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o-(Hydroxyalkyl)phenyl P-Chirogenic Phosphines as Functional Chiral Lewis Bases

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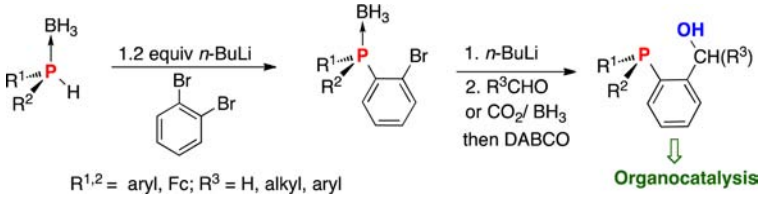
ABSTRACT



The stereoselective synthesis of P-chirogenic phosphines bearing an *o*-hydroxyalkyl chelating arm is described. The synthesis is based either on the hydroxyalkylation of P-chirogenic *o*-bromophenylphosphines (borane) or on their carbonatation and then reduction. The hydroxyalkylation with benzaldehyde or pivalaldehyde affords a mixture of epimers which are isolated by chromatography and characterized by their X-ray structures. Preliminary assays of free P-chirogenic *o*-(hydroxyalkyl)phenyl phosphines, as new functional Lewis bases in catalyzed asymmetric aza-MBH reaction, lead to β-aminoester derivatives with ee values up to 74%.

A chiral organophosphorus bearing a heteroatom or a functional group in the *ortho* position of an aryl substituent is a useful ligand or Lewis base for the development of catalyzed or organocatalyzed asymmetric reactions.[1−4] Among the chiral functional organophosphorus derivatives, those bearing a phenol substituent have gained attention because they could be used in various asymmetric reactions using either transition-metal catalysts[3] or bifunctional organocatalysts.[4] Despite the importance of the functional chiral organophosphorus compounds, few efficient stereoselective syntheses have been described to date.[1] The synthesis of a P-chirogenic organophosphorus bearing a hydroxyalkyl (or aryl) substituent could be achieved by demethylation of a methoxy substituent,[2c,3a] by carbonatation then reduction,[5] or by trapping a C,O-phenol dilithium reagent with a chlorophosphine.[6] A more convenient method has been developed on the basis of the *ortho* Fries-like rearrangement of the corresponding 2-bromoaryl phosphinite borane, with retention of configuration at the phosphorus atom.[7]

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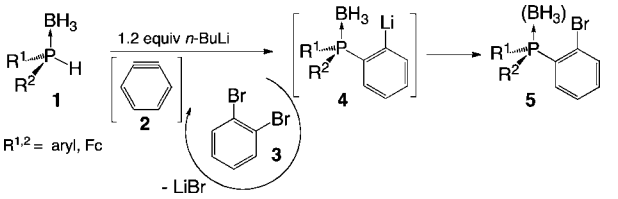
Scheme 1. Stereoselective Synthesis of P-Chirogenic *o*-Bromophenyl Phosphines Using Aryne Chemistry



We have recently described an efficient stereoselective synthesis of *o*-bromophenyl P-chirogenic phosphines **5**, based on the reaction between the secondary phosphine borane **1** and benzyne **2**, generated *in situ* from 1,2-dibromobenzene **3** by metal−halide exchange (Scheme 1).[8] In continuity of this research, we were interested in the synthesis of P-chirogenic phosphines bearing a hydroxyalkyl chelating arm, for the development of a new class of chiral *o*-functional Lewis bases.

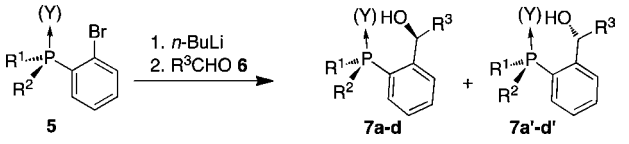
Herein, we report an efficient stereoselective synthesis of P-chirogenic *o*-(hydroxyalkyl)phenyl phosphines, either by hydroxyalkylation of the corresponding *o*-bromophenyl phosphine precursors **5** or by Fries-like rearrangement of a phosphinite borane derived from 2-bromobenzyl alcohol.

In the first case, the hydroxyalkylation was achieved by the reaction of the anion derived from the *o*-bromo phenylphosphine borane **5a**, or the free phosphine **5b**, with the benzaldehyde **6a** or the pivalaldehyde **6b**. The corresponding P-chirogenic *o*-(hydroxyalkyl)phenyl phosphines (borane) were obtained as a mixture of two epimers **7** and **7′** with respect to the absolute configuration at the P-center, with yields ranging from 42% to 72% (Table 1).

Thus, the reaction of the phosphine borane (R_p)-**5a** with the benzaldehyde **6a** affords the epimeric mixture (S_p)-**7a** and (S_p)-**7a′** in the ratio 45:55 (entry 1). The epimers were separated by chromatography, and their enantiomeric purities were checked by HPLC on a chiral column. Crystals of (S_p)-**7a′** were grown from methylene chloride/hexane as solvent, and its drawing is shown in Figure 1. The structure of (S_p)-**7a′** shows a distorted tetrahedral geometry at the P-atom which is typical of phosphine borane adducts, which proves the (S_p)- and (*R*)-configuration at the P- and C-atom, respectively. These absolute configurations are supported by refinement of the Flack parameter (Table S1).

In the case of the reaction of the *o*-bromo ferrocenylphenylphosphine borane (S_p)-**5a** with benzaldehyde **6a**, the *o*-(hydroxyalkyl)phenylphosphine borane (R_p)-**7a** and

Table 1. Synthesis of P-Chirogenic *o*-(Hydroxyalkyl)phenyl Phosphines (Borane) **7a**−**d**[a]



entry	reagents[a]	R^1	R^2	R^3	Y	products[d]	ratio[e] **7**:**7′**	yields (%)[f]
1	(R_p)-**5a**[a,g]	**6a**	Fc	Ph	Ph	BH_3	(S_p)-**7a**, **7a′**	45:55	71
2	(S_p)-**5a**[a,h]	**6a**	Ph	Fc	Ph	BH_3	(R_p)-**7a**, **7a′**	64:36	72
3	(S_p)-**5a**[a,h]	**6b**	Ph	Fc	*t*-Bu	BH_3	(R_p)-**7b**, **7b′**	60:40	66
4	(S_p)-**5b**[a,h]	**6a**	Ph	*o*-An	Ph	..	(R_p)-**7c**, **7c′**	80:20[i]	45
5	(S_p)-**5b**[b,h]	**6a**	Ph	*o*-An	Ph	..	(R_p)-**7c**, **7c′**	70:30[i]	48
6	(S_p)-**5b**[c,h]	**6a**	Ph	*o*-An	Ph	..	(R_p)-**7c**, **7c′**	70:30[i]	42
7	(S_p)-**5b**[a,h]	**6b**	Ph	*o*-An	*t*-Bu	..	(R_p)-**7d**, **7d′**	60:40[i]	50

[a] Reaction conditions: **5** (0.4 mmol), *n*-BuLi (0.44 mmol) in THF (2 mL) at −78 °C for 1 h. Aldehyde (0.8 mmol for benzaldehyde **6a** or 1.6 mmol for pivalaldehyde **6b**) in dry THF (0.5 mL) was added at −78 °C, and the mixture was warmed to rt and stirred again for 1 h 30 min. [b] Benzaldehyde **6a** was added at 0 °C. [c] Toluene solution of benzaldehyde **6a** was added. [d] ee >99% determined by HPLC on chiral column. [e] Determined after isolation by chromatography. [f] Isolated yields after purification by column chromatography. [g] Prepared from (−)-ephedrine. [h] Prepared from (+)-ephedrine. [i] The relative configuration was attributed by comparison with the major epimers (R_pS)-**7a** and (R_pS)-**7b**.

(R_p)-**7a′** were obtained in a 64:36 ratio, 72% yield and with 99% enantiomeric excess (entry 2). The structure of the major isomer has also been determined by single crystal X-ray diffraction, as the enantiomer (R_p,*S*)-**7a** of the *o*-(hydroxyalkyl)phenyl phosphine borane (S_p,*R*)-**7a′** shows in Figure 1.

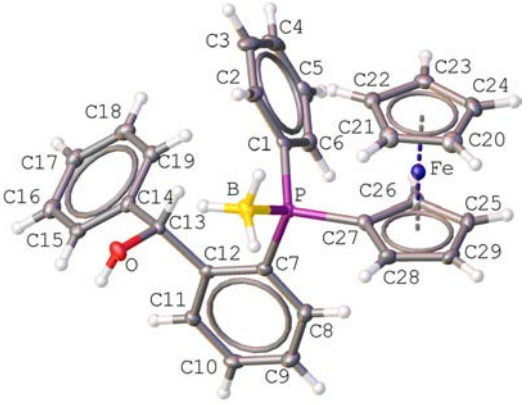


Figure 1. OLEX2 view of the *o*-(hydroxymethyl)phenyl phosphine (S_p,*R*)-**7a′**, showing thermal ellipsoids at the 50% probability level. Selected bond lengths [Å], angles [deg]: C1−P 1.818(4); C7−P 1.831(4); C13−O 1.429(4); C27−P 1.792(4); P−B 1.913(4); C2−C1−P 120.1(3); O−C13−C14 112.8(3); O−C13−C12 110.6(3); C27−P−C1 105.26(16); C27−P−C7 105.91(17); C1−P−C7 104.03(16); C27−P−B 110.35(18); C7−P−B 113.95(18). B−P−C27−C28 30.90(4); B−P−C1−C2 3.5(4); B−P−C7−C12 63.5(3); C7−C12−C13−O −101.4(4).

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When the reaction was achieved with the ferrocenyl-(*o*-bromophenyl)phosphine borane (S_p)-**5a** and the pivalaldehyde **6b**, the corresponding *o*-(hydroxyalkyl) phenyl phosphine borane (R_p)-**7b** (and **7b′**) was obtained in 66% yield and with a 60:40 ratio (entry 3). The structure of the major isomer (R_p)-**7b** has also been determined by single crystal X-ray diffraction (Figure 2).

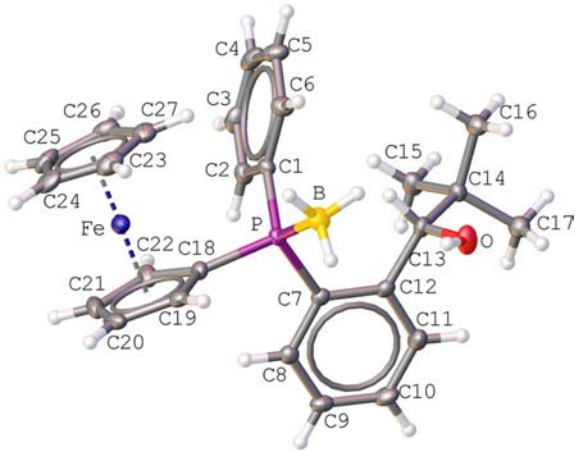

Figure 2. OLEX2 view of the *o*-(hydroxyalkyl)phenylphosphine (R_p,*S*)-**7b**, showing thermal ellipsoids at the 50% probability level. Selected bond lengths [Å], angles [deg]: C1−P 1.818(4); C7−P 1.842(4); C13−O 1.436(5); C18−P 1.792(4); P−B 1.934(5); C2−C1−P 121.2(3); O−C13−C14 108.5(3); O−C13−C12 109.7(3); C18−P−C1 106.5(2); C18−P−C7 104.9(2); C1−P−C7 106.3(2); C18−P−B 110.2(2); C7−P−B 112.9(2); B−P−C18−C22 163.4(4); B−P−C1−C2 173.0(4); B−P−C7−C12 −56.3(4); C7−C12−C13−O 108.0(4).

This structure shows again a distorted tetrahedral geometry at the P-atom which is typical of phosphine borane adducts, proving the (*R*)- and (*S*)-configuration at the P- and C-atom, respectively. These absolute configurations are supported by refinement of the Flack parameter (Table S1).

The structure of the minor isomer (R_p)-**7b′** was also determined by single crystal X-ray diffraction, and its drawing is shown in Figure 3. In this case, the X-ray structure proves the (*R*)-configuration at the P- and C-atom, which is supported by refinement of the Flack parameter (Figure 3, Table S1). After decomplexation of the borane complex using DABCO at room temperature, the anion obtained after metal−halide exchange of the *o*-anisyl-*o*-bromophenyl phenyl phosphine (S_p)-**5b** reacts with the benzaldehyde **6a** to afford the corresponding *o*-(hydroxylalkyl)phenyl derivatives **7c**, **7c′** in 45% yield (entry 4). When the reaction was performed at rt, or in a 4:1 toluene/THF mixture, **7c** and **7c′** were obtained in a 70:30 ratio, showing the poor influence of the temperature or solvent on the diastereoselectivity (entries 5, 6). In the case of the reaction of (S_p)-**5b**, with the pivalaldehyde **6b**, the corresponding *o*-(hydroxylalkyl)phenyl derivatives **7d** and **7d′** were obtained in 50% yield and with a 60:40 ratio (entry 7).

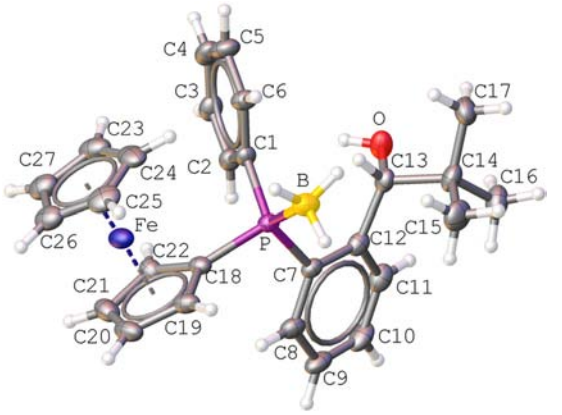

Figure 3. OLEX2 view of *o*-(hydroxymethyl)phenylphosphine borane (R_p*R*)-**7b′** showing thermal ellipsoids at the 50% probability level. Selected bond lengths [Å], angles [deg]: C1−P 1.816(4); C7−P 1.844(4); C13−O 1.440(5); C18−P 1.791(4); P−B 1.923(5); C2−C1−P 121.5(3); O−C13−C14 106.9(4); O−C13−C12 110.7(4); C18−P−C1 104.4(2); C18−P−C7 103.5(2); C1−P−C7 103.8(2); C18−P−B 111.4(2); C7−P−B 118.3(2); B−P−C18−C22 157.4(4); B−P−C1−C2 166.4(4); B−P−C7−C12 −77.5(4) ; C7−C12−C13−O −124.7(4).

On the other hand, as the reaction of paraformaldehyde was sluggish, the stereoselective synthesis of P-chirogenic ferrocenyl-*o*-(hydroxymethyl) phenyl phosphine borane (S_p)-**7e** was achieved in 40% overall yield, by trapping the anion derived from the *o*-bromophenyl phosphine borane (R_p)-**5a** with CO_2, followed by the reduction of the carboxylic acid derivative (S_p)-**8** with $BH_3 \cdot DMS$ (Scheme 2a). The enantiomeric purity of the compound (S_p)-**7e** was checked on a chiral column in regards to a racemic sample, and no racemization was found to occur during this process.

Interestingly, the stereoselective synthesis of the ferrocenyl-*o*-(hydroxymethyl)phenylphosphine (S_p)-**7e** could also be achieved by the intramolecular *ortho* Fries-like rearrangement of the 2-bromobenzylphosphinite borane (R_p)-**11**, mediated by basic conditions (Scheme 2b).

The phosphinite borane **11** was prepared in 51% yield by reaction of the *o*-bromobenzyl alcohol **10** with the P-chirogenic chlorophosphine (S_p)-**9**, previously obtained using the (+)-ephedrine methodology.[9] Finally, the phosphine borane derivative (S_p)-**7e** was obtained in 58% yield by rearrangement mediated by *tert*-butyllithium (Scheme 2b). The stereochemistry with retention of the configuration at the P-atom in the Fries-like rearrangement which was previously described in literature[7] allows the (*S*)-configuration to be attributed to **7e**.

During the past decade, chiral phosphines bearing protic moieties have emerged as powerful catalysts for various asymmetric reactions with C−C bonds formation [Michael, Baylis−Hillmann, aza-Morita−Baylis−Hillmann (aza-M-B-H)].[10] To the best of our knowledge, the use of

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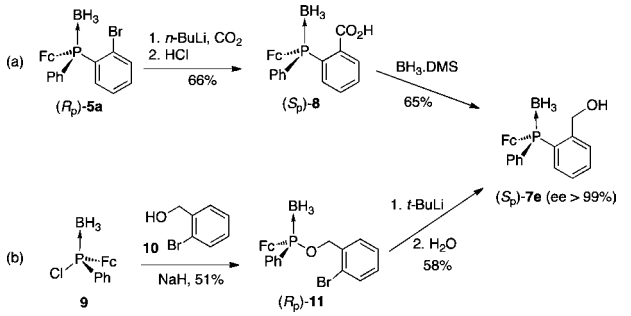
Scheme 2. Stereoselective Synthesis of the P-Chirogenic Ferrocenyl-*o*-(hydroxymethyl)phenylphosphine (S_p)-**7e**

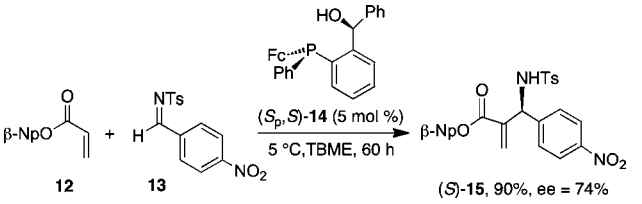


P-chirogenic phosphines as an organocatalyst has been minimally considered to date in this area.[11] In this context, the P-chirogenic *o*-(hydroxyalkyl)phenylphosphines (S_p,*S*)-**14** and (R_p,*R*)-**7c′** were preliminarily evaluated as a functional Lewis base in the asymmetric *aza*-MBH reaction (Scheme 3).[12]

The free phosphine (S_p,*S*)-**14** was prepared in 98% yield by decomplexation of (S_p,*S*)-**7a** with DABCO. When the acrylate **12** reacts with the *N*-tosyl aldimine **13** in TBME at 5 °C, in the presence of 5 mol % of (S_p,*S*)-**14**, the unsaturated β-aminoester (*S*)-**15** was obtained in 90% yield and with 74% ee (Scheme 3). In the case of the use of (R_p,*R*)-**7c′** as an organocatalyst, the β-aminoester (*S*)-**15** was obtained in 82% yield and with 68% ee.

In conclusion, we have developed an efficient stereoselective synthesis of P-chirogenic *o*-(hydroxyalkyl) phenyl phosphine boranes. This synthesis is based on the hydroxyalkylation of the anion formed by metal−halide exchange from the P-chirogenic *o*-bromophenyl phosphines (free or as borane complexes). Under these conditions, a mixture of epimers was obtained in a 45:55 to 80:20 ratio, and they were separated by chromatography. The absolute configurations were determined by the X-ray structure of the P-chirogenic phosphine borane complexes. The stereoselective synthesis of P-chirogenic ferrocenyl-*o*-(hydroxymethyl) phenyl phosphine borane could be achieved either from *o*-bromophenyl phosphine borane by reaction with CO_2 and then reduction with borane or from 2-bromobenzyl phosphinite borane, by an intramolecular Fries-like rearrangement. The use of the P-chirogenic *o*-(hydroxyalkyl)phenyl phosphines as new P-chirogenic functional Lewis bases for an asymmetric aza-MBH reaction leads to the unsaturated β-aminoester **15** with ee values up to 74% in preliminary assays, prompting further development in this area soon.

Scheme 3. Asymmetric aza-MBH Reaction Catalyzed by the P-Chirogenic *o*-(Hydroxyalkyl)phenyl Phosphine (S_p,*S*)-**14**



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Supporting Information Available. Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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