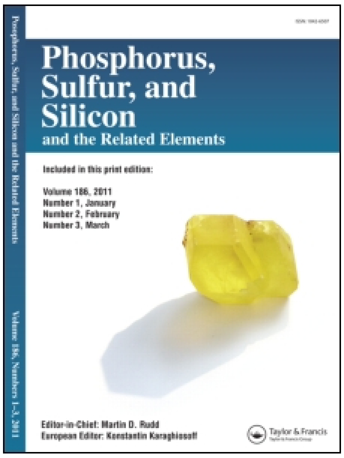

# Phosphorus, Sulfur, and Silicon and the Related Elements

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## Enantioselective Synthesis of P-Chirogenic Phosphorus Compounds via the Ephedrine-Borane Complex Methodology

S. Jugé[a]
[a] Institut de Chimie Moléculaire de l'Université de Bourgogne (ICMUB), Dijon Cedex, France

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# Enantioselective Synthesis of P-Chirogenic Phosphorus Compounds via the Ephedrine-Borane Complex Methodology

**S. Jugé**
Institut de Chimie Moléculaire de l'Université de Bourgogne (ICMUB), Dijon Cedex, France

*The stereoselective synthesis of P-chirogenic organophosphorus compounds using the versatile ephedrine-methodology is reported. The principle of the method is based on the diastereoselective preparation of 1,3,2-oxazaphospholidine borane **3** from ephedrine **2** and regio- and stereoselective ring-opening of the heterocycle leading to an aminophosphine borane **4**. Finally, these ring-opening products **4** are easily transformed into P-chirogenic organophosphorus compounds, by subsequent highly stereoselective reactions involving electrophilic or nucleophilic strategies.*

**Keywords** Asymmetric synthesis; chiral phosphines; phosphinous derivatives; stereoselectivity

## INTRODUCTION

Up until the 1980s, the synthesis of P-chirogenic phosphines was mainly based on either the electrochemical decomposition of quaternary phosphonium salts,[1] or on the Grignard reaction with menthyl phosphinates,[2] or on the decarboxylation of a phosphine oxide menthyl acetate side-chain.[3] However, these methods require the separation of both diasteromeric forms of a P-chirogenic precursor, and exhibit many limitations for the design of P-chirogenic phosphorus compounds. Progressively, a novel strategy emerged from the works of Inch and his collaborators on the stereochemistry of the ring cleavage of a diheterophosphacycloalcane by electrophilic or nucleophilic attack,[4] which led to the current synthesis procedure using ephedrine as chiral auxiliary.[5]

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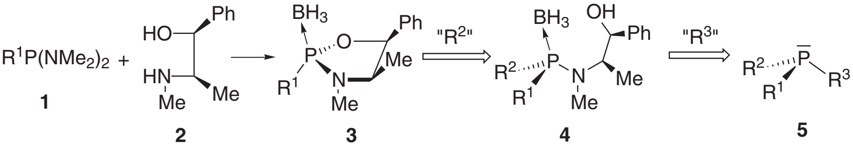
Address correspondence to S. Jugé, Institut de Chimie Moléculaire de l'Université de Bourgogne (ICMUB), UMR CNRS 5260, 9 Avenue A. Savary, BP 47870, 21078 DIJON cedex, France. E-mail: sylvain.juge@u-bourgogne.fr

The principle of this strategy is based on two key steps (Scheme 1):



**SCHEME 1**

- diastereoselective preparation of 1,3,2-oxazaphospholidine borane **3** from ephedrine **2**;
- regio- and stereoselective ring-opening of heterocycle **3** leading to products **4**.

Finally, the ring-opened products **4** are converted into various P-chirogenic compounds **5**, by subsequent reactions involving electrophilic or nucleophilic reagents.

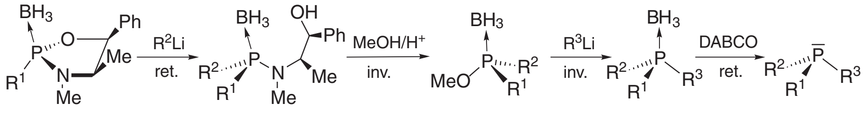
The use of the oxazaphospholidine borane **3** according to the definite strategy is today one of the most efficient methods for the synthesis of P-chirogenic compounds. Indeed, the organophosphorus borane complexes are stable, often crystalline compounds, and give clean reactions on the P-center or in the $\alpha$- or $\beta$-position of one of the phosphorus substituents.[6] On another hand, the borane decomplexation can easily be achieved with an amine,[7] a strong acid,[8] an alcohol,[9] or an olefine[10] to give quantitatively the corresponding P(III)-compound with complete retention of the configuration on the phosphorus center. In addition, the borane complexes could be used in organic synthesis or coordination chemistry for the stereoselective preparation of P-chirogenic organophosphorus derivatives, which can not be easily prepared by alternative approaches or purified in their trivalent form. Using this methodology, quaternary phosphonium salts,[11] (thio)phosphorylated derivatives,[12] and chiral complexes derived from transition metals,[13] become readily accessible.

## RESULTS AND DISCUSSION

The oxazaphospholidine boranes **3** are usually prepared by heating the bis(dimethylamino)-phosphine $R^1P(NMe_2)_2$ **1** in toluene with the ephedrine **2** followed by the addition of $BH_3$.DMS (or $BH_3$.THF)

(Scheme 1).[5,14–16] In these conditions, the condensation occurs under thermodynamic control and the product **3** was obtained with diastereomeric ratios up to 95:5. Crystallization in isopropanol or methanol affords the diastereomerically pure borane complexes **3** in isolated yields up to 84%. Notably, the borane complexes **3** are air stable and moisture resistant compounds and can be stored without any precaution. The relative configuration of the 1,3,2-oxazaphospholidine boranes **3**, which was established by $^1$H NMR or by X-ray structure analysis of their corresponding borane complexes, indicates a *trans*-relationship between the R$^1$-substituent located on the phosphorus atom, and the phenyl, and the methyl group, placed in C(5) and C(4) position, respectively.[17–19]

The complex **3** reacts with alkyl or aryl lithium reagents in THF at −78°C, to afford regio- and stereoselectively the corresponding ring-opened product **4** by P—O bond cleavage of the heterocyclic ring (Scheme 2). Various R$^1$ substituents such as alkyl, cycloalkyl, aryl, or ferrocenyl could be introduced on the P-center of the aminophosphine boranes **24**, which are usually obtained in good or excellent yields as a single detectable diastereomer (d.r. >98:2) (Table I). The recrystallization of the aminophosphine borane **4** in a isopropanol/hexane mixture readily provides the pure diastereomer.



**3** **4** **6** **7** **5**

**SCHEME 2**

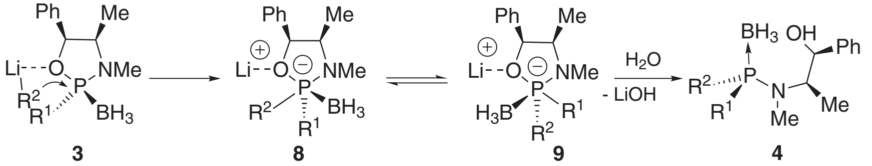
The stereochemistry of the ring-opening step was established by X-ray analysis of several aminophosphine boranes **4**, and proceeds with retention of configuration at the P-center.[14b,20] This stereochemistry was explained by a nucleophilic attack of the organometallic reagent on the less hindered side-face of the P-O bond, which is placed opposite to the bulky NMe group, and assisted by the lithium interactions with the oxygen atom located on the ring (Scheme 3). The proposed mechanism involves the formation of a pentacoordinate intermediate **8**, which undergoes a turnstile rotation of the R$^1$R$^2$PBH$_3$ group to form **9** having the P-O bond at the apical position. The P—O bond cleavage subsequently leads to the aminophosphine borane **4** with retention of configuration at the P-center after hydrolysis. Notably, a reverse stereochemistry

**TABLE I Aminophosphine Boranes 4 from 1,3,2-Oxazaphospholidine Borane Complexes 3**

| Borane complex **3** | | Aminophosphine borane **4** | | | | |
|---|---|---|---|---|---|---|
| | R$^1$ | | R$^2$ | Yield (%) | d.r. | Ref. |
| **3a** | Ph | **4a** | Me | 95 | 97:3 | 5,14 |
| | | **4b** | All | 77 | 8:2[a] | 21 |
| | | **4c** | *n*-Bu | 80 | 97:3 | 5e,22,23 |
| | | **4d** | *t*-Bu | 82 | > 98:2 | 14b |
| | | **4e** | Neophyl | 72 | > 98:2 | 23 |
| | | **4f** | *c*-Hex | 88 | > 98:2 | 23,14b |
| | | **4g** | Vinyl | 96 | > 98:2 | 24 |
| | | **4h** | *o*-An | 95 | 97:3 | 5,14,20,23,25,26,27 |
| | | **4i** | *o*-MEM-Ph | 51 | > 98:2 | 28 |
| | | **4j** | *m*-An | 72 | > 98:2 | 29 |
| | | **4k** | *p*-An | 80 | > 98:2 | 23 |
| | | **4l** | 2,4-diMeOPh | 57 | > 98:2 | 30 |
| | | **4m** | *o*-Tol | 92 | > 98:2 | 14b,23 |
| | | **4n** | *m*-Xyl | 60 | > 98:2 | 28 |
| | | **4o** | *o*-[MeO(CH$_2$)$_2$]Ph | 57 | > 98:2 | 31 |
| | | **4p** | *o*-biPh | 85 | > 98:2 | 14b,23,27 |
| | | **4q** | 1-Np | 87 | > 98:2 | 14b,23,26,27,32 |
| | | **4r** | 2-Np | 89 | > 98:2 | 14b,27 |
| | | **4s** | 3-MeO-2-Np | 66 | > 98:2 | 33 |
| | | **4t** | 9-Phenanthryl | 86 | > 98:2 | 27 |
| | | **4u** | 2-Pyr | 71 | > 98:2 | 28 |
| | | **4v** | Fc | 84 | 91:9 | 34 |
| **3b** | *p*-An | **4w** | 1-Np | 81 | 95:5 | 15 |
| **3c** | 4-CF$_3$Ph | **4x** | 1-Np | 72 | 95:5 | 15 |
| **3d** | Mes | **4y** | Ph | 9 | > 98:2 | 16 |
| **3e** | Ad | **4z** | Ph | — | 3:1 | 35 |

[a] Starting from racemic complex **3a.**

would require an isomerisation of the pentacoordinate intermediate **8** (or **9**) via a mechanism involving a Berry pseudorotation, that is highly disfavored by the five-membered ring involving a OPN angle close to 90°.[36]



**SCHEME 3**

## P-Chirogenic Methyl Phosphinite Boranes

The acidic methanolysis of the aminophosphine boranes **4** affords the phosphinite borane derivatives **6** and the ephedrine salt, by P—N bond cleavage (Scheme 2). This reaction proceeds with inversion of configuration at the P-center, and carries out the phosphinite boranes **6** in high yields and with excellent enantiomeric purities (Table II). The alcoholysis conditions are mild, as illustrated by the following procedure: the aminophosphine boranes 4 was dissolved in freshly distilled methanol in the presence of one equivalent of concentrated sulfuric acid, and the reaction was stirred overnight at room temperature. After filtration over silica, the solvent was removed under vacuum to afford the crude phosphinite boranes 6, which were easily purified by chromatography or recrystallization, and stored without any precaution. Some exceptions to the reaction were found: as the methanolysis of the P-chirogenic *t*-butyl- and ferrocenylaminophosphine borane **4d** and **4v** which did not proceed at all. The lack of reactivity was explained in these cases by the steric hindrance of the side-face, which is opposite to the P—N bond, preventing the approach of the methanol.

The reaction of the methyl phosphinite boranes **6** with an organolithium reagent at −78°C affords the corresponding tertiary phosphine boranes **7** in good yields and with high enantiomeric excesses (>90% e.e.) (Scheme 2, Table II). This last reaction proceeds also with inversion of the configuration at the P-center, and occurs with various alkyl or aryllithium reagents, except with the mesityl group.[16] After recrystallization, the phosphine boranes **7** are obtained enantiomerically pure and were then decomplexed with retention of the configuration into the free phosphines **5** using DABCO or another method in order to remove the borane (Scheme 2).[7–9] The efficiency of this method leads to the possibility to prepare on multigram scale tertiary phosphines **5** in overall yields over 50% starting from ephedrine.

It should be noted that the synthesis of both enantiomers of P-chirogenic phosphines 5 according to this methodology can be performed using either (+)- or (−)-ephedrine as chiral auxiliary. More interestingly, both enantiomers were also obtained from complex **3** by changing the addition order of the organolithium reagents (Scheme 4).[5d,e] Thus, subsequent reactions of complex **3** prepared from (−)-ephedrine with methyllithium, then methanolysis followed by *o*-anisyllithium, led to (*R*)-PAMP **5a** after decomplexation (Scheme 4). In the case where the complex **3** reacts first with *o*-anisyllithium, and then, after methanolysis, with methyllithium, (*S*)-PAMP **5a** is obtained after decomplexation.

**TABLE II For Methyl Phosphinite Boranes 6 and Phosphine Derivatives 7 from Aminophosphine Boranes 4**

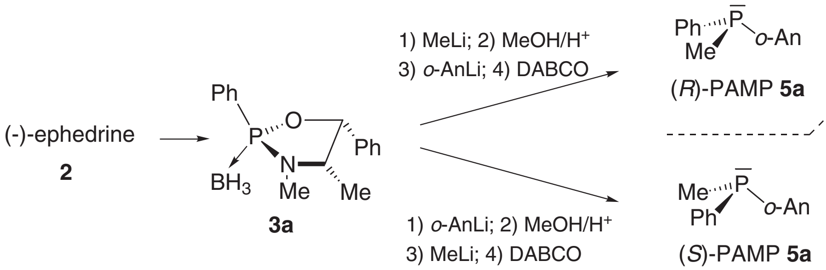
| Methyl phosphinite borane **6** | | | | | Phosphine borane **7** | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | $R^1$ | $R^2$ | Yield (%) | Ref. | | $R^3$ | Yield (%) | e.e. (%) | Ref.[a] |
| **6a** | Ph | Me | 95 | 5c–e,16, 7c,23 | **7a** | *n*-Bu | 91 | — | 5c–e |
| | | | | | **7b** | *t*-Bu | 66 | 92 | 16 |
| | | | | | **7c** | 2-Pic | 77 | — | 7c |
| | | | | | **7d** | 2,6-Lut | 70 | — | 7c |
| | | | | | **7e** | *o*-An | 50 | > 95 | 5c–e |
| | | | | | **7f** | 1-Np | 75 | 85 | 39 |
| | | | | | **7g** | 2-Np | 90 | 85 | 5e, 39 |
| | | | | | **7h** | Fc | 58 | 83 | 23 |
| **6b** | Ph | *n*-Bu | 62 | 23 | **7i** | Fc | 90 | 77 | 23 |
| **6c** | Ph | Neophyl | 65 | 23 | **7j** | Fc | 79 | 98 | 23 |
| **6d** | Ph | *c*-Hex | 29 | 23,29 | **7k** | Fc | 66 | 97 | 23 |
| **6e** | Ph | *o*-An | 95 | 5c–e,7c, 23,27 | **7e** | Me | 95 | > 95 | 5, 39, 40 |
| | | | | | **7l** | *t*-Bu | 92 | 98 | 35, 29 |
| | | | | | **7m** | Ad | 37 | — | 35 |
| | | | | | **7n** | 2-Pic | 70 | — | 7c |
| | | | | | **7o** | 2,6-Lut | 55 | — | 7c |
| | | | | | **7p** | 3,4-diMeOPh | 80 | — | 41 |
| | | | | | **7q** | 2-Np | 90 | > 95 | 39 |
| | | | | | **7r** | Fc | 92 | 98 | 35, 23 |

*(Continued on next page)*

**TABLE II For Methyl Phosphinite Boranes 6 and Phosphine Derivatives 7 from Aminophosphine Boranes 4 (Continued)**

| Methyl phosphinite borane **6** | | | | | Phosphine borane **7** | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | $R^1$ | $R^2$ | Yield (%) | Ref. | | $R^3$ | Yield (%) | e.e. (%) | Ref.[a] |
| **6f** | Ph | *p*-An | 77 | 23 | **7s** | Fc | 85 | 95 | 23 |
| **6g** | Ph | 2,4-diMeOPh | 97 | 30 | **7t** | Me | 86 | > 95 | 30 |
| **6h** | Ph | *o*-Tol | 90 | 23,29,30 | **7u** | Me | 95 | > 95 | 30, 40 |
| | | | | | **7v** | *c*-Hex | 32 | > 99 | 29 |
| | | | | | **7w** | Fc | 70 | 83 | 23 |
| **6i** | Ph | *o*-[MeO$(CH_2)_2$]Ph | 64 | 31 | **7x** | 2-Np | 28 | | 31 |
| **6j** | Ph | *o*-biPh | 77 | 23,27,29, 37,38 | **7y** | Me | — | — | 37 |
| | | | | | **7z** | *i*-Pr | — | — | 37 |
| | | | | | **7aa** | *c*-Hex | 62 | 97 | 29 |
| | | | | | **7ab** | Fc | 69 | 98 | 23,38 |
| **6k** | Ph | 1-Np | 84 | 26,27,37,38 | **7f** | Me | 96 | 93 | 32, 37 |
| | | | | | **7ac** | *i*-Pr | 61 | 99 | 37 |
| | | | | | **7ad** | Fc | > 66 | — | 38 |
| **6l** | Ph | 2-Np | 94 | 5e,27 | **7g** | Me | 90 | > 95 | 30, 39 |
| | | | | | **7q** | *o*-An | — | > 95 | 39 |
| **6m** | Ph | 9-Phenanthryl | 64 | 27,37 | **7ae** | Me | 44 | 99 | 37 |
| **6n** | Ph | Fc | 31 | 34 | — | — | — | — | — |
| **6o** | *p*-An | 1-Np | 84 | 15 | — | — | — | — | — |
| **6p** | 4-$CF_3$Ph | 1-Np | 75 | 15 | — | — | — | — | — |
| **6q** | Mes | Ph | 55 | 16 | — | — | — | — | — |

[a] The synthesis was performed starting from the (+)-ephedrine in the following references: 14b, 23, 27, 29, and 30.



**SCHEME 4**

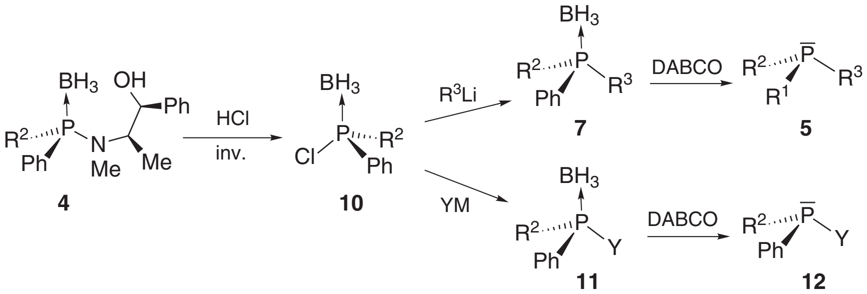
Today, the ephedrine methodology was widely applied for the preparation of various classes of symmetric or dissymmetric P-chirogenic ligands, useful for asymmetric catalyzed reactions by transition metal complexes.[5e,23,32,34,42–44]

However, despite the numerous phosphine borane complexes **7** synthesized and depicted in Table II, the lack of reactivity for the phosphinite boranes **6** with soft nucleophiles such as cyclopentadienyl anion or phenates, constitutes a limitation to perfect new classes of P-chirogenic compounds. For this reason, the chlorophosphine boranes **10** bearing a better leaving group than the methoxy one, recently emerged as new electrophilic P-chirogenic building blocks.

## P-Chirogenic Chlorophosphine Boranes

The configurational stability of the tricoordinate P-chirogenic chlorophosphines is poor, and these compounds slowly racemized at room temperature.[45] This racemization was explained by trace amounts of HCl involving reversible protonation of the phosphorus atom, with a concerted back-side attack of a chloride anion to the P-Cl bond, leading to the reversible formation of an achiral dichloropentacoordinated intermediate.[46] Coordinated to the borane moiety, the chlorophosphines afford the configurationally more stable compounds **10**, which have similar reactivity.[14b]

The chlorophosphine boranes **10** are readily obtained from the ephedrine-methodology, i.e., by acidolysis of the aminophosphine boranes 4 ($R^1$ = Ph) with a toluene solution of HCl inducing the P—N bond cleavage with inversion of configuration at the P-center (Scheme 5).[9a,14] The acidolysis step depends on the steric hindrance of the substituents on the phosphorus atom, the excess of HCl, the concentration of reagents, and the reaction time. Thus, the chemical yields decrease from methyl- **4a** to 2-naphtylaminophosphine borane **4r**, while the cyclohexyl **4f** requires 3 h for a satisfactory yield and the *t*-Butyl



**SCHEME 5**

analogue **4d** leads to no reaction (Table III). The enantiomeric purity of the chlorophosphine boranes **10** was determined by HPLC on a chiral column of the corresponding phosphine boranes **7** resulting from the reaction of **10** with organolithium reagents (Scheme 5, Table III). Due to the moisture sensibility of the chlorophosphine boranes **10**, the best results were obtained when the crude mixture was filtered off to remove the ephedrine salt, and the filtrate used without further purification or storage, after elimination of the excess of HCl by several vacuum/argon cycles.[14*b*] Surprisingly, only of the 1-naphtylaminophosphine borane **4q** leads to racemized products **10h** and **7f**, **7ap**, after acidolysis and organolithium reaction (Table III).

The chlorophosphine boranes **10** are efficient electrophilic building blocks for the synthesis of new classes of P-chirogenic compounds very difficult to synthesize by any other way, and bearing substituents such as cyclopentadienyl, aryloxy, amino, or sulfide. Thus, various carbon, oxygen, nitrogen, or sulfur nucleophiles react with freshly prepared chlorophosphine boranes **10**, to afford the corresponding products with inversion of configuration at the P-center. The results are reported in the Table IV.

On the other hand, the bromoaryl phosphinite boranes **11a**,**b**,**h**,**i**, which are obtained by condensation of the chlorophosphine boranes 10a or **10d** with the corresponding phenates, can be used for the preparation of *o*-hydroxyarylphosphine boranes **7** as depicted on the Scheme 6.[9a] Thus, the reaction of bromoaryl phosphinite boranes **11a**,**b**,**h**,**i**, with *t*-BuLi affords halogen-metal exchange, which carry out the corresponding *o*-hydroxyarylphosphine boranes **7aw**,**ax**,**az**,**ba** in 48–96% yields, by a Fries-like rearrangement (Scheme 6, Table V). This reaction, which proceeds with retention of configuration at the P-center also, leads to the P-chirogenic *o*-hydroxyarylphosphine 5e after decomplexation of the borane by simply stirring in ethanol (Scheme 6).[9a]

**TABLE III Chlorophosphine Boranes 10 and Phosphine Derivatives 7 from Aminophosphine Boranes 4**

| Compound **4** | | Chlorophosphine borane **10** | | | | Phosphine borane **7** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $R^2$ | | HCl (equiv.) | [30] (nM) | Time (h) | | $R^3$ | Yield (%) | e.e. (%) | Ref.[a] |
| **4a** | Me | **10a** | 2.1 | 20 | 1 | **7e** | *o*-An | 80 | 95 | 14 |
| **4b** | All | **10b** | — | — | — | **7af** | Buten-4-yl | 29 | — | 21 |
| **4f** | *c*-Hex | **10c** | 6 | 60 | 3 | **7ag** | Me | 46 | 80 | 14b |
| **4h** | *o*-An | **10d** | 2.1 | 170 | 1 | **7e** | Me | 90 | 98 | 14b |
| | | | | | | **7ah** | *o*-Tol | 93 | 99 | 29 |
| | | | | | | **7ai** | 1-Np | 72 | 99 | 29 |
| | | | | | | **7q** | 2-Np | 69 | 95 | 29 |
| | | | | | | **7aj** | *o*-biPh | 81 | 77 | 29 |
| **4m** | *o*-Tol | **10e** | 6 | 60 | 1 | **7u** | Me | 61 | 98 | 14b |
| | | | | | | **7ak** | *o*-An | 93 | 99 | 29 |
| | | | | | | **7al** | 1-Np | 52 | 66 | 29 |
| | | | | | | **7am** | 2-Np | 83 | 48 | 29 |
| | | | | | | **7an** | *o*-biPh | 75 | 40 | 29 |
| **4n** | *m*-Xyl | **10f** | 6 | 60 | 1 | **7ao** | Me | 99 | 97 | 14b |
| **4p** | *o*-biPh | **10g** | 6 | 20 | 1 | **7y** | Me | 41 | 99 | 14b |
| | | | | | | **7ap** | *o*-An | 70 | 76 | 29 |
| **4q** | 1-Np | **10h** | 2.1 | 20 | 1 | **7f** | Me | 50 | 0 | 14b |
| | | | | | | **7aq** | 2-Np | 39 | 0 | 29 |
| **4r** | 2-Np | **10i** | 3 | 120 | 1 | **7g** | Me | 46 | 85 | 14b |
| **4s** | 3-MeO-2-Np | **10j** | 5 | 20 | 5 | **7ar** | Me | 75 | 96 | 33 |
| **4u** | Fc | **10k** | 6 | 60 | 24 | **7h** | Me | 76 | 95 | 28 |
| | | | | | | **7as** | *o*-An | 78 | 95 | 28 |

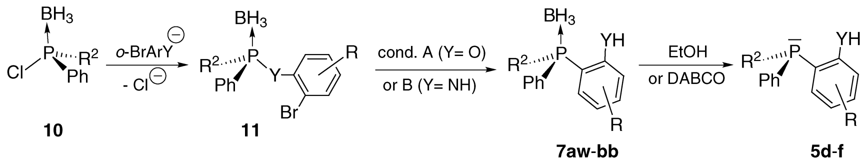
[a] All syntheses were performed starting from the (+)-ephedrine, except for **10b** and **7af**, which were prepared in racemic form.

**TABLE IV P-Chirogenic Organophosphorus Borane Complexes from Chlorophosphine Boranes 10**

| Compound **10** | | | P-Chirogenic Borane Complex | | | |
|---|---|---|---|---|---|---|
| | $R^2$ | $R^3Li$ or YM | | Yield (%) | e.e. (%) | Ref.[a] |
| **10a** | Me | CpNa | **7at** | 83 | 85 | 14 |
| | | IndLi | **7au** | 81 | — | 28 |
| | | 2-BrPhONa | **11a** | 71 | 72 | 9a |
| | | 1-Br-2-NpONa | **11b** | 66 | 91 | 9a |
| | | PhSLi | **11c** | 87 | 60 | 14b |
| | | *o*-$Ph(OLi)_2$ | **11d** | 86 | $> 95$ | 14b |
| | | 2-BrPhNHLi | **11e** | 53 | 99 | 47 |
| **10d** | *o*-An | 2-$FcCH_2N(Me)_2$ | **7av** | 72 | —[b] | 28 |
| | | 2,4-di-(*t*-Bu)PhONa | **11f** | 80 | 94 | 33 |
| | | 4-MePhONa | **11g** | 85 | 97 | 14b |
| | | 2-BrPhONa | **11h** | 70 | 80 | 9a |
| | | 1-Br-2-NpONa | **11i** | 88 | 99 | 9a |
| | | *m*-$Ph(OLi)_2$ | **11j** | 58 | 96 | 33 |
| | | 1,1'-bi$Ph(OLi)_2$ | **11k** | 70 | 96 | 29 |
| | | $Ph_2P(BH_3)N(CH_3)CH(CH_3)CH(Ph)OLi$ | **11l** | 65 | $> 95$ | 48,49 |
| | | 2-BrPhNHLi | **11m** | 75 | 98 | 47 |
| | | $(CH_2NH)_2Na_2$ | **11n** | 89 | 96 | 14b |

[a] All syntheses were performed starting from the (+)-ephedrine; and [b] epimeric mixture 1:1 separated by chromatography.

The *ortho* Fries-like rearrangement of the *o*-bromoarylaminophosphine boranes 11e and 11m was achieved according to a modified procedure,[47] in order to protect the NH group during the metal-halide exchange step. Thus, the aminophosphine boranes **11** was first deprotonated by LDA (1.2 equiv.), then trapped with TMSCl (2.4 equiv.) to afford the rearrangement by metal halide exchange. Under these conditions, the *o*-aminoarylphosphine boranes **7ay** and **7bb** were obtained with retention of configuration at the P-center in 72–88% yields and with e.e. up to 96% (Table V). The of decomplexation was performed by DABCO in toluene at room

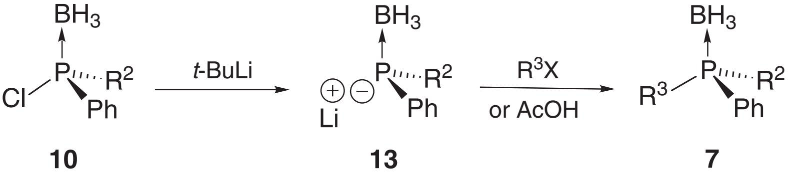


**SCHEME 6**

**TABLE V Synthesis of P-Chirogenic *o*-Hydroxy- or *o*-Aminoarylphosphines 5**

| Compound **11** | | | Phosphine borane **7** | | | | *o*-Hydroxy (or amino) Phosphine **5** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | $R^2$ | Y | | Conditions[a,b] | Yield (%) | e.e. (%) | | Conditions | Yield (%) | e.e. (%) | Ref. |
| **11a** | Me | O | **7aw** | A | 75 | 72 | — | — | — | — | 9a |
| **11b** | Me | O | **7ax** | A | 96 | 91 | — | — | — | — | 9a |
| **11e** | Me | NH | **7ay**[c] | B | 72 | — | **5d**[c] | DABCO/RT/Toluene/12h | 70 | 90 | 47 |
| **11h** | *o*-An | O | **7az** | A | 87 | 80 | — | — | — | — | 9a |
| **11i** | *o*-An | O | **7ba** | A | 48 | 99 | **5e** | EtOH/ RT/12h | 84 | 99 | 9a |
| **11m** | *o*-An | NH | **7bb** | B | 88 | 96 | **5f** | DABCO/RT/ Toluene/12h | 80 | 92 | 47 |

[a] Conditions A: *t*-BuLi (2.7 equiv.)/ −78°C/ 1 h to 0°C. [b] Conditions B: i) LDA (1.2 equiv.)/ −78°C to −30°C; ii) TMSCl (2.4–4.8 equiv.)/ −78°C to RT°C; iii) *t*-BuLi (3.5-7 equiv.)/ −78°C to RT. [c] These products bear $CH_2TMS$ as $R^2$ substituent.



**SCHEME 7**

temperature affording the P-chirogenic *o*-aminoarylphosphine **5d** and **5f** in excellent yields (Table V).

Finally, an unexpected reaction involving the chlorophosphine boranes **10** was observed.[28] Thus, the reaction of *t*-butyllithium (3 equiv.) with the chlorophosphine boranes **10** in toluene at −85°C, afford the corresponding P-chirogenic phosphide boranes **13**, by metal-halide exchange. Subsequent addition of THF followed by an excess of alkyl halide affords the corresponding phosphine boranes **7** in 21–75% yields and with e.e. up to 99% (Scheme 7, Table VI). The stereochemistry of the reaction, which was established by X-ray structure of the phosphine borane **7bh**, was in good agreement with retention of configuration during the metal-halide exchange. When the phosphide boranes **13** were protonated by acetic acid, the corresponding P-chirogenic secondary phosphine boranes **7bc, 7bf** were then obtained in good yields and with e.e. up to 94 % (Scheme 7, Table VI).

**TABLE VI P-Chirogenic Phosphine Boranes 7 from P-Chirogenic Phosphide Borane 13**

| Chlorophosphine borane **10** | | Phosphine borane **7** | | | |
|---|---|---|---|---|---|
| | $R^2$ | | $R^3$ | Yields (%) | e.e. (%)[a] |
| **10d** | *o*-An | **7bc** | H | 95 | 94 |
| | | **7e** | Me | 99 | 99 |
| | | **7bd** | Et | 75 | 99 |
| | | **7be** | Bn | 75 | 95 |
| **10e** | *o*-Tol | **7u** | Me | 95 | 94 |
| **10g** | *o*-biPh | **7y** | Me | 55 | 93 |
| **10k** | Fc | **7bf** | H | 60 | > 90 |
| | | **7h** | Me | 73 | 90 |
| | | **7bg** | Et | 43 | 91 |
| | | **7bh** | Bn | 59 | 87 |

[a] Determined by HPLC on chiral column.

## CONCLUSION

In summary, the stereoselective synthesis of P-chirogenic phosphorus compounds using the commercially available (+)- or (−)-ephedrine as chiral auxiliary was described. The oxazaphospholidone borane complex **3**, prepared in one step from ephedrine, reacts with alkyl or aryl lithium reagents to afford regio- and stereoselectively the corresponding aminophosphine borane **4** by P-O bond cleavage and retention of configuration. These ring opening products are used to prepare electrophilic P-chirogenic building blocks by P—N cleavage, under acid methanolysis or HCl acidolysis conditions. Both reactions proceed with inversion of the configuration at the phosphorus center and lead to the methyl phosphinite boranes **6** or chlorophosphine boranes **10** with high to excellent enantiomeric purity (80–99% e.e.). These compounds are useful electrophilic P-chirogenic building blocks for the synthesis of numerous phosphine ligands **5**, by reaction with organolithium reagents then decomplexation of the borane protecting group. In addition, the chlorophosphine boranes **4** are more versatile than the phosphinite boranes **6** because their reaction occurs also with various nucleophiles, such as carbanions, phenates, thiophenates, or amidures. Thus, organophosphorus borane complexes were prepared by P—C, P—O, P—S, and P—N bond formation, respectively, in high yields and with e.e. up to 99% e.e.

Noteworthy, a novel access to P-chirogenic phosphide boranes **13** was possible using an unexpected metal-chlorine exchange reaction of chlorophosphine boranes **4**. Subsequent addition of alkyl halides to the phosphide boranes **13** or protonation with AcOH, affords the corresponding tertiary or secondary P-chirogenic diarylphosphine boranes **7** (or **14**) in excellent yields and with high e.e..

Finally, these results demonstrate the remarkable efficiency of the ephedrine-methodology for the synthesis of various classes of P-chirogenic phosphorus compounds, using either electrophilic or nucleophilic ways.

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