the basis of the relationships mentioned above were  $1.24 \cdot 10^{-6} \text{ dm}^3/(\text{mol} \cdot \text{s})$ ,  $4.85 \cdot 10^{-6} \text{ dm}^3/(\text{mol} \cdot \text{s})$ , and  $9.67 \cdot 10^{-6} \text{ dm}^3/(\text{mol} \cdot \text{s})$  at 80, 95, and 110 °C, respectively.

The activation parameters of the reaction activation were calculated next, based on the Eyring equation:

$$k = (k_{\text{B}} \cdot T/h) \cdot \exp(\Delta S^{\ddagger}/R) \cdot \exp(-\Delta H^{\ddagger}/R \cdot T) = (k_{\text{B}} \cdot T/h) \cdot \exp(\Delta G^{\ddagger}/R \cdot T) \quad (1)$$

where  $\Delta G^{\ddagger}$  is the Gibbs energy of activation,  $k_{\text{B}}$  is Boltzmann's constant,  $h$  is Planck's constant,  $\Delta S^{\ddagger}$  is the entropy of activation, and  $\Delta H^{\ddagger}$  is the enthalpy of activation.

$\Delta H^{\ddagger} = 17.72 \text{ kcal/mol}$  and  $\Delta S^{\ddagger} = -35.5 \text{ cal}/(\text{mol} \cdot \text{K})$  were calculated from the Eyring plot [ $\ln(k/T)$  vs.  $1/T$ ], where slope =  $\Delta H^{\ddagger}/R$ ; intercept =  $\ln(k_{\text{B}}/h) + \Delta S^{\ddagger}/R$ .

On the basis of activation parameters, it is possible to make a conclusion about the reaction mechanism. In particular, a high negative  $\Delta S^{\ddagger}$  value suggests a high degree of order within the transition state (**TS**). In addition, a relatively low value of  $\Delta H^{\ddagger}$  shows that the changes in the system energy resulting from breakage of the existing  $\sigma$ -bond are compensated to a large extent by the energy changes resulting from the formation of a new  $\sigma$ -bond. Thus, interpretation of Eyring parameters fully complies with the expected  $\text{S}_{\text{N}}2$ -like mechanism.

To shed a deeper light on the molecular mechanism of this reaction, a theoretical study was carried out based on the DFT calculation data. In particular, the reaction pathway was explored using the hybrid, B3LYP functional [37, 38, 57] and 6-31+G(d) basis set. A similar level of theory was successfully verified with regard to a number of organophosphorus compounds, including phosphines and their oxides [45, 58, 59]. For the simulations of the solvent effect, the polarizable continuum model (PCM) was used [39].

The results of the DFT (PCM) computational study prove that the reaction between **1** and **2** should be considered as a one-step, synchronous process. In particular, on the reaction profile, a single transition state (**TS**) is localised between the minimum linked with the existence of individual substrates **1**, **2** and the minimum linked with the existence of products **3**, **4**. Conversion of the reaction system into **TS** involves an increase in the enthalpy by 21.61 kcal/mol. At the same time, the entropy of a more ordered system is reduced by  $-24.6 \text{ cal}/(\text{mol} \cdot \text{K})$  (Fig. 2). The transition state was almost symmetrical with the distance between  $\text{Me}_3\text{P}-\text{BH}_3$  equal to 2.684 Å and the distance between  $\text{C}_2\text{PhP}-\text{BH}_3$  equal to 2.699 Å. Both distances were significantly bigger than those appearing in substrate **1** (1.951 Å) and product **4** (1.935 Å) optimized under identical conditions. The slightly higher degree of development of the  $\text{Me}_3\text{P}-\text{BH}_3$  bond suggests higher stability of the less hindered reaction product **4** over substrate **1**. In the **TS**, the  $\text{BH}_3$  moiety adopts the flat geometry of the  $\text{sp}^2$

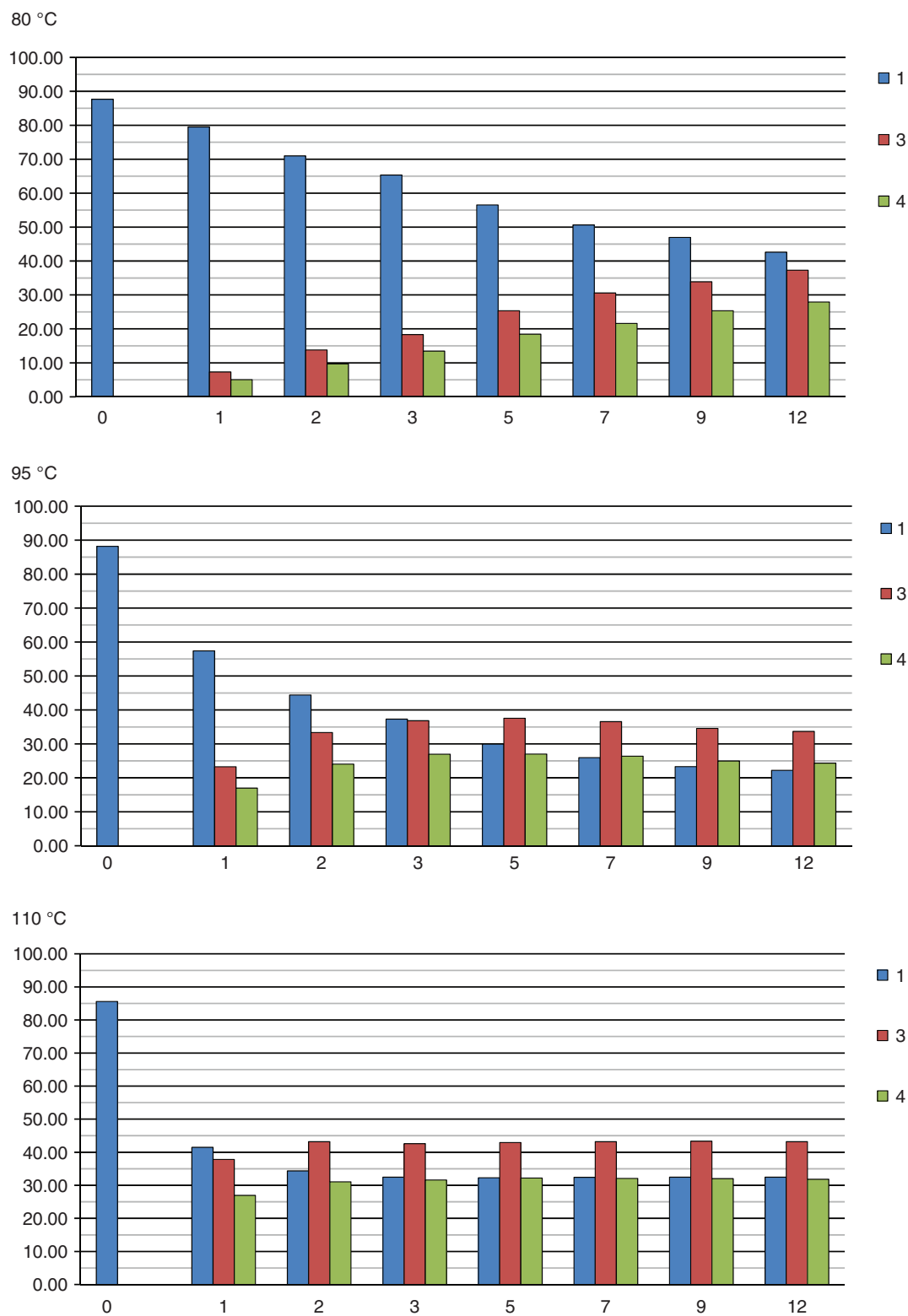


Fig. 1: Visualisation of the reaction progress in time at 80, 95, and 110 °C.

hybridised boron atom. The reliability of the localised transition state was confirmed by IRC calculations and supported by vibrational analysis (one imaginary frequency corresponding to movement along P–B–P bonds was detected at  $-300.78$  L/cm).

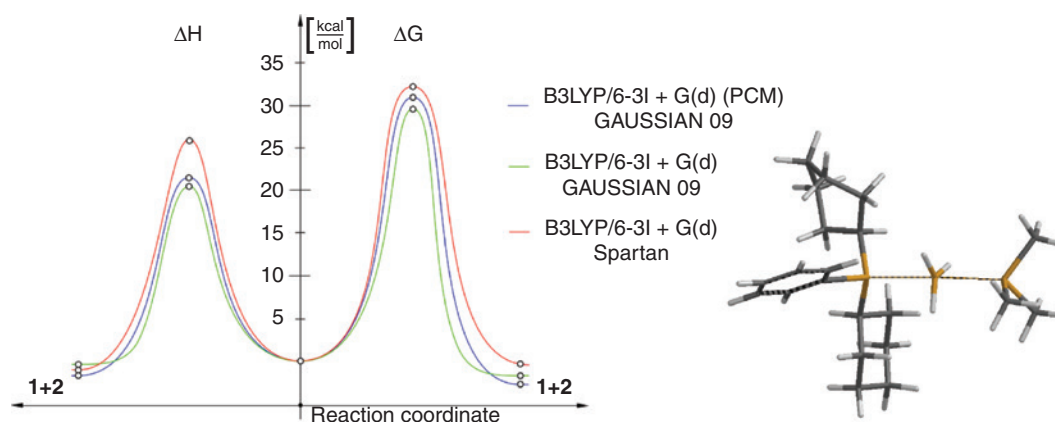


Fig. 2: Enthalpy profile of the reaction between 1 and 2 and view of its TS structure.

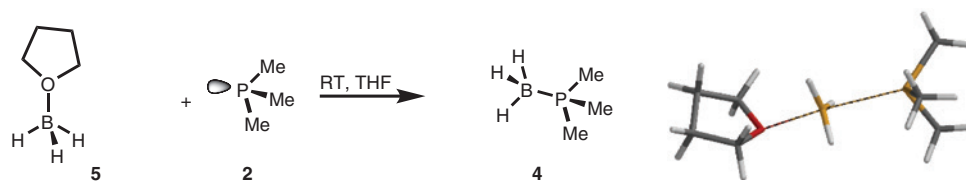
The calculations were performed for simulated presence of toluene (PCM solvation model was used) and, subsequently, for reaction in the gas phase, using the GAUSSIAN 09 package [37] allocated on supercomputer cluster and Spartan PC [38] package on a regular desktop PC. The obtained energetic parameters provide similar energy profiles and the geometrical parameters of critical structures (Table 2). This indicates that the reaction run through non-polar **TS** is not sensitive to the solvent effects and, therefore, could be accomplished not only in toluene, but also in some other solvents, compatible with the  $\text{BH}_3$  and functional groups, which the phosphine borane complex bear. The non-polar nature of **TSs** is additionally confirmed by analysis of their dipole moments, which are less than 0.4 D in the gas phase and about 0.5 D in the simulated presence of toluene). For comparison, typical polar **TSs** are characterised by dipole moments which are higher than 10 D [60, 61].

A similar B3LYP/6-31 + G(d) (PCM) simulation-based approach was applied to elucidate the mechanism of the reaction between the  $\text{THF-BH}_3$  complex and trimethylphosphine (Scheme 3, Table 3). In this case, we have also found that the reaction has an  $\text{S}_{\text{N}}2$ -like mechanism with ordered transition state **TS1**, which is significantly symmetrical in relation to bonds P–B and O–B, forming and backing during the reaction with

Table 2: Kinetic and thermodynamic parameters of reaction 1 + 2 calculated at the B3LYP/6-31 + G(d) theory level and measured experimentally.

Transition	GAUSSIAN 09				Spartan		Experimental	
	Toluene (PCM)		Vacuum		Vacuum		Toluene	
	$\Delta H$ (kcal/mol)	$\Delta S$ [cal/(mol·K)]	$\Delta H$ (kcal/mol)	$\Delta S$ [cal/(mol·K)]	$\Delta H$ (kcal/mol)	$\Delta S$ [cal/(mol·K)]	$\Delta H$ (kcal/mol)	$\Delta S$ [cal/(mol·K)]
1 + 2 → <b>TS</b>	21.61	–25.3	19.99	–24.6	25.98	–46.25	17.72	–35.5
1 + 2 → 3 + 4	–1.80	3.5	–0.96	3.4	–1.19	+1.7	–	–
	$\Delta G = -3.12$		$\Delta G = -2.25$		$\Delta G = -0.54$		$\Delta G = -0.52$	

$\Delta G$  was calculated for the reaction run at 110 °C (kcal/mol).



Scheme 3: Model reaction between  $\text{THF-BH}_3$  5 and trimethylphosphine 2 and view its transition state (**TS**).



**Table 3:** Thermodynamic parameters of reaction 5 + 2 calculated at the B3LYP/6-31+G(d) theory level.

Transition	GAUSSIAN 09				Spartan	
	THF (PCM)		Vacuum		Vacuum	
	$\Delta H$ (kcal/mol)	$\Delta S$ [cal/(mol·K)]	$\Delta H$ (kcal/mol)	$\Delta S$ [cal/(mol·K)]	$\Delta H$ (kcal/mol)	$\Delta S$ [cal/(mol·K)]
5 + 2 → TS1	10.43	-26.3	7.04	-26.5	5.88	-41.4
5 + 2 → 6 + THF	-15.93	0.7	-15.29	1.4	-11.04	0.0
	$\Delta G = -16.14$		$\Delta G = -15.74$		$\Delta G = -11.04$	

$\Delta G$  was calculated for the reaction run at 40 °C (kcal/mol).

distances 2.837 and 2.122 Å, respectively. The shorter distance of the O–B bond in the TS1 corresponds to the geometry of the earlier transition state. The BH<sub>3</sub> group adopts almost flat geometry of the sp<sup>2</sup> hybridised boron atom, with only 2.5° deviation outside the plane of three hydrogens. Despite the reaction of trimethylphosphine with phosphine boranes, the reaction trimethylphosphine with tetrahydrofuran borane complex is rapid and exothermic.

In comparison with non-hindered and electron-rich trimethylphosphine, the reactions of triphenylphosphine and electron-deficient perfluorotriphenylphosphine with the THF–BH<sub>3</sub> complex were less favourable. Thus, in the case of the triphenylphosphine complex, the thermodynamic parameters of formation  $\Delta H$ ,  $\Delta S$ , and  $\Delta G$  were -10.42 kcal/mol, 0.5 cal/(mol·K), and -10.56 kcal/mol (at 25 °C), correspondingly. At the same time, the perfluorotriphenylphosphine borane was not stable at room temperature, with analogous thermodynamic parameters of formation equal to 3.86 kcal/mol, -8.6 cal/(mol·K), and 6.43 kcal/mol (at 25 °C), respectively.

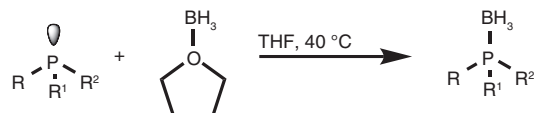
The analysis of the mechanism and kinetic parameters of the protection/deprotection reactions indicates that, in the case of non-electron deficient phosphines, the protection reactions with the THF–BH<sub>3</sub> complex are fast and only a minor excess of borane is required for complete conversion of phosphine at room temperature. At the same time, the reaction of phosphine boranes with trimethylphosphine is much slower and a few-fold excess of trimethylphosphine as well as elevated temperature are required to achieve high yields of the products.

With these considerations, series phosphine boranes **1**, **6–11** and diphosphine bisboranes **13–16** were obtained in the reaction of corresponding phosphines with the THF–BH<sub>3</sub> complex in tetrahydrofuran at 40 °C. Utilisation of a two-fold excess of borane resulted in a very clean fast reaction. The spectrally pure products were obtained after evaporation of the solvent under reduced pressure and washing the crude products with a small amount of cyclohexane. Only in the cases of a few boranes, soluble in cyclohexane, flash column chromatography was applied (Table 4).

The obtained boranes were next subjected to the deprotection procedure. The theoretic consideration, based on the measured reaction rate constant and equilibrium constants, suggested that a three-fold excess of trimethylphosphine should be enough to shift the equilibrium into the direction of the product at the 100 °C reaction temperature. In preliminary experiments, we observed the formation of trace amounts of weakly soluble boric acid derivatives, which contaminated the products. To eliminate the need for further purification of sensitive phosphines, the silica gel sorbent was added to the reaction mixture. A Schlenk-type reactor was charged with phosphine borane and an equal weight amount of silica gel 60. Cyclopentylmethyl ether (usually considered as a green alternative to the ethereal and aromatic solvents) was added and the reactor was degassed and filled back with argon. Next, the solution of trimethylphosphine in toluene was added and the reactor was closed with a glass stopper and heated at 100 °C for 16 h. Upon the cooling down to room temperature, the solution of the products was taken with a needle; then, the solvents and volatile products were evaporated off under pressure reduced down to 5 torr. Application of a dry ice cooled trap allowed collecting the reagents to be reused further. The products were subjected to additional 12 h vacuum degassing, which allowed obtaining spectrally pure (contaminated with less than 5 % of inert Me<sub>3</sub>PO and Me<sub>3</sub>PBH<sub>3</sub>) phosphines in high yields (Table 5).

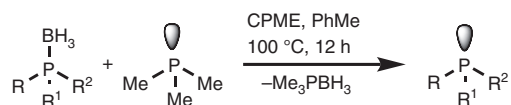


Table 4: Syntheses of phosphine boranes 1, 6–16.



Phosphine borane	Yield (%)	Phosphine borane	Yield (%)
 1	75, purified by flash chromatography	 6	82, washed with cyclohexane
 7	92, washed with cyclohexane	 8	80, washed with cyclohexane
 9	85, purified by flash chromatography	 10	85, washed with cyclohexane
 11 [62, 63]	90, purified by flash chromatography	 12	0
 13	59, purified by flash chromatography	 14	39, washed with cyclohexane
 15	81, washed with cyclohexane	 16	97, washed with cyclohexane

Conditions: solution of phosphine (1 mmol) in dry THF (2 mL), 1.0 M solution of borane in THF (2 mL per mmol of phosphine), argon atmosphere, 40 °C, 1 h.

**Table 5:** Synthesis of phosphines from the phosphine borane complexes 3, 17–29.

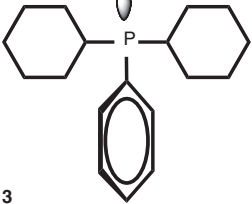
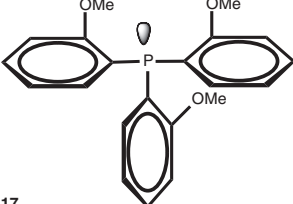
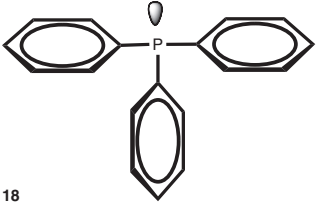
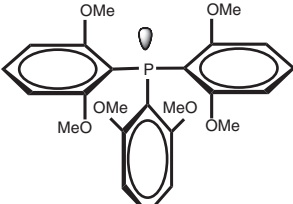
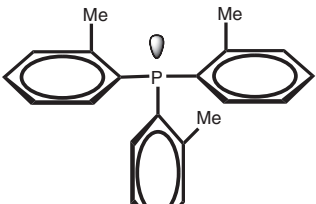
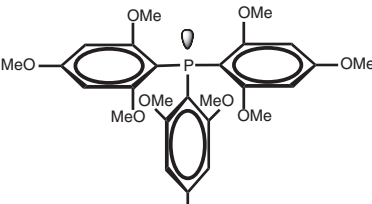
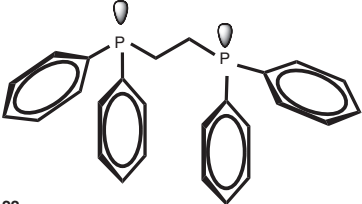
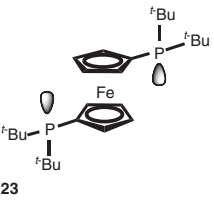
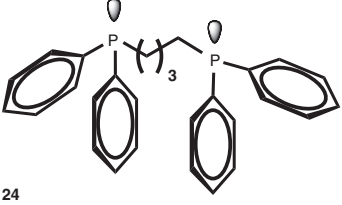
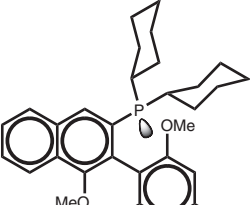
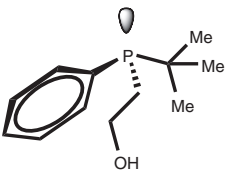
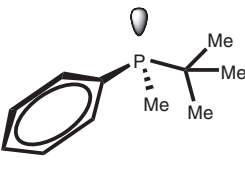
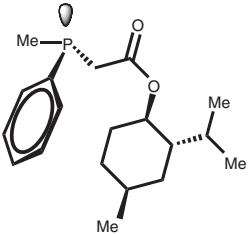
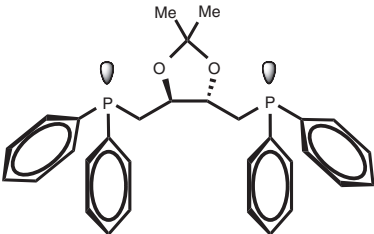
Phosphine	Yield (conversion), (%)	Phosphine	Yield (conversion), (%)
	86 (96)		99 (100)
<b>3</b>		<b>17</b>	
	96 (99) <sup>a</sup>		96 (100)
<b>18</b>		<b>19</b>	
	96 (100)		91 (91)
<b>20</b>		<b>21</b>	
	93 (93) <sup>a</sup>		86 (87)
<b>22</b>		<b>23</b>	
	98 (99) <sup>a</sup>		97 (99)
<b>24</b>		<b>25</b> [41, 42]	
	95 (99)		97 (99)
<b>(R<sub>p</sub>)-26<sup>b</sup></b> [64, 65]		<b>(R<sub>p</sub>)-27<sup>c</sup></b> [66, 32]	

Table 5 (continued)

Phosphine	Yield (conversion), (%)	Phosphine	Yield (conversion), (%)
 $R_p$ -28 <sup>a</sup> [61, 62]	97 (99)	 $R,R$ -29 <sup>e</sup>	93 (99)

Conditions: phosphine borane complex (0.5 mmol), 2 mL of CPME (cyclopentyl methyl ether), 200 mg SiO<sub>2</sub>, 1.0 M solution of trimethylphosphine in toluene (1.5 mL per 0.5 mmol of borane complex), argon atmosphere, 100 °C, 12 h. Conversion was calculated from <sup>31</sup>P NMR spectra of the reaction mixtures. <sup>a</sup>THF was used instead of CPME. <sup>b</sup>borane complex was prepared according to known procedure [64, 65] >75 % ee substrate was used, >71 % ee product was obtained. <sup>c</sup>borane complex was prepared according to known procedure [32, 66] >92 % ee substrate was used, >90 % ee product was obtained (borane complex: HPLC, Chiralcel ad-h column; phosphine converted to oxide: <sup>1</sup>H, <sup>31</sup>P NMR in the presence of Naproxen) [62]. <sup>d</sup>borane complex was prepared according to known procedure [40, 63] Conditions: 60 °C, 18 h, 2 equiv. Me<sub>3</sub>P, 48 % de substrate was used, 46 % de product was obtained (<sup>1</sup>H, <sup>31</sup>P NMR). <sup>e</sup>>98 % de substrate was used, >99 % de product was obtained (ORP).

The stereoselectivity of the transformations of chiral non-racemic phosphines are crucially important because the chiral purification of the sensitive products is not usually possible, and, due to the well known non-linear effects in asymmetric catalysis, even small contamination of the chiral catalysts with the minor stereoisomer may significantly influence the stereochemical outcome of the reaction. To check the assumption that the configuration of the stereogenic centre located at phosphorus and carbon atoms is not changed during the reaction, several chiral *P*-stereogenic **26–28** as well as *C*-stereogenic phosphine boranes **28**, **29** were obtained. The stereo composition of the used boranes and obtained phosphines were measured by means of HPLC-MS chromatography and NMR spectroscopy. To simplify the procedure of determination of samples stereocomposition, the enriched in one of the stereoisomers mixture of the chiral substrates were used. The experiments with chiral substrates were also repeated with corresponding racemic mixtures. In all the cases, no inversion of the configuration at the stereogenic centres or racemisation above the measurement tolerance was observed. Nevertheless we have found that chiral phosphines **26–28** undergo a partial thermal racemisation at the temperature above 100 °C, thus low reaction temperature of 60 °C and prolonged time were applied to prevent the racemisation. Notable, the sensitive to acid/base conditions, phosphines possessing unprotected hydroxy, di-*O*-isopropylidene, and ester functional groups were obtained in excellent yields.

## Conclusions

The straightforward stereospecific protocols of deprotection of phosphorus atom of phosphine boranes in reaction with trimethylphosphine run in mild conditions have been reported for the first time. The proposed reactions tolerate a range of function groups and lead to pure products in excellent yields. The unselective transformations of starting phosphine boranes were not observed, and the isolation of target products do not require the application of post reaction workup and chromatographic or crystallisation purification procedures. The approach to protection of phosphorus atom of phosphines in reaction with THF–BH<sub>3</sub> adduct was also studied. The S<sub>N</sub>2-like mechanisms of both reactions were elucidated. The general conclusions that can be made upon the analysis of the mechanisms of the reactions of protection of phosphines with borane and deprotection of the obtained complexes are as follows:

- a. both reactions are reversible and undergo a second-order nucleophilic substitution mechanism (on the boron atom) with retention of the configuration at phosphorus;
- b. the reaction of non-electron deficient phosphines with the THF–BH<sub>3</sub> complex is fast and the equilibrium is shifted into the direction of products. The small excess of borane may be favourable for complete conversion of phosphine;
- c. the reaction of phosphine boranes with trimethylphosphine is much slower and leads to less hindered trimethylphosphine borane; thus, elevated temperature and a few-fold excess of trimethylphosphine is required to achieve sufficient conversions of the substrates.
- d. The reaction could be performed in different aprotic solvents such as THF, toluene or CPME, considered as a green alternative to the ethereal solvents and aromatic hydrocarbons.
- e. The computer simulation of the reaction is quite simple and can be done on a regular desktop PC in reasonable time by reoptimisation of critical structures of the reactions with consideration of given substituents they bear (see ESI). This allows designing the optimal conditions of the reactions and minimising the cost of syntheses and waste emission.

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