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ARTICLE TYPE

Ring-opening of Enantiomerically Pure Oxa-containing Heterocycles with Phosphorus Nucleophiles

Héctor Fernández-Pérez,[a] Pablo Etayo,[a] José Luis Núñez-Rico,[a] Bugga Balakrishna,[a] and Anton Vidal-Ferran*[a,b]

Various oxa-containing heterocycles (*i.e.* enantiopure epoxide- and oxetane-based substrates) were subjected to ring-opening with phosphorus nucleophiles. The ring-opening reactions proceeded smoothly and the resulting 1,2-, and 1,3-phosphino alcohols were efficiently isolated as stable borane complexes. These derivatives arise from regio- and stereocontrolled syntheses based on ring-opening processes of oxa-containing heterocycles. The regio- and stereochemistry of the resulting chiral products were unequivocally confirmed in many cases *via* single-crystal X-ray diffraction analysis.

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Introduction

The design and preparation of enantiomerically pure phosphorus compounds is of paramount importance in asymmetric catalysis research. These derivatives have typically been employed as chiral ligands in diverse transition metal-mediated asymmetric transformations,[1] and more recently in enantioselective organocatalytic processes.[2] In this context, there is a demand for stereocontrolled, high-yielding synthetic strategies enabling straightforward access to structurally diverse phosphorus derivatives. Enantiomerically pure phosphino alcohols (also known as *hydroxy phosphines*) are an attractive type of phosphorus(III) compounds with major potential for asymmetric catalysis. Firstly, they are valuable chiral building blocks that can be easily transformed into other, more elaborate ligands—namely, hybrid bidentate phosphorus ligands.[1] Secondly, they can also be harnessed as direct precursors of hemilabile P–O ligands, which have found numerous applications in organometallic asymmetric catalysis.[3]

Several stereoselective synthetic routes to these targets can be envisaged and, amongst them, stereocontrolled ring-opening of oxa-containing heterocycles by trivalent phosphorus nucleophiles appears to be an attractive route towards enantiomerically pure phosphino alcohol derivatives. Herein are reported new and optimised synthetic strategies dealing with the ring-opening of an array of structurally diverse enantiopure oxa-containing heterocycles. The regio- and stereochemistry of the resulting chiral products were unequivocally confirmed in most cases *via* single-crystal X-ray diffraction analysis.

Results and discussion

Ring-opening of enantiopure 1,2-disubstituted epoxides

At the onset of our study, we initially selected enantiopure, asymmetrically 1,2-disubstituted epoxides, which have scarcely been explored as substrates in this chemistry,[4] most likely due to the inherent difficulty of regiocontrol. Our group has been using the regio- and stereocontrolled ring-opening of enantiopure Sharpless epoxyethers[5] by trivalent phosphorus nucleophiles as a key step for preparing diverse enantiomerically pure P–OP ligands[1c], which in turn have enabled high enantioselectivity in diverse metal-mediated asymmetric transformations.[6]

We have already reported that ring-opening of the *trans*-(2*S*,3*S*)-1-alkoxy-3-phenyl-2,3-epoxides **1**[6a,c–i] (or their enantiomers *trans*-(2*R*,3*R*)-1-alkoxy-3-phenyl-2,3-epoxides ***ent*-1**[6g,i]) with alkali metal dialkyl- or diarylphosphides is highly regioselective (rr = 94:6 → 99:1 **2/3**). The products arising from ring-opening proved to be rather prone to oxidation: thus, *in-situ* protection as the borane complexes **2/3** allowed for easier handling and storage. The resultant borane derivatives of the *anti*-phosphino alcohols **2** (the major regioisomeric products) were isolated with high yield (63–87%) (see Scheme 1). Whilst the minor regioisomers **3** derived from epoxide **1a** (R^1 = Me) or **1b** (R^1 = CPh_3) and lithium dicyclohexylphosphide were detected by NMR in the corresponding crude mixtures, only the one derived from **1a** could be isolated and fully characterised.[6h]

Recent research activities in this field have allowed for the growth of single crystals of several phosphine-borane alcohols **2** and analysis of their structure by X-ray diffraction (**2a** [R^1 = Me, R^2_2 = Ph], *ent*-**2b** [R^1 = CPh_3, R^2_2 = Ph], **2c** [R^1 = Me, R^2_2 = Cy] and **2d** [R^1 = CPh_3, R^2_2 = Cy]).[7] These studies have confirmed previously published results[6a,c–h] on the regio- and absolute stereo-chemistry of the products derived from the ring-opening of *trans*-epoxides: *anti*-arrangement of the hydroxyl and phosphino functionalities, arising from a stereospecific S_N2 epoxide ring-opening (inversion at the attacked carbon, and retention at the other one). This recently obtained crystallographic information is included herein and can be found in the Supporting Information.

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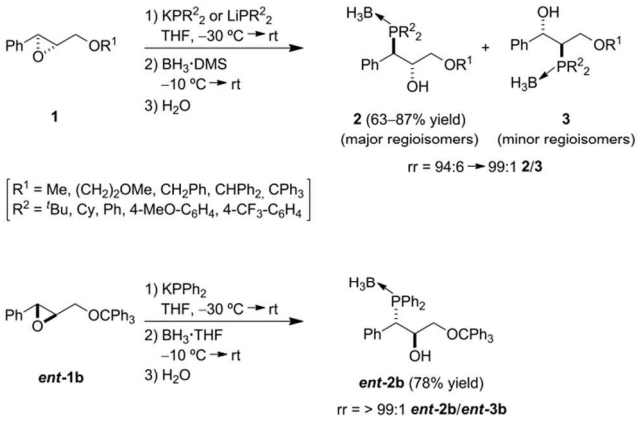
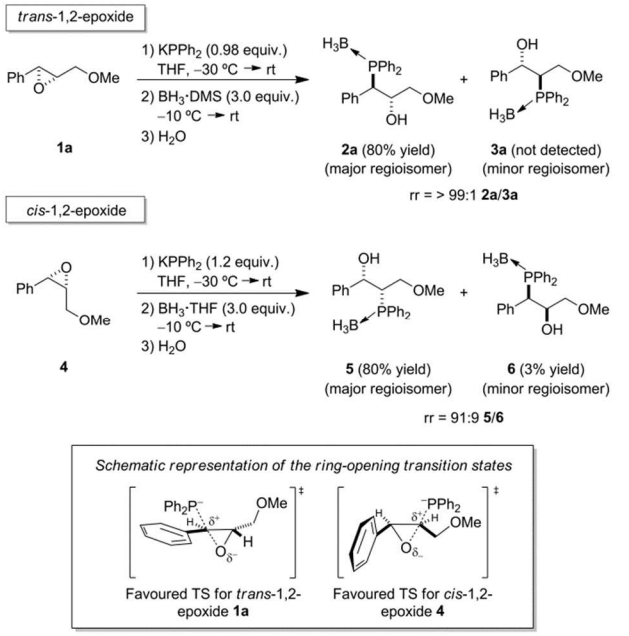


Scheme 1. Ring-opening of Sharpless epoxyethers with trivalent phosphorus nucleophiles.

Whilst a number of examples of ring-opening of *trans*-1,2-disubstituted epoxides with phosphorus nucleophiles have been published thus far [4,6a,c–h] (most of them from our research group), studies of this chemistry involving their *cis*-analogues is, to the best of our knowledge, unreported. With the reactivity studies of the ring-opening of *trans*-epoxyethers **1** in hand, the authors then turned their attention to the ring-opening of the *cis*-analogue **4**, as they considered that this chemistry would be a promising route to P–OP ligands being stereochemically different to those previously reported.[6] It was envisioned that *cis*-1,2-disubstituted epoxyethers should provide enantiomerically pure phosphine-borane alcohol derivatives having a *syn* relative configuration of the phosphorus and hydroxyl groups.



Scheme 2. Regio-alternation observed upon ring-opening of the *trans*-1,2-epoxide **1a** (top) and the *cis*-1,2-epoxide **4** (bottom) with $KPPh_2$.

The enantiopure *cis*-1,2-epoxide **4** was readily prepared following reported synthetic methodologies.[8] The ring-opening of enantiopure *cis*-1,2-epoxide **4** with $KPPh_2$ under the reaction conditions reported for the *trans* derivative **1a** revealed near-complete reversion of the previously observed regiochemistry: in this case the major regioisomer was the phosphine-borane alcohol **5** (rr = 91:9 **5/6**[9]), which was isolated in 80% yield (Scheme 2).

The unusual regiochemical outcome found in the ring-opening product of the *cis*-epoxyether **4** was unequivocally confirmed by X-ray diffraction analysis (Figure 1, left).[7] This technique enabled identification of the *syn* arrangement of the alcohol and the phosphine-borane groups, and of the absolute (2*S*,3*S*) configuration of these substituents. These results agree with a stereospecific, S_N2 epoxide ring-opening of epoxyether **4** (*i.e.* inversion at the attacked carbon, and retention at the other one).

The aforementioned results indicate that, under the same reaction conditions, the regiochemical outcome of the ring opening of 1,2-disubstituted epoxides is mainly controlled by the relative disposition of the substituents in the starting epoxides. There are several literature reports evidencing that *cis*-1,2-epoxides generally offer lower regioselectivity than do the corresponding *trans* isomers,[10] though a near-complete reversion of the regiochemical outcome between a *cis*- and *trans*-disubstituted epoxide was unexpected. A proven justification to the reversion of the regiochemical outcome cannot be provided. However, the authors hypothesise that this behaviour may be a combination of electronic and steric effects. Ring-opening at the benzylic position may predominate in *trans*-epoxides **1** due to stabilisation of the transition state by resonance effects involving the attacked carbon and the coplanar phenyl ring (Scheme 2). On the contrary, such resonance stabilisation effects cannot probably be met in the ring-opening of *cis*-epoxide **4**, as the CH_2OMe group prevents the phenyl ring adopting the required conformation in the corresponding transition state for effective resonance effects (Scheme 2). Such rationalisation has been reported for the ring-opening of related epoxides.[11]

Ring-opening of trisubtituted epoxides

With regard to other types of epoxides as starting materials for this chemistry, we turned our attention to natural products, as the chiral pool remains an attractive and economic source for enantiomerically pure, highly functionalised compounds. For instance, diastereomeric mixtures of limonene oxides **7** have been subjected to ring-opening with phosphorus nucleophiles,[12] and the expected phosphino alcohols were isolated as air-sensitive solids that required immediate transformation into the corresponding phosphine oxides[12a] or into a number of metal complexes.[12b] Unfortunately, the resulting products preserve the original C=C bond from the limonene skeleton, which might pose a problem in future applications of these compounds (or their derivatives) as catalysts in transformations involving reagents that normally add to carbon-carbon unsaturated bonds. Interestingly, ring-opening reactions of the saturated limonene oxide's analogue **8** (also known as *carvomenthene oxide*, *8,9-dihydrolimonene 1,2-epoxide* or p-*menthene oxide*) by phosphorus nucleophiles have not been reported in the literature.

The required epoxide **8** was prepared following a reported procedure from limonene oxide **7** by chemoselective hydrogenation of **7** in THF using catalytic amounts of PtO_2 (Scheme 3).[13] The desired enantiopure carvomenthene oxide **8** was obtained in quantitative yield and in the original diastereomeric ratio (47:53 *cis*/*trans*, as determined by ^1H NMR).

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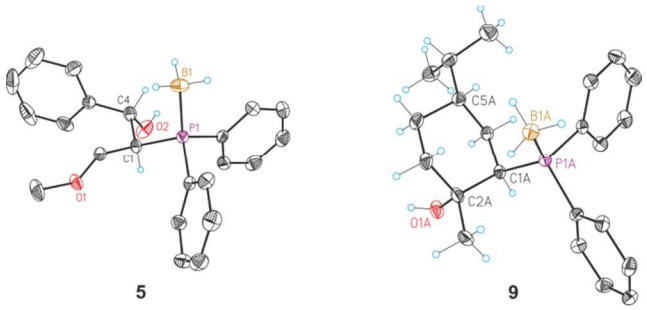
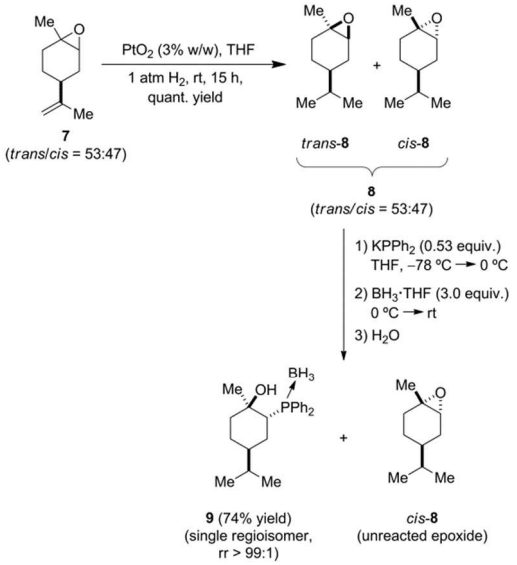


Figure 1 (Left) Crystal structure of **5**. (Right) Crystal structure of **9** (ORTEP drawings showing thermal ellipsoids at 50% probability). Non-relevant hydrogen atoms have been omitted for clarity.

However, the resultant carvomenthene oxide diastereoisomers could not be separated by silica gel column chromatography. Ring-opening of enantiomerically pure (4*S*)-carvomenthene 1,2-epoxides **8** (as diastereoisomeric mixture: *ca.* 1:1 *cis*/*trans*) with $KPPh_2$ (0.53 equiv. with respect to the overall mixture; 1.0 equiv. with respect to *trans*-**8**) proceeded smoothly at –78 ºC to 0 ºC (Scheme 3). Diastereoisomer *cis*-**8** remained mostly unreacted under ring-opening conditions and could be easily separated from product **9** by column chromatography. The ring-opening reaction was totally regioselective and proceeded exclusively through attack of C-2 in *trans*-**8** by diphenylphosphide. After *in situ* protection, the enantiopure borane-protected 1,2-phosphino alcohol **9** was isolated in 74% yield as a single regioisomer.

Structural characterisation of **9** with standard spectroscopic techniques was complemented with X-ray diffraction analysis (Figure 1, right), which confirmed both the regiochemistry and the absolute configuration of the resultant product. The chair-like conformation observed in the solid state (Figure 1, right) for the borane-protected phosphino alcohol **9** evidenced the 1,2-diaxial-*trans* orientation of the hydroxyl and phosphine-borane functionalities at C-1 and C-2, respectively, in the cyclohexane ring in the solid state, with the isopropyl substituent at the C-4 stereocentre exhibiting an equatorial disposition.



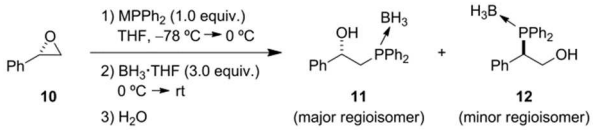
Scheme 3. Hydrogenation of *cis*/*trans*-limonene 1,2-epoxides **7** to form *cis*/*trans*-carvomenthene 1,2-epoxides **8** and subsequent ring-opening with $KPPh_2$.

Ring-opening of enantiopure monosubstituted epoxides

Altough ring-opening of enantiopure monosubstituted epoxides by trivalent phosphorus nucleophiles has already been studied,[14] we also turned our attention to the ring-opening of the terminally-monosubstituted styrene oxide **10**. Several research groups have reported the use of the diphenylphosphide anion for ring-opening of racemic[12c,15] or enantiomerically pure styrene oxide.[16] With the exception of Pellon[15c], who described the reaction as being totally regioselective, no regioselectivity issues were considered by the authors, who simply accounted for the formation of the regioisomer resulting from nucleophilic attack of $MPPh_2$ at the unsubstituted carbon of styrene oxide. Among literature reports, only Muller *et al.* took into account the formation of regioisomeric mixtures of ring-opened products derived from (*S*)-**10** and $LiPPh_2$. They found a regioisomer ratio (rr) of 70:30, which they determined by ^{31}P NMR analysis of the crude mixture.[12a]

Prompted by the lack of systematic investigation into the regio- and stereochemistry of the ring-opening of enantiomerically pure styrene oxide **10** with $MPPh_2$, the authors of the present article revisited this transformation. Using Muller's procedure[12a] as a reference and the general conditions indicated in Scheme 4, we studied the influence of the diphenylphosphide source, and the order of addition between the nucleophile ($HPPh_2$/*n*BuLi or $KPPh_2$) and the electrophile ((*S*)-styrene oxide (**10**)[17]). The results are summarised in Table 1.

As shown in Table 1, all the ring-opening reactions were highly regioselective (rr = 88:12 → 97:3 **11**/**12**), enabling gram scale isolation of the phosphine-borane alcohol **11**, which was formed by nucleophilic attack of diphenylphosphide anions at the unsubstituted carbon of (*S*)-styrene oxide **10**, in high yield (74–86% yield). This regiochemistry was consistent with literature reports:[15–16] compound **11** was the major regioisomer.



Scheme 4. Ring-opening of (*S*)-styrene oxide with $MPPh_2$.

Use of commercially available $KPPh_2$ as nucleophile gave almost complete regioselectivity (rr **11**/**12** = 97:3), regardless of the order of addition of the reactants (Table 1, entries 1 and 2). Under these conditions, the major regioisomer **11** was isolated in up to 86% yield (entry 2), whereas the minor one, **12**, was isolated in a maximum of only 3% yield (entry 2). The structure of product **11** could be unambiguously confirmed by X-ray diffraction analysis.[7] Conversely, when Muller's procedure[12a] was followed, the minor regioisomer **12** was obtained in a markedly higher proportion (rr **11**/**12** = 88:12); this method involved dropwise addition of *n*BuLi to a solution of the starting epoxide **10** and $HPPh_2$ in THF previously cooled to –78 ºC (Table 1, entry 3). Using Muller's procedure, compounds **11** and **12** were isolated in 74% and 12% yield, respectively, after column chromatography.

The ee values for regioisomers **11** and **12** varied significantly depending on the reaction conditions—basically, on the order of reagent addition, as evidenced by Table 1. Addition of $KPPh_2$ to the epoxide **10** proved to be a reliable and robust method for

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Table 1. Regioselective ring-opening of (*S*)-styrene oxide (**10**) using alkali metal diphenylphosphides ($MPPh_2$; M = K or Li).

Entry	Reaction conditions[a]	rr[b] (**11**/**12**)	Major regioisomer (**11**):		Minor regioisomer (**12**):	
			Yield[c]	ee[d] (%)	Yield[c]	ee[d] (%)
1	$KPPh_2$ added to **10**	97:3	78	99	– [e]	– [e]
2	**10** added to $KPPh_2$	97:3	86	96	3	86
3	*n*BuLi added to **10**/$HPPh_2$	88:12	74	98	12	98 (> 99)[f]

[a] For general reaction conditions, see Scheme 4 and the Experimental Section. [b] Regioisomer ratio (rr) determined by ^{1}H NMR analysis of the crude mixture. [c] Isolated yield of pure compound. [d] Determined by HPLC analysis of isolated pure product using chiral stationary phases. [e] Product not isolated. [f] Compound **12** was isolated in 10% yield and in > 99% ee after two recrystallisations.

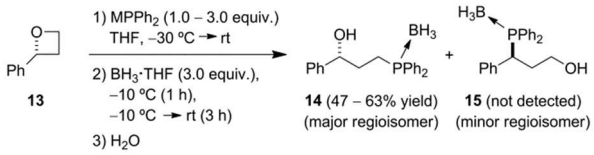
obtaining the major regioisomer **11** in enantiomerically pure form (99% ee) on the gram scale (Table 1, entry 1). Surprisingly, the reverse order of addition was detrimental to the enantiomeric purity of compounds **11** and **12** (Table 1, entry 2): their enantiopurity (96% and 86% ee, respectively) was lower than that of the starting material (99% ee).[17] These results indicate that a defect of the nucleophile with respect to the epoxide throughout the reaction (conditions indicated in entry 1) is beneficial for avoiding erosion of the optical purity of the final products *via* undesired processes (*i.e.* metallation of the carbon alpha to oxygen and/or S_N1 epoxide ring-opening).

Under Muller's conditions[12a] the ee for either compound **11** or **12** (*ca*. 98% ee for both compounds; Table 1, entry 3) was very close to that of the starting material. Interestingly, the enantiopurity of **12** (isolated under the previous conditions in 12% yield and in 97.7% ee, Table 1) was enhanced by recrystallisation (10% yield, > 99% ee). Accordingly, this study enabled synthesis of significant quantities of compounds **11** and **12**, isolated as single regioisomers in enantiomerically pure form, under optimised reaction conditions.

Ring-opening of enantiopure oxetanes

Considering the importance of introducing structural and stereochemical diversity into enantiomerically pure phosphine-borane alcohols, we finally envisaged that 1,3-phosphino alcohol derivatives could be available by ring-opening of larger-membered oxa-containing heterocycles than epoxides (*i.e.* oxetanes) with phosphorus nucleophiles. Reports on the ring-opening of these type of compounds are very scarce in the literature.[18]

Accordingly, the enantiopure (*R*)-2-phenyloxetane **13**[19] was selected as the model substrate. Ring-opening of (*R*)-2-phenyloxetane **13** with $KPPh_2$ (1 equiv.) proceeded smoothly at –30 ºC to rt (Scheme 5). Unlike enantiomerically pure styrene oxide **10**, full conversion was not accomplished under these conditions (68% conv.), however the ring-opening was regioselective and proceeded through attack at the oxetane unsubstituted carbon alpha to oxygen. After *in situ* protection, the enantiopure borane-protected 1,3-phosphino alcohol **14** was obtained in 47% yield. The isolated yield of **14** could be increased up to 63%, respectively, by using 3 equiv. of $KPPh_2$. The use of $LiPPh_2$ (generated from $HPPh_2$ and *n*BuLi) instead of $KPPh_2$ did not bring any advantage, as the conversion and isolated yield were lower than those observed for $KPPh_2$ under the same reaction conditions.



Scheme 5. Ring-opening of (*R*)-2-phenyloxetane with $MPPh_2$.

Conclusions

Efficient and convenient syntheses of diverse, enantiomerically pure, borane-protected 1,2-, and 1,3-phosphino alcohols have been developed. The regioselective ring-opening of diversely substituted, enantiomerically pure epoxides and oxetanes with nucleophilic phosphorus reagents provided ready access to structurally diverse 1,2-, and 1,3-phosphino alcohols derivatives with full stereocontrol. Noteworthy examples include synthetic routes starting from chiral pool-derived carvomenthene oxide. The authors of this work are currently endeavouring to use these phosphorus derivatives as chiral building blocks for the preparation of new ligands for asymmetric catalysis.

Experimental Section

General Information

All syntheses were done using chemicals as purchased from commercial sources, unless otherwise stated. All manipulations and reactions were run under inert atmosphere in anhydrous solvents by using standard Schlenk-type techniques. Glassware was dried under vacuum and heated with a heat gun before use. All solvents were dried by using a Solvent Purification System (SPS). Silica gel 60 (230–400 mesh) was used for column chromatography. NMR spectra were recorded in $CDCl_3$ unless otherwise cited, using a 400 MHz or 500 MHz spectrometer. ^{1}H NMR and ^{13}C NMR chemical shifts are quoted in ppm relative to residual solvent peaks, whereas $^{31}P\{^1H\}$ NMR chemical shifts are quoted in ppm relative to 85% phosphoric acid in water and $^{11}B\{^1H\}$ NMR chemical shifts are quoted in ppm relative to $BF_3{\cdot}OEt_2$ in $CDCl_3$. High resolution mass spectra (HRMS) were recorded by using a ESI method in positive mode. Enantiomeric excess (ee) values were determined by HPLC, using chiral stationary phases in a chromatograph equipped with a diode array

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UV detector. Unless otherwise specified, materials were obtained from commercial suppliers and were used without further purification: *cis*/*trans*-(1*S*/*R*,2*R*/*S*,4*S*)-limonene 1,2-epoxide (**7**), (*S*)-styrene oxide (**10**). Compounds **4**[8] and **13**[19] were prepared according to the cited literature procedures.

X-Ray Data: Single crystals of enantiopure compounds **2a**, ***ent*-2b**, **2c**, **2d**, **5**, and **11** suitable for X-ray diffraction analysis were grown by slow diffusion of *n*-hexane into EtOAc solutions of each compound at room temperature. Single crystals of enantiopure compound **9** suitable for X-ray diffraction analysis were grown by slow diffusion of *n*-hexane into DCM solutions of the compound at room temperature. For more details on the X-Ray analysis see the Supporting Information. CCDC 931316-931319, 931321, 931323 and 931325 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(1*S*,2*S*)-2-(Diphenylphosphino borane)-3-methoxy-1-phenyl-1-propanol (**5**): A 0.5 M solution of $KPPh_2$ in THF (7.4 mL, 3.72 mmol) was added dropwise by syringe (over 5 min) to a flame-dried Schlenk flask under Ar atmosphere containing a solution of the *cis*-(2*R*,3*S*)-1,2-epoxy methyl ether **4**[8] (0.51 g, 3.10 mmol) in anhydrous THF (25.0 mL) cooled to −30 ºC. The mixture was stirred for 1 h, and then allowed to slowly reach room temperature, which took *ca*. 4 h. It was then stirred for another 1 h at room temperature. After this time, a 1.0 M solution of BH_3·THF in THF (9.3 mL, 9.30 mmol) was added dropwise (over *ca*. 15 min) by syringe to the reaction mixture previously cooled to −10 ºC. The mixture was stirred for 30 min at −10 ºC, and then allowed to warm to room temperature. It was then stirred for another 1 h. The reaction mixture was carefully quenched with water (25 mL) and diluted with EtOAc (15 mL). After the phases were separated, the resulting aqueous phase was extracted with EtOAc (2 x 25 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Based on ^{1}H and ^{31}P{^{1}H} NMR analyses, the crude product was found to comprise a 91:9 mixture of compound **5** and compound **6**, respectively. Purification of the resulting residue by silica gel column chromatography (CombiFlash® system, 40 g SiO_2 cartridge, 1st eluent: hexanes, 2nd eluent: 20:80 EtOAc/hexanes, 3rd eluent: 50:50 EtOAc/hexanes) afforded 0.91 g (80% isolated yield) of pure borane-protected phosphino alcohol **5** (major regioisomer) as a sticky foamy white solid. The minor regioisomer **6** could only be isolated in impure form and small quantities (*ca*. 30 mg, *ca*. 3% isolated yield). Data for the major regioisomer **5**: $[\alpha]_D^{25}$ = +78.4 (*c* 1.24, $CHCl_3$). IR (neat): υ = 3486 (O–H), 2382 (B–H, BH_3) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.72–1.76 (m, 3H, B*H*$_3$), 2.82–2.99 (m, 1H, O*H*), 2.88 (s, 3H, O*Me*), 3.00–3.23 (m, 3H, C*H*$_2$OMe and C*H*–PPh$_2$), 5.19 (bdd, *J* = 8.6 and 8.6 Hz, 1H, C*H*–OH), 7.22–7.39 (m, 5H, 5*H*$_{arom}$), 7.39–7.52 (m, 6H, 6*H*$_{arom}$), 7.74–7.93 (m, 4H, 4*H*$_{arom}$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 44.4 (d, J_{C-P} = 31.4 Hz, *C*H–PPh$_2$), 58.2 (O*Me*), 69.5 (*C*H$_2$–OMe), 73.0 (d, J_{C-P} = 1.5 Hz, *C*H–OH), 126.7 (*C*H$_{arom}$), 128.0 (*C*H$_{arom}$), 128.3 (d, J_{C-P} = 10.0 Hz, *C*H$_{arom}$), 128.3 (*C*H$_{arom}$), 128.4 (d, J_{C-P} = 10.5 Hz, *C*H$_{arom}$), 128.9 (d, J_{C-P} = 53.2 Hz, $C_{q\ arom}$–P), 129.5 (d, J_{C-P} = 53.4 Hz, $C_{q\ arom}$–P), 130.8 (d, J_{C-P} = 1.1 Hz, *C*H$_{arom}$), 130.9 (d, J_{C-P} = 2.6 Hz, *C*H$_{arom}$), 132.9 (d, J_{C-P} = 9.3 Hz, *C*H$_{arom}$), 133.3 (d, J_{C-P} = 8.9 Hz, *C*H$_{arom}$), 141.8 (d, J_{C-P} = 8.4 Hz, $C_{q\ arom}$) ppm. ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ = 22.5–25.0 (m, Ph$_2$*P*→BH$_3$) ppm. ^{11}B{^{1}H} NMR (128 MHz, $CDCl_3$): δ = (−40.5)–(−35.7) (m, Ph$_2$P→*B*H$_3$) ppm. HRMS (ESI$^+$): *m*/*z* calcd. for $C_{22}H_{26}BO_2PNa$ $[M + Na]^+$ 386.1698; found 386.1687.

***cis*/*trans*-(1*S*/*R*,2*R*/*S*,4*S*)-carvomenthene 1,2-epoxide** (**8**): Adams' catalyst PtO_2 (140 mg, *ca*. 3% w/w) was loaded into a two-necked flask containing a solution of a 47:53 *cis*/*trans* diastereomeric mixture of **7** (4.65 g, 30.2 mmol) in anhydrous THF (68.0 mL). The reaction flask was connected to a H_2 balloon, and the reaction mixture was vigorously stirred under atmospheric pressure of H_2 for 15 h at room temperature. After this period, the reaction mixture was diluted with hexanes (20 mL) and filtered through a Celite® 521 pad, which was washed with EtOAc (60 mL). The filtrate was concentrated under vacuum to afford 4.68 g (100% isolated yield) of pure carvomenthene 1,2-epoxide **8** as a colorless liquid. Compound **8** was obtained as a diastereomeric mixture comprising *cis*-**8** and *trans*-**8** in a *cis*/*trans* ratio of 47:53 (determined by ^{1}H NMR). The physical and spectroscopic data obtained for this diastereomeric mixture agree with literature reports.[13]

(1*R*,2*R*,4*S*)-2-(Diphenylphosphino borane)-4-isopropyl-1-methyl-cyclohexanol (**9**): A 0.5 M solution of $KPPh_2$ in THF (27.5 mL, 13.7 mmol) was added dropwise by syringe (over 15 min) to a flame-dried Schlenk flask under Ar atmosphere containing a solution of a 47:53 *cis*/*trans* diastereomeric mixture of **8** (4.00 g, 25.9 mmol of mixture containing 13.7 mmol of *trans*-**8**) in anhydrous THF (40.0 mL) cooled to −78 ºC. The mixture was stirred for 1 h, and then allowed to slowly reach 0 ºC, which took around 4 h. It was then stirred for another 1 h at 0 ºC. After this time, a 1.0 M solution of BH_3·THF in THF (41.2 mL, 41.2 mmol) was added dropwise (over *ca*. 30 min) by syringe to the previous reaction mixture maintained at 0 ºC. The mixture was subsequently allowed to warm to room temperature, and then stirred for another 1 h. The reaction mixture was carefully quenched with water (100 mL) and diluted with EtOAc (50 mL). After the phases were separated, the resulting aqueous phase was extracted with EtOAc (2 x 80 mL). The combined organic layers were washed with brine (2 x 150 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. ^{1}H and ^{31}P{^{1}H} NMR analyses of the crude mixture confirmed the complete regioselectivity of the ring-opening process to the formation of compound **9** as a single regioisomer and evidenced that the diastereoisomer *cis*-**8** of the starting epoxide remained unreacted. Purification of the resulting residue by silica gel column chromatography (CombiFlash® system, 120 g SiO_2 cartridge, 1st eluent: hexanes, 2nd eluent: 10:90 EtOAc/hexanes, 3rd eluent: 30:70 EtOAc/hexanes) afforded 3.59 g (74% isolated yield) of pure borane-protected phosphino alcohol **9** as a foamy white solid. M.p. 49.0–51.6 ºC. $[\alpha]_D^{26}$ = −42.1 (*c* 0.86, $CHCl_3$). IR (neat): υ = 3483 (O–H), 2389 (B–H, BH_3) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.64 (d, *J* = 6.6 Hz, 3H, CH(*Me*)$_2$), 0.82 (d, *J* = 6.7 Hz, 3H, CH(*Me*)$_2$), 0.97–1.56 (m, 3H, B*H*$_3$), 1.15 (s, 3H, *Me*–C–OH), 1.39–1.53 (m, 3H, C*H*$_2$ and C*H*–CH(Me)$_2$), 1.55–1.71 (m, 3H, C*H*$_2$ and C*H*(Me)$_2$), 1.76–1.94

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DOI: 10.1039/C4RA10432C

Published on 30 October 2014. Downloaded by Temple University on 31/10/2014 13:26:36.

(m, 2H, CH_2), 2.56 (bs, 1H, OH), 3.00 (ddd, J = 13.0, 8.9 and 3.9 Hz, 1H, CH–PPh_2), 7.40–7.55 (m, 6H, 6H_{arom}), 7.75–7.91 (m, 4H, 4H_{arom}) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 20.3 (CH(Me)$_2$), 20.4 (CH(Me)$_2$), 24.9 (CH_2), 26.6 (Me–C–OH), 28.1 (CH_2), 28.3 (CH(Me)$_2$), 37.0 (d, J_{C-P} = 5.2 Hz, CH_2), 39.1 (d, J_{C-P} = 5.1 Hz, CH–CH(Me)$_2$), 41.8 (d, J_{C-P} = 27.5 Hz, CH–PPh_2), 73.1 (d, J_{C-P} = 4.5 Hz, C–OH), 128.0 (d, J_{C-P} = 53.7 Hz, $C_{q\ arom}$–P), 128.5 (d, J_{C-P} = 9.9 Hz, CH_{arom}), 128.7 (d, J_{C-P} = 9.5 Hz, CH_{arom}), 130.1 (d, J_{C-P} = 56.5 Hz, $C_{q\ arom}$–P), 130.9 (d, J_{C-P} = 2.4 Hz, CH_{arom}), 131.3 (d, J_{C-P} = 2.1 Hz, CH_{arom}), 132.1 (d, J_{C-P} = 8.2 Hz, CH_{arom}), 134.0 (d, J_{C-P} = 8.8 Hz, CH_{arom}) ppm. $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ = 17.0–21.2 (m, Ph_2P→BH_3) ppm. $^{11}B\{^1H\}$ NMR (128 MHz, $CDCl_3$): δ = (–40.2)–(–32.2) (m, Ph_2P→BH_3) ppm. HRMS (ESI$^+$): m/z calcd. for $C_{22}H_{32}BOPNa$ [M + Na]$^+$ 376.2218; found 376.2234.

(*S*)-2-(Diphenylphosphino borane)-1-phenylethanol (**11**; see Table 1, entry 1): A 0.5 M solution of $KPPh_2$ in THF (32.6 mL, 16.3 mmol) was added dropwise (over 15 min) by syringe to a flame-dried Schlenk flask under Ar atmosphere containing a solution of (*S*)-styrene oxide **10** (2.00 g, 16.3 mmol) in anhydrous THF (40.0 mL) cooled to −78 ºC. The mixture was stirred for 1 h, and then allowed to slowly reach 0 ºC, which took *ca*. 4 h. It was then stirred for another 1 h at 0 ºC. After this time, a 1.0 M solution of BH_3·THF in THF (16.3 mL, 16.3 mmol) was added dropwise (over *ca.* 30 min) by syringe to the previous reaction mixture, maintained at 0 ºC. The mixture was subsequently allowed to warm to room temperature, then stirred for another 1 h, carefully quenched with water (100 mL) and diluted with EtOAc (50 mL). After the phases were separated, the aqueous phase was extracted with EtOAc (2 x 80 mL). The combined organic layers were washed with brine (2 x 150 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Based on ^1H NMR analysis, the crude product was found to comprise a 97:3 mixture of compound **11** and compound **12**, respectively. Purification of the resulting residue by silica gel column chromatography (CombiFlash® system, 120 g SiO_2 cartridge, 1st eluent: hexanes, 2nd eluent: 10:90 EtOAc/hexanes) afforded 4.06 g (78% isolated yield) of pure borane-protected phosphino alcohol **11** (major regioisomer) as a crystalline white solid. The minor regioisomer **12** was not isolated. The enantiomeric purity of the isolated pure compound **11** was determined to be 99.0% ee by HPLC analysis on a chiral stationary phase. HPLC conditions were optimised for the racemate of **11**, prepared from racemic styrene oxide *rac*-**10** and are the following ones: Daicel Chiralpak® AD-H (25 cm x 0.46 cm x 5 µm), 95:5 *n*-hexane/2-propanol, 1.0 mL/min, 216 nm, $t_R(R)$ = 33.4 min, $t_R(S)$ = 40.1 min. Data for the major regioisomer **11**: M.p. 94.4–99.3 ºC. $[\alpha]_D^{26}$ = +46.2 (*c* 1.10, $CHCl_3$). IR (neat): υ = 3507 (O–H), 2407 and 2366 (B–H, BH_3) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.85–1.70 (m, 3H, BH_3), 2.69 (ddd, J = 14.9, 12.7 and 2.4 Hz, 1H, CHH–PPh_2), 2.79 (ddd, J = 14.9, 9.7 and 8.0 Hz, 1H, CHH–PPh_2), 3.03 (bs, 1H, OH), 5.12 (ddd, J = 9.7, 9.6 and 2.4 Hz, 1H, CH–OH), 7.25–7.31 (m, 1H, 1H_{arom}), 7.31–7.38 (m, 4H, 4H_{arom}), 7.43–7.57 (m, 6H, 6H_{arom}), 7.70–7.78 (m, 4H, 4H_{arom}) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 37.1 (d, J_{C-P} = 34.0 Hz, CH_2–PPh_2), 69.6 (CH–OH), 125.5 (CH_{arom}), 127.9 (CH_{arom}), 128.6 (CH_{arom}), 128.8 (d, J_{C-P} = 55.5 Hz, $C_{q\ arom}$–P), 128.9 (d, J_{C-P} = 10.2 Hz, CH_{arom}), 129.0 (d, J_{C-P} = 10.1 Hz, CH_{arom}), 129.5 (d, J_{C-P} = 57.4 Hz, $C_{q\ arom}$–P), 131.3 (d, J_{C-P} = 2.1 Hz, CH_{arom}), 131.5 (d, J_{C-P} = 2.0 Hz, CH_{arom}), 132.0 (d, J_{C-P} = 9.7 Hz, CH_{arom}), 132.4 (d, J_{C-P} = 9.2 Hz, CH_{arom}), 143.8 (d, J_{C-P} = 11.3 Hz, $C_{q\ arom}$) ppm. $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ = 14.3–16.1 (m, Ph_2P→BH_3) ppm. $^{11}B\{^1H\}$ NMR (160 MHz, $CDCl_3$): δ = (–41.0)–(–37.0) (m, Ph_2P→BH_3) ppm. HRMS (ESI$^+$): m/z calcd. for $C_{20}H_{22}BOPNa$ [M + Na]$^+$ 342.1435; found 342.1419.

(*R*)-2-(Diphenylphosphino borane)-2-phenylethanol (**12**; see Table 1, entry 3): A 2.5 M solution of *n*BuLi in hexanes (6.5 mL, 16.3 mmol) was added dropwise by syringe (over 15 min) to a flame-dried Schlenk flask under Ar atmosphere containing a solution of (*S*)-styrene oxide **10** (2.00 g, 16.3 mmol) and $HPPh_2$ (2.8 mL, 16.3 mmol) in anhydrous THF (40.0 mL) cooled to −78 ºC. The mixture was stirred for 1 h, and then allowed to slowly reach 0 ºC, which took around 4 h. It was then stirred for another 1 h at 0 ºC. After this time, a 1.0 M solution of BH_3·THF in THF (16.3 mL, 16.3 mmol) was added dropwise (over *ca*. 30 min) by syringe to the previous reaction mixture maintained at 0 ºC. The mixture was subsequently allowed to warm to room temperature, and then stirred for another 1 h. The reaction mixture was carefully quenched with water (100 mL) and diluted with EtOAc (50 mL). After the phases were separated, the resulting aqueous phase was extracted with EtOAc (2 x 80 mL). The combined organic layers were washed with brine (2 x 150 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Based on ^1H NMR analysis, the crude product was found to comprise an 88:12 mixture of compound **11** and compound **12**, respectively. Purification of the resulting residue by silica gel column chromatography (CombiFlash® system, 120 g SiO_2 cartridge, 1st eluent: hexanes, 2nd eluent: 10:90 EtOAc/hexanes, 3rd eluent: 30:70 EtOAc/hexanes) afforded 3.85 g (74% isolated yield) of pure borane-protected phosphino alcohol **11** (major regioisomer) as a crystalline white solid and 0.60 g (12% isolated yield) of pure borane-protected phosphino alcohol **12** (minor regioisomer) as a foamy white solid. The enantiomeric purity of the isolated pure compounds **11** and **12** was determined to be 97.6% ee (*S* enantiomer) and 97.7% ee (*R* enantiomer), respectively, by HPLC analysis on chiral stationary phases. Two subsequent recrystallisations from diluted solutions of **12** in the solvent mixture 1:4 Et_2O/*n*-hexane (150 and 100 mL of mixture used for the first and second recrystallisation, respectively) by refrigerating the latter solutions overnight at 5 ºC furnished the minor regioisomer **12** with 10% yield (0.50 g isolated) and in greater than 99% ee. HPLC conditions were optimised for the racemate of **12**, prepared from racemic styrene oxide *rac*-**10**, and comprise: Daicel Chiralcel® OD-H (25 cm x 0.46 cm x 5 µm), 95:5 *n*-hexane/2-propanol, 1.0 mL/min, 216 nm, $t_R(S)$ = 20.7 min, $t_R(R)$ = 23.6 min. Data for the minor regioisomer **12**: M.p. 103.5–107.0 ºC. $[\alpha]_D^{26}$ = −161.2 (*c* 1.11, $CHCl_3$). IR (neat): υ = 3416 (O–H), 2399 (B–H, BH_3) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.69–1.49 (m, 3H, BH_3), 1.79 (bs, 1H, OH), 4.01 (ddd, J = 14.2, 8.9 and 5.1 Hz, 1H, CH–PPh_2), 4.06–4.16 (m, 1H, CHH–OH), 4.24–4.34 (m, 1H, CHH–OH), 7.15–7.27 (m, 7H, 7H_{arom}), 7.32–7.39 (m, 3H, 3H_{arom}), 7.50–7.61 (m, 3H, 3H_{arom}), 7.91–7.98 (m, 2H, 2H_{arom}) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 46.2 (d, J_{C-P} = 29.2 Hz, CH–PPh_2), 62.9 (d, J_{C-P} = 10.4 Hz, CH_2–OH), 127.5 (d, J_{C-P} = 55.7 Hz, C_q

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DOI: 10.1039/C4RA10432C

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$_{arom}$–P), 127.7 (d, $J_{C–P}$ = 2.0 Hz, CH_{arom}), 128.0 (d, $J_{C–P}$ = 53.7 Hz, $C_{q\ arom}$–P), 128.2 (d, $J_{C–P}$ = 10.2 Hz, CH_{arom}), 128.4 (d, $J_{C–P}$ = 1.7 Hz, CH_{arom}), 129.0 (d, $J_{C–P}$ = 10.0 Hz, CH_{arom}), 129.9 (d, $J_{C–P}$ = 4.6 Hz, CH_{arom}), 131.0 (d, $J_{C–P}$ = 2.6 Hz, CH_{arom}), 131.5 (d, $J_{C–P}$ = 2.0 Hz, CH_{arom}), 132.8 (d, $J_{C–P}$ = 8.7 Hz, CH_{arom}), 132.9 (d, $J_{C–P}$ = 8.6 Hz, CH_{arom}), 134.0 (d, $J_{C–P}$ = 1.7 Hz, $C_{q\ arom}$) ppm. $^{31}P\{^{1}H\}$ NMR (202 MHz, $CDCl_3$): δ = 21.2–22.7 (m, $Ph_2P{\rightarrow}BH_3$) ppm. $^{11}B\{^{1}H\}$ NMR (160 MHz, $CDCl_3$): δ = (–48.9)–(–38.2) (m, $Ph_2P{\rightarrow}BH_3$) ppm. HRMS (ESI^+): *m*/*z* calcd. for $C_{20}H_{22}BOPNa$ $[M + Na]^+$ 342.1435; found 342.1425.

(*R*)-3-(Diphenylphosphino borane)-1-phenyl-1-propanol (**14**): A 0.5 M solution of $KPPh_2$ in THF (2.2 mL, 1.14 mmol) was added dropwise by syringe (over 5 min) to a flame-dried Schlenk flask under Ar atmosphere containing a solution of the (*R*)-2-phenyloxetane **13** (0.051 g, 0.38 mmol) in anhydrous THF (3.2 mL) cooled to −30 ºC. The mixture was stirred for 1 h, and then allowed to slowly reach room temperature, which took *ca*. 4 h. It was then stirred for another 1 h at room temperature. After this time, a 1.0 M solution of BH_3·THF in THF (1.14 mL, 1.14 mmol) was added dropwise (over *ca*. 15 min) by syringe to the reaction mixture previously cooled to −10 ºC. The mixture was stirred for 1 h at −10 ºC, and then allowed to warm to room temperature. It was then stirred for another 3 h. The reaction mixture was carefully quenched with water (3 mL) and diluted with EtOAc (5 mL). After the phases were separated, the resulting aqueous phase was extracted with EtOAc (2 x 5 mL). The combined organic layers were washed with brine (2 x 6 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Based on ^{1}H and $^{31}P\{^{1}H\}$ NMR analyses of the crude mixture, the regioisomer **15** was not detected. Purification of the resulting residue by silica gel column chromatography (CombiFlash® system, 12 g SiO_2 cartridge, 1st eluent: hexanes, 2nd eluent: 30:70 EtOAc/hexanes) afforded 0.080 g (63% isolated yield) of pure borane-protected phosphino alcohol **14** as a sticky foamy white solid. The physical and spectroscopic data obtained for the compound **14** agree with literature reports.[20]

Acknowledgements

The authors thank *MINECO* (grant CTQ2011-28512), *DURSI* (grant 2014SGR618) and the ICIQ Foundation for financial support. Dr. J. Benet-Buchholz and E. C. Escudero are acknowledged for X-ray crystallographic data.

Notes and references

[a] *Institute of Chemical Research of Catalonia (ICIQ), Avgda. Països Catalans 16, 43007 Tarragona, Spain. Fax: (+) 34 977928228; E-mail: avidal@iciq.cat; Homepage: http://www.iciq.es/portal/359/Vidal.aspx*
[b] *Catalan Institution for Research and Advanced Studies (ICREA), Passeig Lluís Companys 23, 08010 Barcelona, Spain. Homepage: http://www.icrea.cat/Web/ScientificForm.aspx?key=288*

† Electronic Supplementary Information (ESI) available: X-Ray analysis data of enantiopure compounds **2a**, ***ent*-2b**, **2c**, **2d**, **5**, **9** and **11**, and copies of ^{1}H, ^{13}C, ^{31}P and ^{11}B NMR spectra for all newly reported compounds.

1 See, for example, the following references and those cited therein: (a) A. Börner, ed., *Phosphorus Ligands in Asymmetric Catalysis*, 1st edn., Wiley-VCH, Weinheim, 2008; Vols. I-III; (b) P. W. N. M. van Leeuwen, P. C. J. Kamer, C. Claver, O. Pamies and M. Dieguez, *Chem. Rev.*, 2011, **111**, 2077; (c) H. Fernández-Pérez, P. Etayo, A. Panossian and A. Vidal-Ferran, *Chem. Rev.*, 2011, **111**, 2119; (d) J. Wassenaar and J. N. H. Reek, *Org. Biomol. Chem.*, 2011, **9**, 1704; (e) S. Luehr, J. Holz and A. Boerner, *ChemCatChem*, 2011, **3**, 1708; (f) P. Etayo and A. Vidal-Ferran, *Chem. Soc. Rev.*, 2013, **42**, 728; (g) M. Raynal, P. Ballester, A. Vidal-Ferran and P. W. N. M. van Leeuwen, *Chem. Soc. Rev.*, 2014, **43**, 1660; (h) M. Raynal, P. Ballester, A. Vidal-Ferran and P. W. N. M. van Leeuwen, *Chem. Soc. Rev.*, 2014, **43**, 1734.
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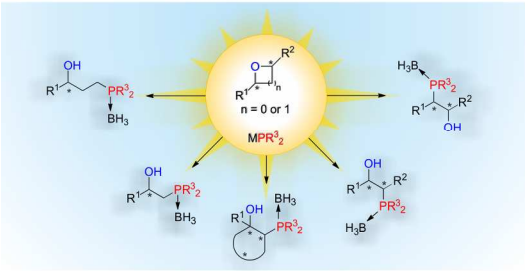

Borane complexes of phosphino alcohols were efficiently obtained by ring-opening of oxa-containing heterocycles with phosphorus nucleophiles.

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