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Myrtenal and Myrtanal as Auxiliaries in the Synthesis of Some C,P-Stereogenic Hydroxyphosphine Oxides and Hydroxyphosphine-Boranes Possessing up to Four Contiguous Centers of Chirality

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Abstract: 1,4- and 1,2-additons of secondary phosphine oxides to (1*R*)-myrtenal and (1*S*)-myrtanal were evaluated as potential routes to P,C-stereogenic phosphine oxides bearing additional hydroxyl or aldehyde functions. 1,4-Additions of racemic secondary phosphine oxides to (1*R*)-myrtenal were found to offer moderate to good stereoselectivity which shows some promise for utility in kinetic resolution processes, especially at lower conversions. In case of 1,2-additions making the process doubly asymmetric by using an enantiomerically pure secondary phosphine oxide as substrate turned out to be practical. The stereochemical course of the addition reactions under study is presented. The P-resolved 1,2-addition products were demonstrated to undergo facile reduction by BH_3 at room temperature leading to the formation of the corresponding α-hydroxyphosphine-boranes with clean inversion of configuration at the P-centre. All P,C-stereogenic phosphine oxides and boranes that were isolated in the form of a single diastereoisomer were assigned their absolute configurations by means of X-ray crystallography and/or 2D NMR spectral techniques.

Keywords: hydroxyphosphine oxides; hydroxyphosphine-boranes; P-stereogenic; kinetic resolution; doubly asymmetric additions; absolute configuration; reduction of P=O by BH_3

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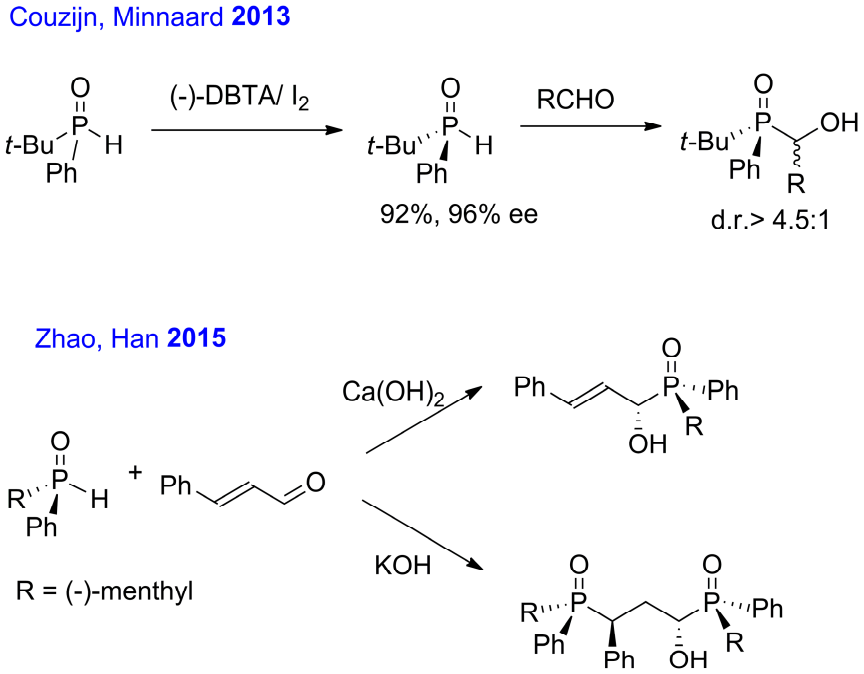
1. Introduction

The development of new methodologies leading to P-stereogenic phosphorus compounds is an important topic because these compounds find widespread use as reagents, biologically active compounds, and as ligands and organocatalysts in asymmetric synthesis [1–6]. Among them, bifunctional P-stereogenic α-hydroxyphosphine derivatives have become a motif of growing interest [7–10]. A typical synthesis of P,C-stereogenic α-hydroxyphosphine oxides is based on deprotonation of a resolved P-stereogenic secondary phosphine oxide, followed by 1,2-addition to an aldehyde which proceeds without losing optical purity of the P centre [11–14]. Nowadays, access to a wider spectrum of optically pure secondary phosphine oxides enables the formation of many derivatives having P,C-stereogenic α-hydroxyphosphine skeletons (e.g., Scheme 1) [15–18]. An interesting synthesis of P,C-stereogenic 1,3-bis(phosphinyl)hydroxypropanes by reaction of (R_P)-menthylphenylphosphine oxide with α,β-unsaturated aldehydes has been presented recently [19] (Scheme 1).

In this communication we wish to present a preliminary study that aims to explore a reverse approach, i.e., to check whether a racemic stereogenic P-centre can be effectively resolved in analogous 1,2-addition (or 1,4-addition) reactions utilizing naturally occurring (1*R*)-myrtenal and (1*S*)-myrtanal and racemic secondary phosphine oxides. Interestingly, in

contrast to the frequent use of menthol [19–22] as well as other terpenoids [23] to resolve or to generate chirality at a P-centre neither myrtenal nor myrtanal have been used previously as chiral auxiliaries or chiral scaffolds for the synthesis of P,C-stereogenic phosphorus compounds. Unlike the case with menthol, myrtenal-derived phosphine oxides allow further functionalization to be carried out easily. New myrtenal-based resolution protocols may therefore provide valuable contributions to the field of the synthesis of P,C-chiral phosphine oxides.



Scheme 1. Some recent examples of the preparations of P−stereogenic hydroxyphosphine oxides [14,19].

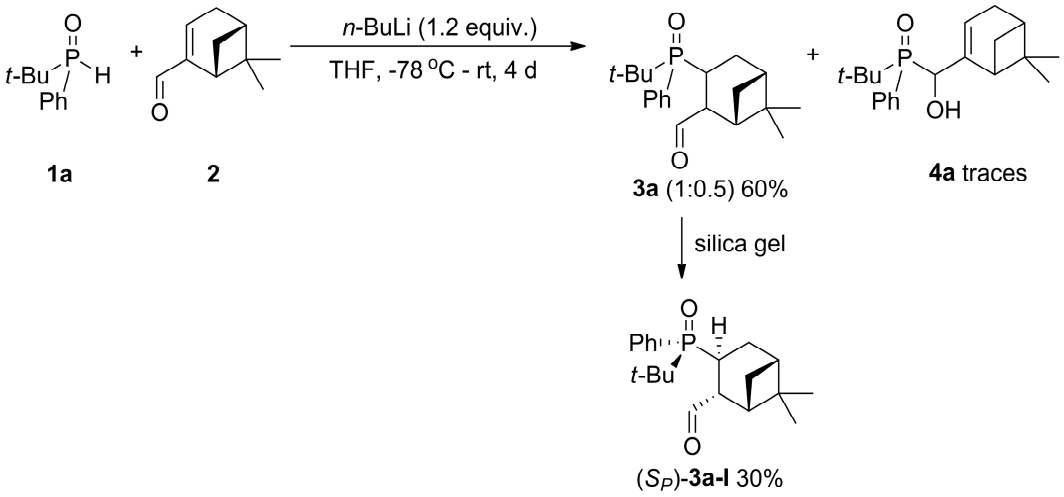
2. Results and Discussion

2.1. 1,4-Addition of Secondary Phosphine Oxides to (1R)-Myrtenal

First, we chose to study selectivity of addition of racemic *tert*-butyl(phenyl)phosphine oxide (**1a**) [16] to (1*R*)-myrtenal (**2**) using *n*-BuLi as a base (Scheme 2). The reaction afforded 1,4-addition product **3a** which was formed as a mixture of two isomers in a ratio of 1:0.5 (60%). Only traces of 1,2-addition product **4a** could be detected. Interestingly, formation of a bis(phosphinoyl) product resulting from tandem 1,4- and 1,2-addition observed recently in similar additions of secondary phosphine oxides to acyclic α,β-unsaturated aldehydes was not observed [19]. Due to the low stability of **3a** on silica gel column, we were able to isolate only one pure isomer (**3a-I**, δ_P 57.03, major) in 30% yield. The minor isomer of **3a** (δ_P 58.04) could not be separated and it was identified only spectrally in a minute fraction also containing trace amounts of 1,2-addition product **4a** (δ_P 53.79). (The structure of **4a** was deduced from the characteristic peaks of vinyl protons at δ_H 6.65 ppm and the CH-OH proton at δ_H 4.49).

The molecular structure of the isolated major adduct **3a-I** was determined by means of the X-ray crystallographic analysis and it is displayed in Figure 1. As can be seen, the absolute configuration at the P centre is S_P and the configurational array of the substituents at the P1-C3-C2-C10 bond is *anti* (torsion angle 111°). It appears that attack of the P-nucleophile and subsequent protonation both occurred from the less hindered side of the (1*R*)-myrtenal molecule. This observation is in agreement with the recent literature reporting that 1,4-additions of a sulfur nucleophile proceeded from the less hindered side of myrtenal molecule and led exclusively to the formation of *anti*-configured adducts [24]. Based on this apparent stereochemical preference it seems reasonable to assume that both the major and the minor isomer of **3a** have relative *anti* configuration and that they differ

only in the configuration of the phosphorus atom. The observed predominance of (S_P)-**3a-I** in the product mixture at 60% conversion indicates that the S_P enantiomer of **1a** reacts faster with (1*R*)-myrtenal than its R_P counterpart and that this finding may constitute a basis for development of a useful kinetic resolution process, especially at lower conversion. It can also be conjectured that (S_P)-**1a** composes with (1*R*)-myrtenal (**2**) a 'matched pair' in terms of a doubly asymmetric 1,4-addition process.



Scheme 2. Reaction of *rac*−**1a** with (*R*) −myrtenal.

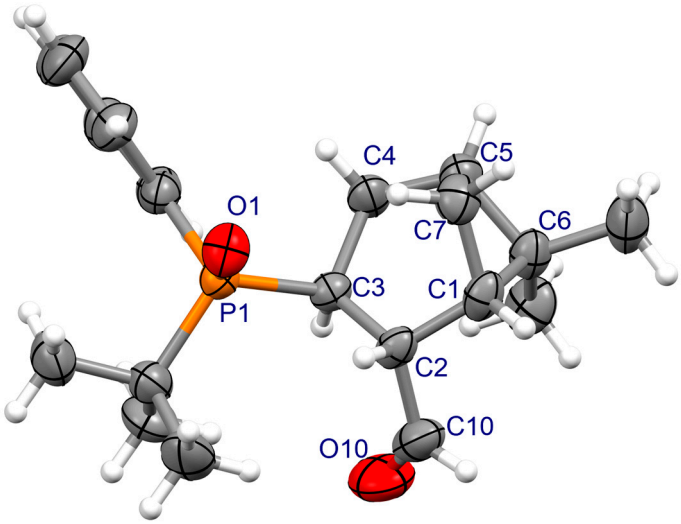
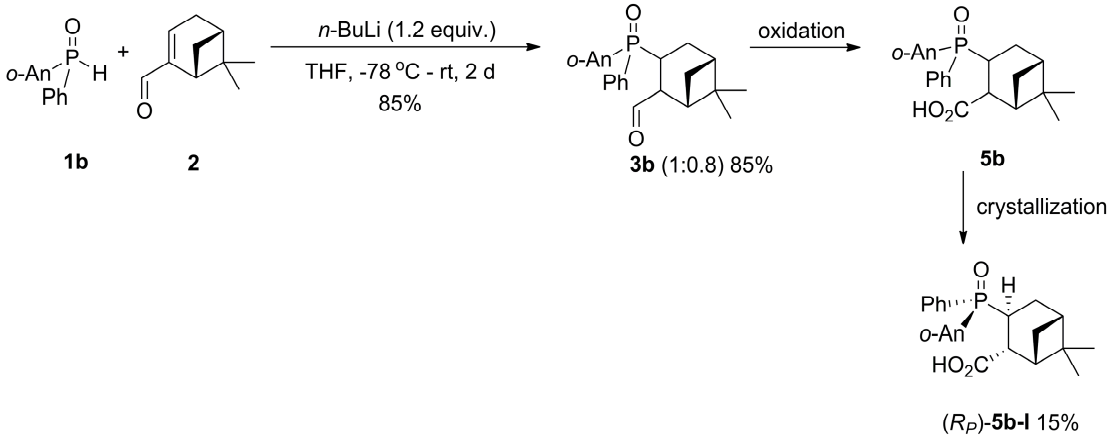


Figure 1. The molecular structure of S_P−**3a-I**.

The addition of racemic *o*-anisyl(phenyl)phosphine oxide (**1b**) was tried next under the same conditions (Scheme 3). Again, the reaction afforded only 1,4-addition product **3b** as a mixture of two diastereoisomers (δ_P, 36.23 and 36.56) in a 1:0.8 ratio (85%). A higher conversion this time inevitably resulted in lower stereoselectivity. Again, only traces of 1,2-addition product could be detected, if any. An attempted separation of the mixture of diastereoisomeric adducts **3b** on silica gel proved unsuccessful. However, when the mixture was exposed to air some tiny crystals started to separate from the mixture upon standing as a result of a partial oxidation of adducts **3b** to the corresponding acids **5b** (δ_P, 41.49 and 41.22). Collection and recrystallization of those crystals from methanol led to isolation of a single diastereoisomer **5b-I** (δ_P 42.03) in 15% yield. The X-ray crystal structure analysis of this diastereoisomer allowed its absolute configuration at phosphorus to be determined as R_P as well as to assign an *anti*-configuration of the P1-C3-C2-C10 fragment (torsion angle 110°) (Figure 2). The structure of **5b-I** further corroborates the previous

observation that, in these 1,4-additions, the attack of a P-nucleophile and subsequent protonation both prefer to take place from the less hindered side of (*R*)-myrtenal molecule to yield an *anti*-configured adduct.



Scheme 3. Reaction of *rac*−**1b** with (*R*)−myrtenal.

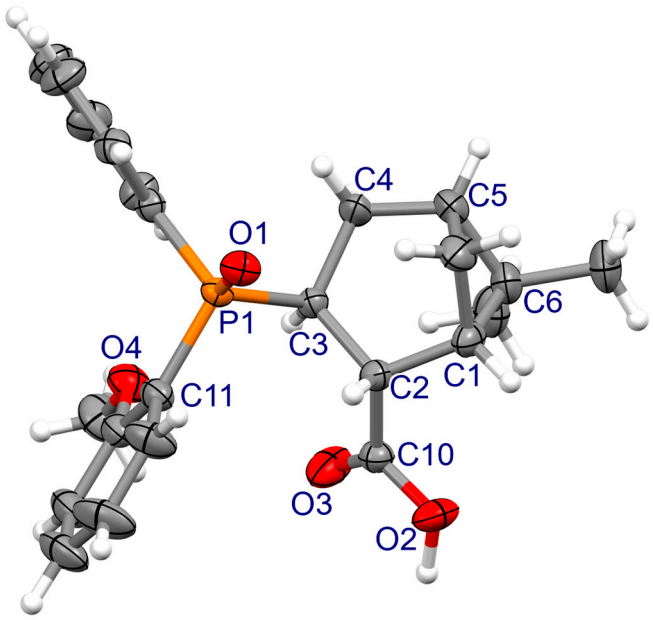
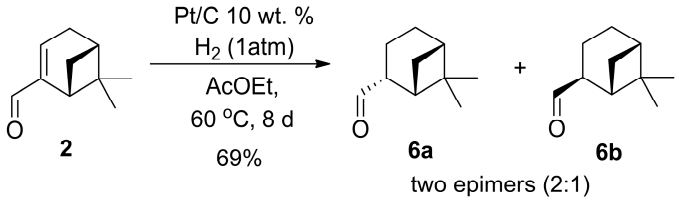


Figure 2. The molecular structure of (R_P)−**5b-I**.

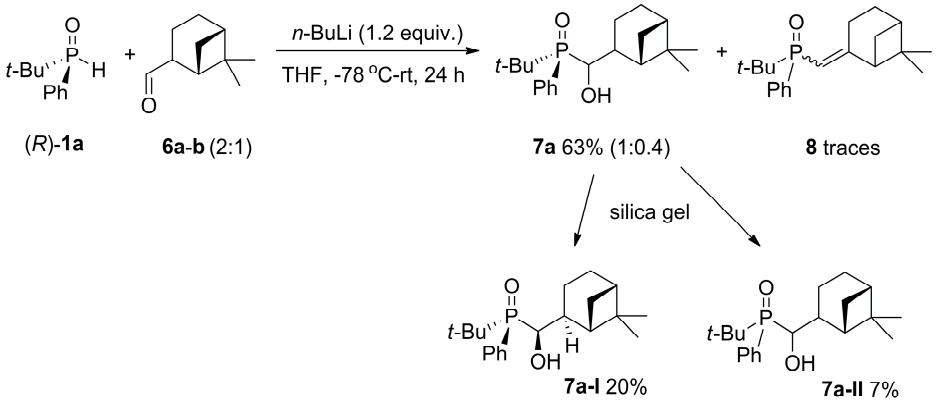
2.2. 1,2-Addition of Secondary Phosphine Oxides to (1R,2R/2S)-Myrtanal

Since reactions of (1*R*)-myrtenal (**2**) with secondary phosphine oxides **1a,b** led exclusively to the formation of 1,4-addition products **3** it became necessary to hydrogenate its double bond in order to obtain access to 1,2-addition products. The hydrogenation of (1*R*)-myrtenal was most conveniently carried out in AcOEt at 1 atm pressure of hydrogen using platinum on carbon as catalyst (*cf.*, Supporting Information) and gave myrtanal (**6**) as a mixture of two C2-epimers **6a** and **6b** in a 2:1 (2*R*:2*S*) ratio (Scheme 4) [25]. Due to possible epimerization of their C2-centers under basic conditions of the planned additions the epimers were not separated and were used as a mixture in further studies.

Having in hand saturated aldehyde **6** as a mixture of two C2-epimers we decided to react it with enantiomerically pure *tert*-butyl(phenyl)phosphine oxide (R_P)-**1a** [16] rather than with *rac*-**1a** in order to cut the number of possible diastereoisomeric adducts and to facilitate their separation. By this maneuver, the studied 1,2-adition reaction turned into a doubly asymmetric one (Scheme 5).



Scheme 4. Hydrogenation of (1*R*)−myrtenal over Pt/C catalyst.



Scheme 5. Synthesis of α-hydroxyphosphine oxide **7a** using (R_P)−**1a** and myrtanal (**6**) in the presence of *n*-BuLi.

In effect, we obtained only two diastereoisomeric 1,2-adducts **7a** (δ_P 44.13 and δ_P 50.01) in a 1:0.4 ratio (63%). In addition, the formation of traces of unsaturated phosphine oxide **8** (1 dia; δ_P 49.9) that originated from dehydration of **7a** was observed. We were able to isolate the major diastereoisomer (**7a-I**) in 14% yield and a fraction consisting of a mixture of the two diastereoisomers in a 1:0.7 ratio (49%). Further attempts to separate this mixture resulted in additional isolation of **7a-I** (major) and **7a-II** (minor) in 6 and 7% yield, respectively as well as the mixture of both pure diastereoisomers (7%).

The confirmation of structure and assignment of configuration for the major diastereoisomer (**7a-I**) was obtained by means of X-ray crystallography (Figure 3). The absolute configuration at P was established to be R_P in accord with the configuration of the starting (R_P)-**1a**. In turn, the absolute configurations at C10 and at C2 were found to be *S*. The observed *S* configuration at C2 suggested that the major product of the 1,2-addition resulted from the addition of (R_P)-**1a** to the minor (S_P)-epimer of myrtanal (**6b**) and that two C2 epimers of myrtanal **6a** and **6b** must have equilibrated under the basic reaction conditions.

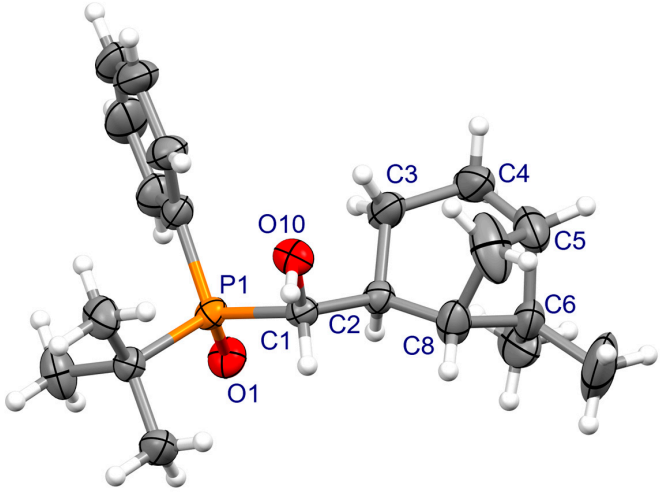
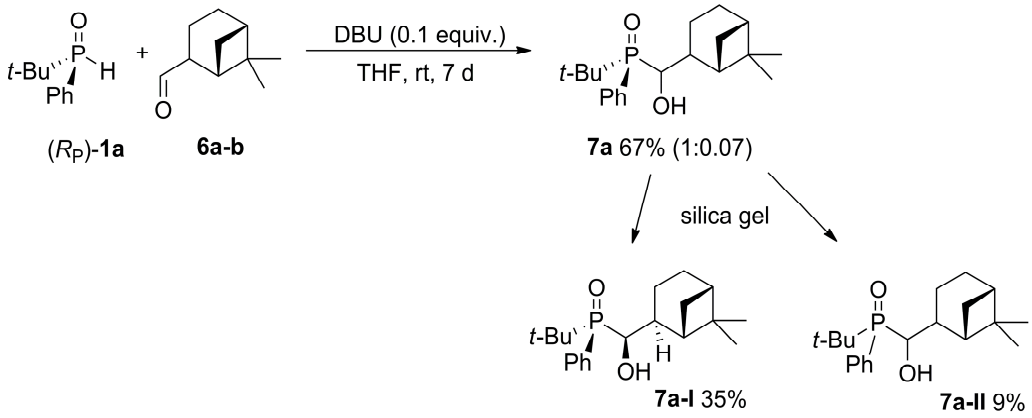


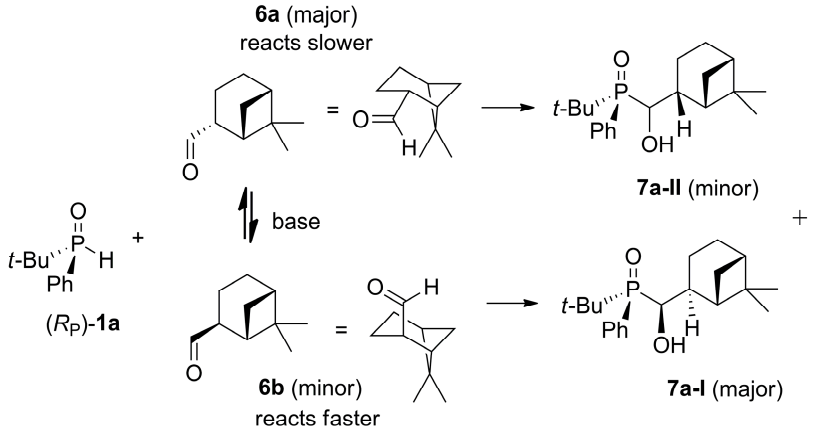
Figure 3. The molecular structure of R_P−**7a-I**.

This reasoning led us to attempt the reaction using the same enantiomerically pure (R_P)-**1a**, whilst changing the base to DBU to secure better equilibrating conditions and running the reaction at room temperature during prolonged time (7 d), we were able to markedly increase the yield and stereoselectivity of this addition. Under these conditions the two diastereoisomeric adducts **7a** were formed in a 1:0.07 ratio in 67% overall yield. Chromatographic separation of these adducts afforded the major one, **7a-I**, and the minor one, **7a-II**, in 35 and 9% isolated yield, respectively (Scheme 6). Additionally, a fraction containing the two isomers in a mixture was isolated in 20% yield.



Scheme 6. Synthesis of α-hydroxyphosphine oxide **7a** using (R_P)−**1a** and myrtanal (**6**) in the presence of DBU.

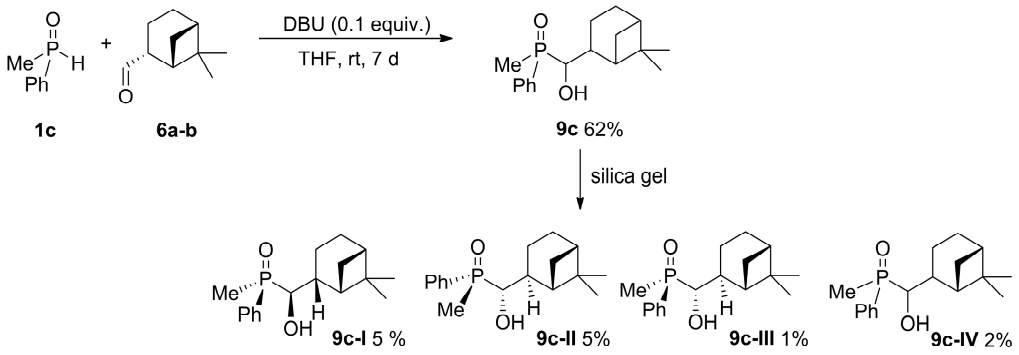
Apparently, as shown by the very high diastereomeric ratio of the adducts **7a-I** and **7a-II** (1:0.07) observed in the crude product mixture, the minor (2S_P)-epimer (**6b**) reacted much faster with (R_P)-**1a** than did the major (2R_P)-epimer (**6a**). It can thus be concluded that in the studied doubly asymmetric process (R_P)-**1a** and the minor (2S_P)-epimer of myrtanal (**6b**) constituted the 'matched pair' of reactants. A plausible course of this process is sketched in Scheme 7.



Scheme 7. Doubly asymmetric 1,2-addition of (R_P)−**1a** to **6a,b**.

Next, we used the same reaction conditions to test a possibility of resolution of racemic phenyl(methyl)phosphine oxide (**1c**) in its reaction with myrtanal (**6**). We used racemic form of **1c** due to difficult access to its nonracemic form. This reaction led to the formation of a mixture of all possible diastereoisomers of **9c** (δ_P, 44.22; 42.82; 42.04; 41.38; 40.94; 40.89; 40.52; 39.57) in 62% overall yield (Scheme 8). This time, despite the presence of many isomers, silica gel column chromatography provided the fractions each of which was enriched in pairs of diastereoisomers of **9c** of close retention time (for more details see Supporting Information, pp. S62–S68). Each of these fractions was then subjected to

crystallization from ethyl acetate. In this way, we obtained three single diastereoisomers of **9c**, i.e., **9c-I** and **9c-II** in 5% yield each, and **9c-III** in 1% yield. Isomer **9c-IV** was obtained in one of the fractions coming from the chromatography column in 2% yield. Additionally, two fractions containing mixtures of other diastereoisomers were isolated, both in 3% yield. The structures of diastereoisomers **9c-I** and **9c-III** were established by X-ray analysis. In **9c-I**, the stereogenic centres at P, C10 and C2 were found to be of R_P,*S*,*R* configuration, respectively (Figure 4). In **9c-III**, the absolute configurations at P, C10 and C2 were assigned as R_P,*R*,*S* (Figure 5).



Scheme 8. Reaction of *rac*−**1c** with myrtanal (**6**).

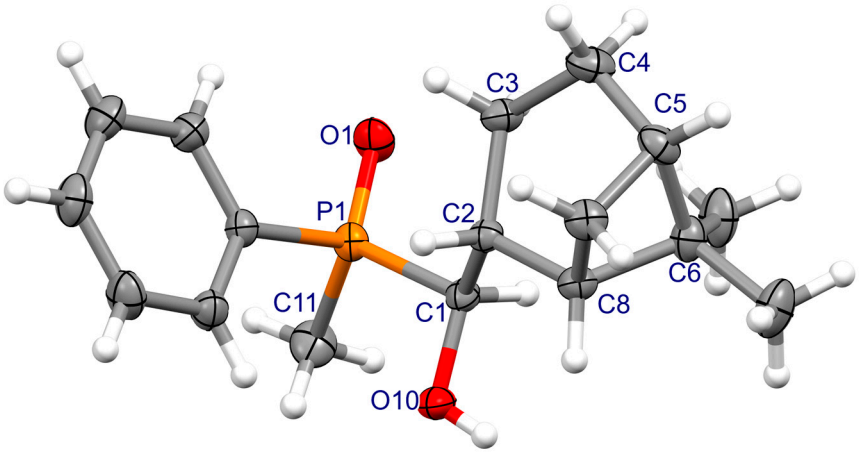


Figure 4. The molecular structure of (R_P)−**9c-I**.

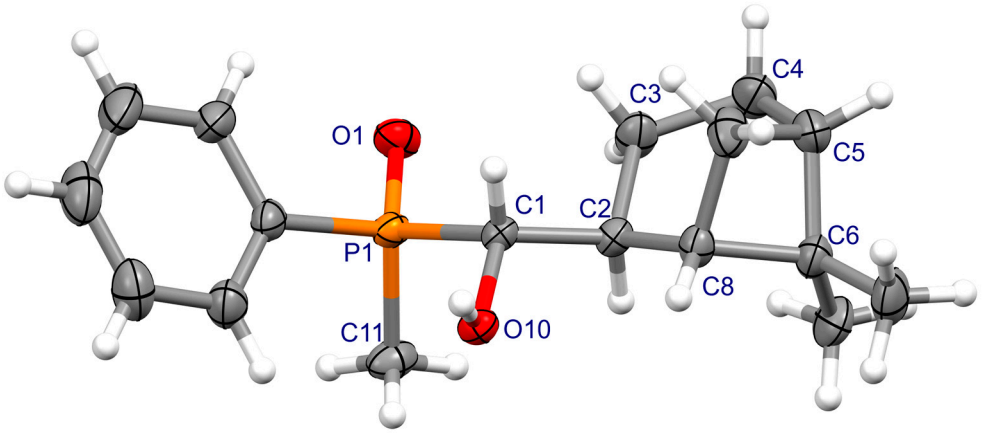


Figure 5. The molecular structure of (R_P)−**9c-III**.

For determination of the structure of **9c-II** a two-dimensional NMR technique was used. In a NOESY spectrum of **9c-II** it was found that proton **H1** interacts with protons **H11**

of the P-methyl group. The interactions of protons **H1** and **H2** with protons of the P-phenyl ring were not detected. Therefore, we have assigned the configuration at the phosphorus atom as S_p. In turn, the detected interactions of proton **H1** with proton **H8** allowed the absolute configuration at C1 to be assigned as *R*. The interactions of **H2** with protons **H9** indicated that **H2** occupies an equatorial position. Hence, the phenylmethylphosphinoyl(hydroxy)metine group has to occupy an axial position which implies that the absolute configuration at C2 is *S* (Figure 6). It appears then that **9c-I** and **9c-II** are the P-epimers.

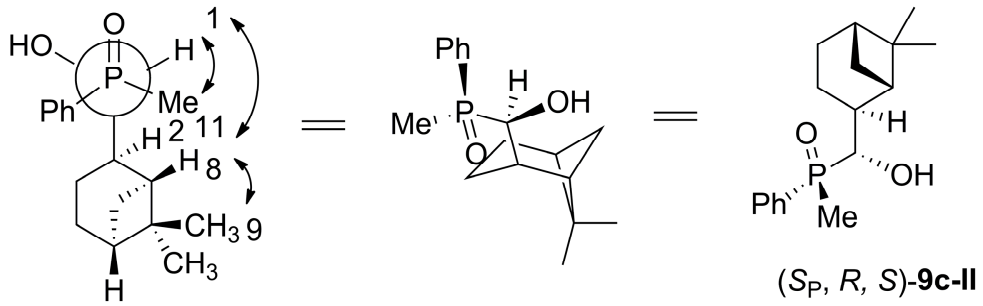
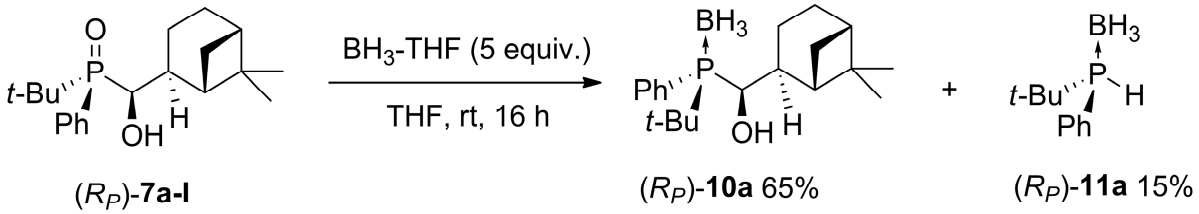


Figure 6. The stereochemistry of **9c-II** according to NOESY spectrum.

2.3. Synthesis of P-Stereogenic α-Hydroxyphosphine-Boranes

One of the important features of α-hydroxyphosphine oxides is their ability to undergo very facile reduction upon treatment with BH_3 at room temperature, to give directly the corresponding borane-protected α-hydroxyphosphines with clean inversion of configuration at the P-centre [26–29]. To further explore this possibility, two of the synthesized P,C-stereogenic α-hydroxyphosphine oxides, i.e., (R_P)-**7a-I**, and (S_P)-**9c-II** were subjected to such reductions under the previously reported conditions [26]. In the case of (R_P)-**7a-I** the reduction of the P=O bond with 5 equiv. of BH_3-THF at room temperature for 16 h afforded the corresponding α-hydroxyphosphine-borane **10a** together with a secondary phosphine-borane **11a** in 65 and 15% isolated yield, respectively (Scheme 9). The formation of a secondary phosphine borane as a side product in such reduction has not been reported before [26,27]. Even more surprisingly, when **7a-I** was subjected to reaction with 3 equiv. of BH_3-THF at 60 °C for 20 h, **11a** was formed as the major product and could be isolated from the product mixture in 80% yield.



Scheme 9. The synthesis of P−stereogenic phosphine-borane **10a**.

Based on the previous literature data and the known mechanism of this reduction we could expect that the formation of phosphine-borane **10a** would occur with clean inversion of configuration at the P-centre [30–32]. Indeed, inspection of a NOESY spectrum of **10a** revealed interactions between proton **H1** and protons***o*-H** of the P-phenyl ring attesting to the change in configuration of substituents at the phosphorus atom (Figure 7). This allowed the absolute configuration at the P atom in **10a** to be assigned as R_P and to confirm again the stereoinvertive course of reduction of α-hydroxyphosphine oxides by BH_3.

The absolute configuration of phosphine-borane **11a** was assigned as R_P on the basis of the sign of its specific optical rotatory power ($[\alpha]_D = -2.0$ (c 1.03, $CHCl_3$)) by correlation with the literature data [32]. Since phosphine-borane **11a** has preserved configuration at P atom (R_P, retention), it can be deduced that it resulted from a stereoretentive reduction of

(*R*)-*t*-butyl(phenyl)phosphine oxide regenerated from **7a-I** in a retro-addition process [30–32]. It has already been established that reduction of secondary phosphine oxides by BH_3 complexes proceeds with retention of configuration [31]. However, the low optical rotatory power for **11a** suggests that some optical purity was lost, probably due to racemisation of secondary phosphine before complexation with BH_3 [32].

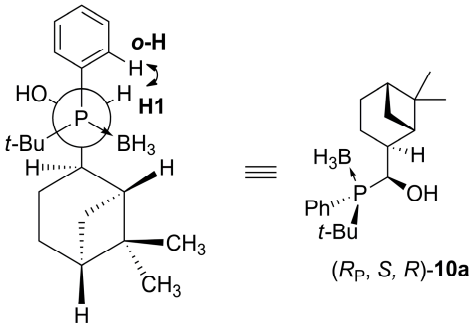
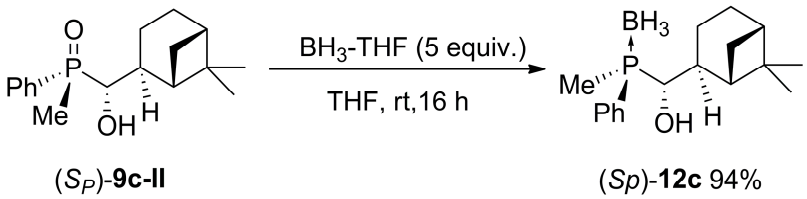


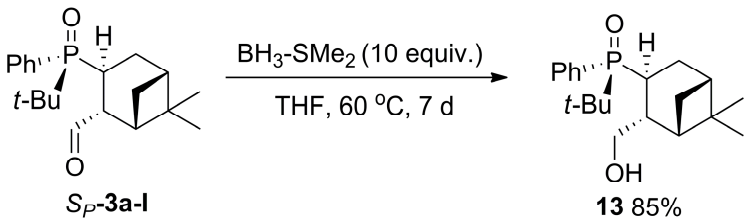
Figure 7. The stereochemistry of **10a** according to NOESY spectrum.

The second reduction was conducted with phosphine oxide (S_P)-**9c-II** which, under the same reduction conditions, was successfully converted into the corresponding phosphine-borane **12c** that was isolated in 94% yield (Scheme 10). Taking into consideration the inversion during the reduction process, the absolute configuration of **12c** was assigned as S_P [26,27]. This time, formation of a secondary phosphine-borane by-product was not observed. It seems likely, that in case of **7a-I** it was steric crowding that facilitated a retro-addition process and eventually led to the formation of **11a**.



Scheme 10. The reduction of phosphine oxide **9c-II** using BH_3-THF.

Finally, an attempt was made to reduce a phosphine oxide **3a-I**, which features a reducible aldehyde group, under the same conditions (Scheme 11). The experiment revealed that only the aldehyde group underwent the reduction and that the P=O group present in the formed γ-hydroxyphosphine oxide **13** remained intact. We have previously reported a similar outcome of the reaction of a different γ-hydroxyphosphine oxide with BH_3 [26]. We proved in that work that γ-positioned hydroxyl group is too remote from P=O bond to generate the cycle required to enable the reduction process by BH_3.



Scheme 11. The reaction of (S_P)−**3a-I** with BH_3 complex.

3. Materials and Methods

3.1. General

^1H, $^{31}P\{^1H\}$, $^{13}C\{^1H\}$ NMR spectra were recorded on Bruker Advance 500 or 300, or Varian 400 spectrometer at ambient temperature ($CDCl_3$ as a standard solvent or MeOD-*d*4).

Chemical shifts (δ) are reported chemical shift in ppm from tetramethylsilane and peaks are labelled using as singlets (s), doublets (d), triplets (t), ect., broad (b) and multiplets (m). Mass spectra were recorded on Shimadzu GC-MS QP2010S in electron ionization (EI). Melting points were determined on Büchi Melting Point M-560 and were uncorrected. The HRMS analysis performed on the HPLC system coupled to a linear trap quadrupole-Orbitrap mass spectrometer (LTQ-Orbitrap Velos from Thermo Fisher Scientific, San Jose, CA, USA) equipped with an ESI source. Chromatographic separation was performed using isocratic elution with the composition of the mobile phase equal 25% 25 mM formic acid in water and 75% 25 mM formic acid in acetonitrile. The total run time was 30 min at a mobile phase flow rate of 0.5 mL/min. Specific optical rotations were measured on Perkin Elmer 341LC (1 mL cell, 10 mm path length) and are reported as follows: $[\alpha]^{25}_{D}$ (c: g/100 mL, in solvent). Elementary analyses were performed on PERKIN ELMER CHN 2400. Thin-layer chromatography (TLC) was performed with precoated silica gel plates and subjected to visualization (UV, $KMnO_4$ solution or iodine/silica gel). The purification of compounds was performed on column chromatography (silica gel, 60–240 mesh).

3.2. X-ray Crystallography

The single crystal diffraction data were collected at room temperature with a SuperNova (for **3a-I**, **5b-I**, **7a-I** and **9c-III**) and an Xcalibur Gemini (for **9c-I**) diffractometer (Oxford Diffraction, Oxford, UK) using the graphite monochromated CuKα radiation. The data collection, cell refinement, and data reduction was obtained using CrysAlisPro program system [33]. The intensities were corrected for Lorentz and polarization effects, and additionally a multi-scan absorption corrections were applied. The SHELXT program was used to solve the crystal structure by direct methods. SHELXL-97 program was applied to refine crystal structures by the full-matrix least squares method on F^2 using the [34,35]. The experimental details and final atomic parameters for the analysed crystals were deposited with the Cambridge Crystallographic Data Centre as Supplementary Material. (CCDC Nos 2162093–2162097).

4. Experimental

The starting compounds: *t*-butylphenylphosphine oxide (**1a**) [16], *o*-anisylphenylphosphine oxide (**1b**) [36], phenyl(methyl)phosphine oxide (**1c**) [37] were obtained according to reported methods. Celite® was purchased from Sigma-Aldrich (Buchs, Switzerland).

4.1. General Procedure of the Reaction of Phosphine Oxides with (R)-Myrtenal

In a Schlenk tube (50 mL) equipped with an argon inlet, secondary phosphine oxide **1** (2 mmol) in anhydrous THF (5 mL) was dissolved. Then, the mixture was cooled to −78 °C and *n*-BuLi (1.38 mL, 2.2 mmol, 1.6 M in hexanes) was added. The reaction mixture was stirred at this temperature for 15 min. After that time, (1*R*)-myrtenal (304 µL, 2 mmol) and the mixture was left at rt for 48 h. Then, the saturated solution of NH_4Cl (5 mL) was added to quench the reaction. Then, the reactions mixture was extracted with CH_2Cl_2 (3 × 30 mL) and collected organic phases were dried using $MgSO_4$. The solvent was evaporated and the crude product was checked using NMR technique. The purification of the crude product was performed on silica gel column using $CHCl_3$/MeOH (v/v = 50:1) as eluent. The following products were synthesized according to this method.

*2-(1-(t-Butylphenylphosphinoyl)-1-hydroxymethyl)-6,6-dimethylbicyklo[3.1.1]heptane (**4a**).* ^{31}P NMR (162 MHz, $CDCl_3$): δ 53.79.

*3-(t-Butylphenylphosphinoyl)-6,6-dimethylbicyclo[3.1.1]heptane-2-carboaldehyde (**3a**).* Yield 60% (0.398 g). An yellow oil; mixture of diastereoisomers (d.r. = 1:0.5). Separation of this mixture via chromatography column gave pure **3a-I** (Figure 8).

*Trans-(S_P,1S,2R,3S,5R)-3-(t-butylphenylphosphinoyl)-6,6-dimethylbicyclo[3.1.1]heptane-2-carboaldehyde (**3a-I**).* White solid. m.p. = 307–308 °C (dec.). Yield 30% (0.199 g). R_f = 0.52 (AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.71 (s, 3H, C(9)H), 1.08 (d, $J_{P\text{-}H}$ = 14.09 Hz, 9H), 1.16 (s, 3H, C(8)H), 1.70–1.90 (m, 4H, C(4)H_2, C(1)H, C(7)H), 2.29–2.36 (m, 1H, C(7)H),

2.56–2.61 (m, 1H, C(5)H), 3.56–3.64 (m, 2H, C(2)H, C(1)H), 7.43–7.52 (m, 3H), 7.73–7.78 (m, 2H), 9.75 (s, 1H, C(10)H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.8 (d, $^1J_{P\text{-}C}$ = 60.9 Hz, C3), 21.9 (s, C9), 25.1, 26.5 (s, C8), 28.7 (s, C7), 29.1 (d, $J_{P\text{-}C}$ = 2.9 Hz, C4), 34.4 (d, $^1J_{P\text{-}C}$ = 64.4 Hz), 38.7 (s, C6), 40.2 (d, $^3J_{P\text{-}C}$ = 2.9 Hz, C5), 40.8 (d, $^3J_{P\text{-}C}$ = 2.9 Hz, C1), 53.5 (d, $^2J_{P\text{-}C}$ = 2.3 Hz, C2), 128.5 (d, $^3J_{P\text{-}C}$ = 10.4 Hz, CH), 131.1 (d, $^1J_{P\text{-}C}$ = 87.9 Hz, C), 131.6 (d, $^4J_{P\text{-}C}$ = 2.9 Hz, CH), 132.5 (d, $^2J_{P\text{-}C}$ = 7.5 Hz, CH), 203.8 (d, $^3J_{P\text{-}C}$ = 4.0 Hz, C10); ^{31}P NMR (162 MHz, $CDCl_3$): δ 57.03 (s); Anal calcd for $C_{20}H_{29}O_2P$: C, 72.26; H, 8.79; Found: C, 72.33; H, 8.80. HRMS (ESI-LTQ) m/z calcd for $C_{20}H_{30}O_2P$ $[M+H]^+$: 333.19834, found: 333.19821.

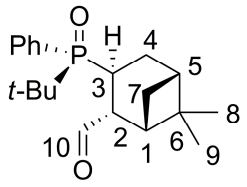


Figure 8. The structure of S_P−**3a-I** with atom numbering.

Crystal data for S_P−**3a-I**: Mw = 332.40, crystal system orthorhombic, space group $P2_12_12_1$, unit cell dimensions a = 6.3861(2) Å, b = 13.1765(4) Å, c = 22.1096(8) Å, V = 1860.44(11) Å^3, Z = 4, Density (calc) = 1.187 g/cm^3, absorption coeff. 1.356 mm^{-1}, F(000) = 720. Collected/independent reflections 13,077/3820 [R(int) = 0.0267], data/restraints/parameters 3820/0/208. Goodness-of-fit on F^2 1.057; final R indices [I > 2σ(I)] R1 = 0.0291, wR2 = 0.0762, absolute structure parameter x = −0.010(9). CCDC No. 2162093.

*3-(o-Anisylphenylphosphinoyl)-6,6-dimethylbicyclo[3.1.1]heptane-2-carboaldehyde (**3b**).* Yield 85% (0.649 g). R_f = 0.59 ($CHCl_3$/MeOH = 50:1). A yellow oil; mixture of diastereoisomers (d.r. = 1:0.8). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.72 (s, 3H, minor), 0.76 (s, 3H, major), 1.18 (s, 6H), 1.81–1.85 (m, 2H), 1.86–1.92 (m, 1H), 1.95–2.24 (m, 5H), 2.32–2.40 (m, 2H), 2.45–2.52 (m, 2H), 2.97–3.05 (m 1H, major), 3.15–3.23 (m, 1H, minor), 3.86 (s, 3H, major), 3.93–4.00 (m, 1H, major), 4.00 (s, 3H, minor), 4.05–4.13 (m, 1H, minor), 6.75–6.79 (m, 1H, major), 6.91–6.95 (m, 1H, minor), 7.00–7.04 (m, 1H, major), 7.06–7.10 (m, 1H, minor), 7.33–7,49 (m, 8H), 7.94–8.01 (m, 4H), 8.03–8.07 (m, 1H, major), 8.07–8.13 (m, 1H, minor), 9.31 (s, 1H, major), 9.32 (s, 1H, minor); ^{31}P NMR (162 MHz, $CDCl_3$): δ 36.32 (s, minor); 36.56 (s, major). ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.0 (s, CH_3, minor), 22.4 (d, $J_{C\text{-}P}$ = 72.7 Hz, CH, major), 22.5 (s, CH_3, major), 23.9 (d, $J_{C\text{-}P}$ = 71.8 Hz, CH, minor), 25.3 (d, $J_{C\text{-}P}$ = 1.8 Hz, CH_2, minor), 25.9 (d, $J_{C\text{-}P}$ = 2.7 Hz, CH_2, major), 26.3 (s, CH, major), 26.4 (s, CH, minor), 28.4 (s, CH_2, major), 28.7 (s, CH_2, minor), 38.7 (s, C, major), 38.8 (s, C, minor), 39.6 (d, $J_{C\text{-}P}$ = 3.6 Hz, CH, minor), 39.7 (d, $J_{C\text{-}P}$ = 3.6 Hz, CH, major), 40.5 (d, $J_{C\text{-}P}$ = 3.6 Hz, CH, minor), 40.9 (d, $J_{C\text{-}P}$ = 3.6 Hz, CH, major), 51.7 (d, $J_{C\text{-}P}$ = 2.7 Hz, CH, minor), 51.9 (d, $J_{C\text{-}P}$ = 2.7 Hz, CH, major), 54.8 (s, CH_3, major), 55.2 (s, CH_3, minor), 110.3 (d, $J_{C\text{-}P}$ = 7.3 Hz, CH, major), 110.6 (d, $J_{C\text{-}P}$ = 7.3 Hz, CH, minor), 119.1 (d, $J_{C\text{-}P}$ = 93.6 Hz, C, major), 120.3 (d, $J_{C\text{-}P}$ = 95.4 Hz, C, minor), 120.5 (d, $J_{C\text{-}P}$ = 10.0 Hz, CH, major), 121.1 (d, $J_{C\text{-}P}$ = 10.9 Hz, CH, minor), 127.7 (d, $J_{C\text{-}P}$ = 11.8 Hz, CH, minor), 127.8 (d, $J_{C\text{-}P}$ = 11.8 Hz, CH, major), 131.1 (d, $J_{C\text{-}P}$ = 2.7 Hz, CH, major), 131.4 (d, $J_{C\text{-}P}$ = 2.7 Hz, CH, minor), 131.5 (d, $J_{C\text{-}P}$ = 10.0 Hz, CH, minor), 131.8 (d, $J_{C\text{-}P}$ = 10.0 Hz, CH, major), 132.1 (d, $J_{C\text{-}P}$ = 100.8 Hz, C, minor), 132.2 (d, $J_{C\text{-}P}$ = 100.8 Hz, C, major), 133.6 (d, $J_{C\text{-}P}$ = 1.8 Hz, CH, minor), 133.9 (d, $J_{C\text{-}P}$ = 1.8 Hz, CH, major), 134.7 (d, $J_{C\text{-}P}$ = 3.6 Hz, CH, major), 137.1 (d, $J_{C\text{-}P}$ = 3.6 Hz, CH, minor), 158.8 (d, $J_{C\text{-}P}$ = 5.5 Hz, C, minor), 159.4 (d, $J_{C\text{-}P}$ = 5.5 Hz, C, major), 201.8 (d, $J_{C\text{-}P}$ = 4.5 Hz, C, minor), 201.9 (d, $J_{C\text{-}P}$ = 3.6 Hz, C, major). HRMS (ESI-LTQ) m/z calcd for $C_{23}H_{28}O_3P$ $[M+H]^+$: 383.17761; found: 383.17777.

*3-(o-Anisylphenylphosphinoil)-6,6-dimethylbicyclo[3.1.1]heptane-2-carboxylic acid (**5b**).* Compound **3b** oxidized spontaneously to **5b** upon standing. Crystallization of **5b** gave **5b-I** (15%) and mixture of both isomers (**5b-I** and **5b-II**).

*Trans-(R_P,1S,2R,3S,5R)-3-(o-anisylphenylphosphinoil)-6,6-dimethylbicyclo[3.1.1]heptane-2-carboxylic acid (**5b-I**).* Yield 15% (0.12 g). White solid, m.p. = 314–315 °C (methanol). R_f = 0.39 ($CHCl_3$/MeOH = 30:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.65–0.67 (m, 1H), 1.00 (s, 3H), 1.20 (s, 3H), 1.84–1.88 (m, 1H), 2.06–2.11 (m, 2H), 2.42–2.46 (m, 1H), 2.41–2.43 (m, 1H), 3.13–3.19

(m, 1H), 3.79 (s, 3H), 3.98–4.00 (m, 1H), 6.86–6.89 (m, 1H), 7.03–7.07 (m, 1H), 7.48–7.53 (m, 3H), 7.57–7.60 (m, 1H), 7.77–7.79 (m, 1H), 7.89–7.92 (m, 2H). ^{31}P NMR (162 MHz, $CDCl_3$): δ 42.03 (s). ^{13}C NMR (75 MHz, CD_3OD): δ 21.9 (s), 25.8 (d, $J_{C\text{-}P}$ = 72.4 Hz, CH), 26.4 (s), 27.7 (d, $J_{C\text{-}P}$ = 2.9 Hz, CH_2), 28.8 (s, CH_2), 39.9 (s, C), 41.2 (d, $J_{C\text{-}P}$ = 3.4 Hz, CH), 45.1 (d, $J_{C\text{-}P}$ = 4.6 Hz, CH), 45.2 (d, $J_{C\text{-}P}$ = 2.0 Hz, CH), 55.5 (s, CH_3), 112.1 (d, $J_{C\text{-}P}$ = 7.2 Hz, CH), 119.7 (d, $J_{C\text{-}P}$ = 96.9 Hz, C), 121.5 (d, $J_{C\text{-}P}$ = 10.3 Hz, CH), 129.3 (d, $J_{C\text{-}P}$ = 12.1 Hz, CH), 132.9 (d, $J_{C\text{-}P}$ = 2.6 Hz, CH), 133.1 (d, $J_{C\text{-}P}$ = 102.1 Hz, C), 133.3 (d, $J_{C\text{-}P}$ = 9.5 Hz, CH), 135.1 (d, $J_{C\text{-}P}$ = 4.3 Hz, CH), 135.8 (d, $J_{C\text{-}P}$ = 2.0 Hz, CH), 161.9 (d, $J_{C\text{-}P}$ = 5.6 Hz, C), 177.0 (d, $J_{C\text{-}P}$ = 4.0 Hz, C). HRMS (ESI-LTQ) m/z calcd for $C_{23}H_{28}O_4P$ $[M+H]^+$: 399.17252, found: 399.17262.

Crystal data for R_P-**5b-I**: Mw = 398.41, crystal system orthorhombic, space group $P2_12_12_1$, Unit cell dimensions a = 10.6346(3) Å, b = 11.0832(3) Å, c = 18.1288(4) Å; V = 2136.76(10) Å^3, Z = 4, Density (calc) 1.238 g/cm^3, absorption coeff. 1.344 mm^{-1}, F(000) = 848. Collected/independent reflections 15423/4396 [R(int) = 0.0274], Data/restraints/parameters 4396/0/258. Goodness-of-fit on F^2 1.075; final R indices [I > 2σ(I)] R1 = 0.0346, wR2 = 0.0968, absolute structure parameter x = −0.035(9). CCDC No. 2162094.

*3-(o-Anisylphenylphosphinoil)-6,6-dimethylbicyclo[3.1.1]heptane-2-carboxylic acid (**5b-II**)*, Signals identified in a mixture (with **5b-I**, d.r. = 1:0.37) which left after crystallization. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00 (s, 3H), 1.20 (s, 3H), 1.84–1.88 (m, 1H), 2.06–2.11 (m, 2H), 2.42–2.46 (m, 1H), 2.41–2.43 (m, 1H), 3.13–3.19 (m, 1H), 3.79 (s, 3H), 3.98–4.00 (m, 1H), 6.86–6.89 (m, 1H), 7.03–7.07 (m, 1H), 7.48–7.53 (m, 3H), 7.57–7.60 (m, 1H), 7.77–7.79 (m, 1H), 7.89–7.92 (m, 2H). ^{31}P NMR (162 MHz, $CDCl_3$): δ 40.69 (s). ^{13}C NMR (125 MHz, DMSO-*d6*): δ 21.4 (s, CH_3), 21.6 (s, CH_3), 24.1 (d, $J_{C\text{-}P}$ = 71.8 Hz, CH), 25.7 (s, CH_2), 26.1 (d, $J_{C\text{-}P}$ = 72.5 Hz, CH), 26.5 (s, CH_2), 27.1 (s, CH), 27.2 (s, CH), 28.1 (s, CH_2), 28.4 (s, CH_2), 38.7 (d, $J_{C\text{-}P}$ = 4.5 Hz, CH), 39.9 (d, $J_{C\text{-}P}$ = 4.5 Hz, CH), 40.04 (s, CH), 40.2 (s, CH), 43.2 (d, $J_{C\text{-}P}$ = 3.7 Hz, CH), 43.3 (d, $J_{C\text{-}P}$ = 3.7 Hz, CH), 43.4 (d, $J_{C\text{-}P}$ = 1.8 Hz, CH), 43.6 (d, $J_{C\text{-}P}$ = 1.2 Hz, CH), 55.3 (s, CH_3), 56.2 (s, CH_3), 111.3 (d, J = 6.8 Hz, CH), 112.2 (d, J = 6.8 Hz, CH), 120.4 (d, J = 6.8 Hz, CH), 118.4 (d, J = 92.6 Hz, C), 120.5 (d, J = 10.0 Hz, CH), 118.4 (d, J = 92.6 Hz, C), 121.4 (d, J = 91.7 Hz, C), 128.3 (d, J = 11.8 Hz, CH), 128.4 (d, J = 10.9 Hz, CH), 131.6 (d, J = 2.6 Hz, CH), 131.8 (d, J = 9.8 Hz, CH), 131.8 (d, J = 2.6 Hz, CH), 131.7 (d, J = 9.8 Hz, CH), 131.7 (d, J = 2.6 Hz, CH), 132.3 (d, J = 10.0 Hz, CH), 132.7 (d, J = 2.6 Hz, CH), 132.4 (d, J = 10.0 Hz, CH), 133.1 (d, J = 99.0 Hz, C), 133.3 (d, J = 95.0 Hz, C), 134.4 (d, $J_{C\text{-}P}$ = 4.5 Hz, CH), 134.6 (d, $J_{C\text{-}P}$ = 5.5 Hz, CH), 132.6 (d, $J_{C\text{-}P}$ = 4.5 Hz, CH), 159.4 (d, $J_{C\text{-}P}$ = 4.5 Hz, C), 160.2 (d, $J_{C\text{-}P}$ = 4.5 Hz, C), 175.3 (d, $J_{C\text{-}P}$ = 4.5 Hz, C), 175.6 (d, $J_{C\text{-}P}$ = 4.5 Hz, C).

4.2. Procedure of Reduction of (R)-Myrtenal (2) to Myrtanal (6) [25]

In a hydrogenation vessel (100 mL) (*R*)-myrtenal (8.77 g, 58.4 mol) and Pt/C (0.88 g) was placed in anhydrous AcOEt (20 mL). The vessel was degassed three times and connected to balloon with hydrogen (1 atm). The mixture was heated at 60 °C for 8 d. After completion of the reaction, the crude reaction mixture was filtered through Celite® and washed three times with AcOEt (3 × 5 mL). The solvent was evaporated and the crude product was purified by distillation under reduced pressure to afford myrtanal (**6**).

Myrtanal (**6**). Yield 69% (6.13 g). Colorless liquid, b.p. = 110–120 °C (15 mmHg). A mixture of diastereoisomers (d.r. = 2:1). R_f = 0.79 (hexane/AcOEt = 10:1). ^{1}H NMR (500 MHz, $CDCl_3$): *major diastereoisomer:* δ 0.70 (s, 3H), 1.20 (s, 4H), 1.57–1.62 (m, 1H), 1.86–1.93 (m, 3H), 2.24–2.06 (m, 1H), 2.36–2.39 (m, 1H), 2.52–2.55 (m, 1H), 2.72–2.75 (m, 1H), 9.75 (s, 1H); *minor diastereoisomer:* δ 0.88 (s, 3H), 1.25 (s, 4H), 1.68–1.77 (m, 1H), 1.82–1.88 (m, 3H), 2.09–2.13 (m, 2H), 2.26–2.30 (m, 1H), 2.75–2.80 (m, 1H), 9.59 (s, 1H). *These data are consistent with those reported previously* [38,39].

4.3. Procedure of the Synthesis of [6,6-dimethylbicyclo[3.1.1]heptan-2-yl)(hydroxy)methyl](t-butyl) (phenyl)phosphine Oxide (7a) Using n-BuLi

In a Schlenk tube (50 mL) equipped with a magnetic stirrer and an argon inlet, secondary phosphine oxide (R_P)-**1a** (0.33 g, 1.81 mmol) in anhydrous THF (5 mL) was added. Then, the reactions mixture was cooled to −78 °C, and *n*-BuLi (1.47 mL, 2.36 mmol, 1.6 M in hexanes) was added and stirred at this temperature for 15 min. After that time, myrtanal (6) (360 µL, 2.36 mmol) was added, the cooling bath was removed, and the mixture was left at rt for 48 h. Then, the saturated solution NH_4Cl (5 mL) was added to quench the reaction. The reactions mixture was extracted with CH_2Cl_2 (3 × 30 mL), collected organic phases were dried over $MgSO_4$, filtered and evaporated. The crude residue was checked using NMR technique and showed a mixture of two diastereoisomers **7a-I** and **7a-II** in a 1:0.4 ratio accompanied by traces of a side product **8**. The purification of the crude product was performed on silica gel using $CHCl_3$/MeOH (*v*/*v* = 50:1) as eluent. The following products were synthesized according to this method.

[6,6-Dimethylbicyclo[3.1.1]heptan-2-yl)(hydroxy)methyl](methyl)(phenyl)phosphine oxide (R_P)-(***7a***) as a mixture of two diastereoisomers (d.r. = 1:0.7). Yield 49% (0.296 g).

[6,6-Dimethylbicyclo[3.1.1]heptan-2-yl)(hydroxy)methyl](methyl)(phenyl)phosphine oxide (R_P)-(***7a-I***) *(major).* Yield 20% (0.121 g). $[\alpha]_D$ = -198.3 (c 2.5, MeOH).

[6,6-Dimethylbicyclo[3.1.1]heptan-2-yl)(hydroxy)methyl](methyl)(phenyl)phosphine oxide (R_P)-(***7a-II***) *(minor)* Yield 7% (0.042 g). $[\alpha]_D$ = −1.65 (c 2.24, MeOH).

For full identification of these adducts see below.

tert-Butyl((6,6-dimethylbicyclo[3.1.1]heptan-2-ylidene)methyl)(phenyl)phosphine oxide (**8**). Analyzed in the reaction mixture. R_f = 0.43 ($CHCl_3$/AcOEt = 5:1). ^{1}H NMR (500 MHz, $CDCl_3$) (signals assigned in mixture): δ 0.76 (s, 3H), 0.92 (d, $J_{P\text{-}H}$ = 9.46 Hz, 1H), 0.96 (s, 3H), 1.16 (d, $J_{P\text{-}H}$ = 15.76 Hz, 9H), 1.41–1.47 (m, 1H), 2.22–2.25 (m, 2H), 2.31–2.32 (m, 1H), 2.34–2.45 (m, 2H), 2.59–2.62 (m, 1H), 6.16–6.20 (m, 1H), 7.44–7.47 (m, 2H), 7.52–7.55 (m, 1H), 7.72–7.76 (m, 2H); ^{31}P NMR (202 MHz, $CDCl_3$): δ 49.90 (s).

4.4. Procedure of the Synthesis of 6,6-dimethylbicyclo[3.1.1]heptan-2-yl)(hydroxy)methyl)(t-butyl) (phenyl)phosphine Oxide (7a) from (R_P)-1a and Myrtanal (6) Using DBU as a Base

In a Schlenk tube (50 mL) equipped with a magnetic stirrer and an argon inlet, secondary phosphine oxide (R_P)-**1a** (0.544 g, 3 mmol) in anhydrous THF (15 mL). Then, DBU (45 µL, 0.3 mmol) was added followed by myrtanal (**6**) (690 µL, 4.5 mmol). Then, the mixture was stirred at rt for 7 d. Then, solid NH_4Cl (200 mg) was added to quench the reaction. Then, the reaction mixture was filtered through Celite® and evaporated. The purification of the crude product was performed on silica gel using gradient elution from $CHCl_3$:AcOEt 50:1 to 1:1 a and then AcOEt to AcOEt/MeOH (*v*/*v* = 40:1).

(R_P)-[(6,6-Dimethylbicyclo[3.1.1]heptan-2-yl)(hydroxy)methyl](t-butyl) (phenyl)phosphine oxide (R_P)-(***7a-I***) *(major)* (Figure 9). Yield 35% (0.351 g). White solid, m.p. = 163–164 °C. R_f = 0.28 ($CHCl_3$/AcOEt = 5:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.71 (s, 3H, C(9)$\underline{H}_3$), 1.15 (s, 3H, C(10)$\underline{H}_3$), 1.22 (d, $^2J_{P\text{-}H}$ = 14.0 Hz, 9H), 1.21–1.26 (m, 1H, C(3)$\underline{H}$), 1.46–1.54 (m, 1H, C(3)$\underline{H}$), 1.53 (d, $J_{H\text{-}H}$ = 10.09 Hz, C(7)$\underline{H}$), 1.57–1.69 (m, 2H, C(4)$\underline{H}_2$), 1.73–1.76 (m, 1H, C(5)$\underline{H}$), 1.98 (bs, 1H), 2.01–2.03 (m, 1H, C(2)$\underline{H}$), 2.07–2.13 (m, 1H, C(7)$\underline{H}$), 2.54–2.59 (m, 1H, C(8)$\underline{H}$), 4.45–4.46 (m, 1H, C(1)$\underline{H}$), 7.42–7.46 (m, 2H), 7.48–7.53 (m, 1H), 7.98–8.02 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.0 (s, C3), 20.0 (s, C9), 23.9 (s, C4), 24.2 (C7), 25.0 (s, C), 26.6 (C10), 33.4 (d, $^1J_{P\text{-}C}$ = 63.6 Hz), 36.6 (s, C8), 40.0 (C5), 40.5 (C6), 49.5 (C2), 74.7 (d, $J_{P\text{-}C}$ = 78.1 Hz, C1), 127.7 (d, $^3J_{P\text{-}C}$ = 10.9 Hz), 130.2 (d, $^1J_{P\text{-}C}$ = 79.9 Hz), 131.2 (d, $^4J_{P\text{-}C}$ = 2.7 Hz), 132.7 (d, $^2J_{P\text{-}C}$ = 8.2 Hz); ^{31}P NMR (202 MHz, $CDCl_3$): δ 42.43 (s); Anal. Calcd for $C_{20}H_{31}O_2P$: C, 71.83; H, 9.34; Found: C, 71.50 H, 9.37; $[\alpha]_D$ = −198.3 (c 2.5, MeOH). HRMS (ESI-LTQ) *m*/*z* calcd for $C_{20}H_{32}O_2P$ $[M+H]^+$: 335.21399, found: 335.21369.

Crystal data for R_P−**7a-I**: Mw = 334.42, crystal system tetragonal, space group *P* 4_1, unit cell dimensions a = b = 10.7713(8) Å, V = 2020.1(3) Å^3, Z = 4, Density (calculated) 1.100 g/cm^3, absorption coefficient 1.249 mm^{-1}, F(000) = 728. Collected/independent reflections 5471/3301 [R(int) = 0.0236]. data/restraints/parameters 3301/1/212. Goodness-

of-fit on F^2 1.032, final R indices [I > 2σ(I)] R1 = 0.0424, wR2 = 0.1092, absolute structure parameter x = 0.006(19). CCDC No. 2162097.

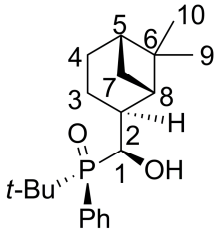


Figure 9. The structure of R_P−**7a-I** with atom numbering.

(R_P)-[6,6-Dimethylbicyclo[3.1.1]heptan-2-yl)(hydroxy)methyl](t-butyl)(phenyl)phosphine oxide (***7a-II***) *(minor)*. Yield 7% (0.07 g). Colorless oil. R_f = 0.40 ($CHCl_3$/AcOEt = 5:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.28 (s, 3H), 0.98 (s, 3H), 1.19 (d, $J_{P\text{-}H}$ = 14.19 Hz, 9H), 1.21–1.30 (m, 1H), 1.51 (d, $J_{P\text{-}H}$ = 10.90 Hz, 1H), 1.64–1.68 (m, 2H), 1.73–1.80 (m, 1H), 2.01–2.04 (m, 1H), 2.10–2.14 (m, 2H), 3.20 (dd, $J_{H\text{-}H}$ = 6.31 Hz, $J_{P\text{-}H}$ = 11.03 Hz, 1H), 4.16–4.20 (m, 1H), 7.43–7.47 (m, 2H), 7.50–7.53 (m, 1H), 7.68–7.72 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.8 (d, $J_{P\text{-}C}$ = 9.1 Hz, CH), 19.4 (s), 23.4 (d, $J_{P\text{-}C}$ = 2.7 Hz, CH_2), 23.7 (s), 23.9 (d, $J_{P\text{-}C}$ = 1.8 Hz, CH_2), 25.1 (s, CH_3), 26.4 (s), 33.7 (d, $^1J_{P\text{-}C}$ = 64.5 Hz, C), 36.9 (d, $J_{P\text{-}C}$ = 1.8 Hz, CH), 39.5 (s, CH), 40.4 (d, $J_{P\text{-}C}$ = 3.6 Hz, CH), 70.9 (d, $^1J_{P\text{-}C}$ = 68.2 Hz, CH), 128.1 (d, $J_{P\text{-}C}$ = 10.9 Hz, CH), 129.8 (d, $J_{P\text{-}C}$ = 118.0 Hz, C), 131.4 (d, $J_{P\text{-}C}$ = 2.7 Hz, CH), 131.7 (d, $J_{P\text{-}C}$ = 8.2 Hz, CH); ^{31}P NMR (202 MHz, $CDCl_3$): δ 47.76 (s); Anal. Calcd for $C_{20}H_{31}O_2P$: C, 71.83; H, 9.34; Found: C, 71.50; H, 9.37; $[\alpha]_D$ = −1.65 (c 2.24, MeOH). HRMS (ESI-LTQ) *m*/*z* calcd for $C_{20}H_{32}O_2P$ $[M+H]^+$: 335.21399, found: 335.21379.

4.5. General Procedure of the Synthesis of [6,6-dimethylbicyclo[3.1.1]heptan-2-yl)(hydroxy)methyl](methyl)(phenyl)phosphine Oxide (9c) from rac-1c and Myrtanal (6) Using DBU as a Base

In a Schlenk tube (50 mL) equipped with a magnetic stirrer and an argon inlet, secondary phosphine oxide *rac*-**1c** (9 mmol) was placed in anhydrous THF (15 mL). Then, to the mixture DBU (135 µL, 0.9 mmol) was added followed by myrtanal (**6**) (1.65 mL, 10.8 mmol). The mixture was stirred at rt for 7 d and monitored by TLC. Upon completion, the reaction quenched with solid NH_4Cl (200 mg). Then, the reaction mixture was filtered through Celite® and evaporated. The purification of the crude product was performed on silica gel using CH_2Cl_2/AcOEt/MeOH (*v*/*v* = 50:10:1) to give the product **9c** as mixture of all four diastereoisomers in 62% yield (1.629 g). By dividing the product into fractions enriched with specific diastereoisomers and their subsequent crystallization from AcOEt The following products were synthesized.

*(R_P)-6,6-Dimethylbicyclo[3.1.1]heptan-2-yl)(hydroxy)methyl)(methyl)(phenyl)phosphine oxide (R_P)-**9c-I***. (Figure 10). Yield 5% (0.131 g) as a solid, m.p.= 157.7–158.2 °C (AcOEt). R_f = 0.38 ($CHCl_3$/AcOEt/MeOH = 30:5:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.79 (d, $J_{H\text{-}H}$ = 9.77 Hz, 1H, C(7)H), 1.05 (s, 3H C(9)H_3), 1.16 (s, 3H, C(10)H_3), 1.75–1.81 (m, 3H, C(3)H, C(4)H), 1.82 (d, $J_{P\text{-}H}$ = 12.93 Hz, 3H, C(11)H_3), 1.83–1.88 (m, 1H, C(8)H), 1.91–1.94 (m, 1H, C(4)H), 2.04–2.13 (m, 1H, C(2)H), 2.18–2.22 (m, 1H, C(5)H), 2.26–2.31 (m, 1H, C(7)H), 3.21 (bs, 1H), 4.09–4.11 (m, 1H, C(1)H), 7.47–7.51 (m, 2H), 7.54–7.57 (m, 1H), 7.79–7.83 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9 (d, $^1J_{P\text{-}C}$ = 68.1 Hz, C11), 18.4 (s, C3), 22.9 (s, C9), 26.1 (s, C4), 27.8 (s, C10), 32.2 (s, C7), 38.5 (s, C6), 41.0 (s, C5), 41.2 (d, *J* = 9.9 Hz, C8), 42.9 (s, C2), 74.3 (d, $^1J_{P\text{-}C}$ = 82.7 Hz, C1), 128.5 (d, $^3J_{P\text{-}C}$ = 9.1 Hz), 131.3 (d, $^1J_{P\text{-}C}$ = 90.8 Hz), 131.2 (d, $^2J_{P\text{-}C}$ = 9.1 Hz), 131.9 (d, $^4J_{P\text{-}C}$ = 2.7 Hz); ^{31}P NMR (202 MHz, $CDCl_3$): δ 41.91 (s); Anal. Calcd for $C_{17}H_{25}O_2P$: C, 69.84; H, 8.62; Found: C, 69.99; H, 8.74; $[\alpha]_D$ = −43.9 (c 1.025, $CHCl_3$). HRMS (ESI-LTQ) *m*/*z* calcd for $C_{17}H_{26}O_2P$ $[M+H]^+$: 293.16704, found: 293.16721.

Crystal data for R_P−**9c-I**: Mw = 292.34, crystal system monoclinic, space group *P* 2_1, unit cell dimensions a = 6.9985(5) Å, b = 10.5591(8) Å, c = 11.2596(8) Å, β= 104.303(5)°, V = 806.27(10) Å^3, Z = 2, Density (calc) 1.204 g/cm^3, absorption coeff. 1.496 mm^{-1}, F(000) = 316.

Collected/independent reflections 11,414/2893 [R(int) = 0.0217], data/restraints/parameters 2893/1/188. Goodness-of-fit on F^2 1.028, final R indices [I > 2σ(I)] R1 = 0.0264, wR2 = 0.0709, absolute structure parameter x = 0.003(13). CCDC No. 2162095.

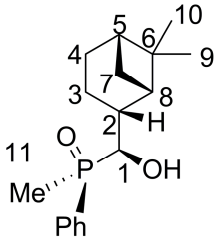


Figure 10. The structure of R_P−**9c-I** with atom numbering.

*(S_P)-6,6-Dimethylbicyclo[3.1.1]heptan-2-yl)(hydroxy)methyl)(methyl)(phenyl)phosphine oxide (S_P)-**9c-II*** (Figure 11). Yield 5% (0.131 g). White solid, m.p.= 157.9–158.2 °C (AcOEt). R_f = 0.42 ($CHCl_3$/AcOEt/MeOH = 30:5:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.73 (s, 3H, C(9)H), 1.18 (s, 3H, C(10)H), 1.29–1.32 (m, 1H, C(3)H), 1.36 (d, $J_{H\text{-}H}$ = 10.09 Hz, 1H, C(7)H), 1.40–1.47 (m, 1H, C(3)H), 1.60–1.69 (m, 2H, C(4)H_2), 1.74 (d, $J_{H\text{-}P}$ = 12.61 Hz, 3H, C(11)H_3), 1.78–1.81 (m, 1H, C(5)H), 2.01–2.05 (m, 1H, C(7)H), 2.25–2.27 (m, 1H, C(8)H), 2.34–2.37 (m, 1H, C(2)H), 3.64 (d, $J_{H\text{-}P}$ = 7.57 Hz, C(1)H, 3.85 (bs, 1H), 7.41–7.48 (m, 2H), 7.48–7.53 (m, 1H), 7.70–7.73 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.3 (d, $J_{P\text{-}C}$ = 68.2 Hz, C11), 18.7 (d, $J_{P\text{-}C}$ = 4.6 Hz, C3), 19.9 (s, C9), 23.3 (s, C7), 24.1 (s, C4), 26.7 (s, C10), 37.2 (d, $J_{P\text{-}C}$ = 2.3 Hz, C2), 39.1 (s, C6), 40.2 (s, C5), 41.1 (d, J = 8.09 Hz, C8), 74.0 (d, $J_{P\text{-}C}$ = 80.9 Hz, C1), 128.4 (d, $^3J_{P\text{-}C}$ = 10.1 Hz), 130.7 (d, $^2J_{P\text{-}C}$ = 9.1 Hz), 131.6 (d, $^4J_{P\text{-}C}$ = 2.7 Hz), 133.0 (d, $^1J_{P\text{-}C}$ = 90.2 Hz); ^{31}P NMR (202 MHz, $CDCl_3$): δ 40.43 (s); Anal. Calcd for $C_{17}H_{25}O_2P$: C, 69.84; H, 8.62; Found: C, 69.81; H, 8.62; $[\alpha]_D$ = −44.0 (c 1.0, $CHCl_3$). HRMS (ESI-LTQ) m/z calcd for $C_{17}H_{26}O_2P$ $[M+H]^+$: 293.16704, found: 293.16719.

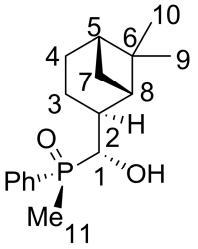


Figure 11. The structure of R_P−**9c-III** with atom numbering.

*(R_P)-6,6-Dimethylbicyclo[3.1.1]heptan-2-yl)(hydroxy)methyl)(methyl)(phenyl)phosphine oxide (R_P)-**9c-III***. Yield 1% (0.026 g). Waxy solid. R_f = 0.43 (CH_2Cl_2/AcOEt/MeOH = 50:10:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.70 (s, 3H), 1.18 (s, 3H), 1.33–1.46 (m, 2H), 1.39 (d, $J_{H\text{-}H}$ = 10.4 Hz, 1H), 1.63–1.74 (m, 2H), 1.80 (d, $J_{H\text{-}H}$ = 4.73 Hz, 1H), 1.87 (d, $J_{H\text{-}P}$ = 10.40 Hz, 3H), 2.04–2.08 (m, 1H), 2.24–2.26 (m, 1H), 2.29–2.38 (m, 1H), 3.81 (bs, 1H), 3.86 (bs, 1H), 7.50–7.53 (m, 2H), 7.55–7.59 (m, 1H), 7.73–7.79 (m, 2H). ^{31}P NMR (202 MHz, $CDCl_3$): δ 44.22 (s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.3 (d, $J_{P\text{-}C}$ = 68.2 Hz, C11), 18.7 (s, CH_2), 19.9 (s), 23.4 (s, CH_2), 24.1 (s, CH_2), 26.7 (s), 37.1 (s), 39.2 (s, C), 40.1 (s), 41.1 (d, J = 7.2 Hz), 74.0 (d, $J_{P\text{-}C}$ = 80.9 Hz, C1), 128.8 (d, $^3J_{P\text{-}C}$ = 10.9 Hz), 130.8 (d, $^2J_{P\text{-}C}$ = 8.2 Hz), 132.2 (d, $^4J_{P\text{-}C}$ = 2.7 Hz).Anal. Calcd for $C_{17}H_{25}O_2P$: C, 69.84; H, 8.62; Found: C, 69.81; H, 8.62. $[\alpha]_D$ = −41.5 (c 0.265, $CHCl_3$).

Crystal data for R_P−**9c-III**; Mw = 292.34, crystal system monoclinic, space group P 2_1, unit cell dimensions a = 6.0752(3) Å, b = 10.4200(5) Å, c = 13.1252(6) Å, β = 100.740(10)°, V = 816.32(7) Å^3, Z = 2, Density (calc) 1.189 g/cm^3, absorption coefficient 1.478 mm^{-1}, F(000) = 316. Collected/independent reflections 5311/3075 [R(int) = 0.0315], data/restraints/parameters 3075/1/188. Goodness-of-fit on F^2 1.083, final R indices [I > 2σ(I)] R1 = 0.0368, wR2 = 0.0945, absolute structure parameter x = 0.013(19). CCDC No. 2162096.

6,6-Dimethylbicyclo[3.1.1]heptan-2-yl)(hydroxy)methyl)(methyl)(phenyl)phosphine oxide ***9c-IV***. An oil. Yield 2% (0.0526 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.70 (s, 3H), 1.13 (s, 3H), 1.40 (d, $J_{H\text{-}H}$ = 9.46 Hz, 1H), 1.53–1.69 (m, 2H), 1.72–1.76 (m, 2H), 1.80–1.83 (m, 1H), 1.82 (d, $J_{H\text{-}P}$ = 12.93 Hz, 3H), 2.00–2.03 (m, 2H), 2.08–2.15 (m, 1H), 3.19 (bs, 1H), 3.83 (d, $J_{H\text{-}P}$ = 5.10 Hz, 1H), 7.47–7.51 (m, 2H), 7.54–7.57 (m, 1H), 7.78–7.82 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9 (d, $J_{P\text{-}C}$ = 68.9 Hz, CH_3), 18.3 (d, $J_{P\text{-}C}$ = 3.6 Hz, CH_2), 19.9 (s), 23.4 (s, CH_2), 24.1 (s, CH_2), 26.7 (s), 37.8 (s), 39.0 (s, C), 40.3 (s), 41.0 (s), 41.1 (s), 73.8 (d, $J_{P\text{-}C}$ = 83.6 Hz, CH), 128.5 (d, $J_{P\text{-}C}$ = 10.9 Hz), 130.9 (d, $J_{P\text{-}C}$ = 9.1 Hz), 131.6 (d, $J_{P\text{-}C}$ = 90.8 Hz), 131.8 (d, $J_{P\text{-}C}$ = 2.7 Hz).^{31}P NMR (202 MHz, $CDCl_3$): δ 41.04 (s); Anal. Calcd for $C_{17}H_{25}O_2P$: C, 69.84; H, 8.62; Found: C, 69.99; H, 8.74.

4.6. General Procedure for the Reaction of α-Hydroxyphosphine Oxides with BH_3-THF

In a Schenk tube (25 mL) equipped with a magnetic stirrer and an argon inlet, hydroxymethylphosphine oxide (0.3 mmol) was dissolved in anhydrous THF (2 mL). Then, BH_3-THF complex (1.5 mL, 1.5 mmol, 1 M solution in THF) was added slowly to avoid uncontrolled bubbling. Then, the reaction mixture was stirred at rt for 16 h. Then, the reaction mixture was evaporated to dryness, and the residue was purified by column chromatography using hexane/ethyl acetate (v/v = 10:1) as eluent. The following products were synthesized.

*(R_P)-6,6-Dimethylbicyclo[3.1.1]heptan-2-yl)(hydroxy)methyl)(t-butyl)(phenyl)phosphine-borane (R_P)-****10a*** (Figure 12). Yield 65% (0.0647 g). White solid, m.p. = 98–101 °C. R_f = 0.64 (hexane/AcOEt = 6:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.33–0.87 (bm, 3H), 0.60 (s, 3H, C(9)$\underline{H}_3$), 0.98 (s, 3H, C(10)$\underline{H}_3$), 1.16 (d, $J_{P\text{-}H}$ = 13.24 Hz, 9H, C(12)$\underline{H}_3$), 1.38 (d, J = 10.09 Hz, 1H, C(7)$\underline{H}$), 1.47–1.49 (m, 1H, C(8)$\underline{H}$), 1.52–1.56 (m, 1H, C(3)$\underline{H}$), 1.63–1.67 (m, 1H, C(5)$\underline{H}$), 1.68–1.73 (m, 3H, C(4)$\underline{H}_2$, C(3)$\underline{H}$), 1.80–1.84 (m, 1H, C(7)$\underline{H}$), 2.25–2.30 (m, 1H, C(2)$\underline{H}$), 4.58–4.63 (m, 1H, C(1)$\underline{H}$), 7.41–7.45 (m, 2H), 7.48–7.52 (m, 1H), 7.64–7.68 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.4 (d, $J_{P\text{-}C}$ = 4.5 Hz, C3), 19.7 (s, C9), 23.9 (s, C4), 24.1 (s, C7), 26.3, 26.4 (s, C10), 30.51 (d, $^{1}J_{P\text{-}C}$ = 30.9 Hz, C11), 38.9 (d, $J_{P\text{-}C}$ = 6.4 Hz, C2), 39.7 (d, $J_{P\text{-}C}$ = 8.2 Hz, C8), 45.5 (d, $J_{P\text{-}C}$ = 4.5 Hz, C5), 71.6 (d, $^{1}J_{P\text{-}C}$ = 34.5 Hz, C1), 127.1 (d, $^{1}J_{P\text{-}C}$ = 46.3 Hz), 128.2 (d, $^{3}J_{P\text{-}C}$ = 9.1 Hz), 131.2 (d, $^{4}J_{P\text{-}C}$ = 2.7 Hz), 133.4 (d, $^{2}J_{P\text{-}C}$ = 6.4 Hz); ^{31}P NMR (202 MHz, $CDCl_3$): δ 32.67 (bm); Anal. Calcd for $C_{20}H_{31}O_2P$: C, 72.30; H, 10.31; Found: C, 72.64; H, 9.91; $[\alpha]_D$ = −29.3 (c 1.76, $CHCl_3$).

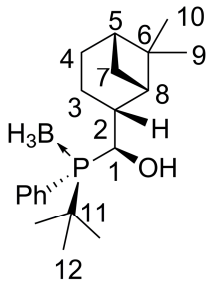


Figure 12. The structure of R_P−**10a** with atom numbering.

*(R_P)-(-)-t-Butylphenylphosphine-borane (R_P)-(-)-****11a***. Yield 15% (0.0081 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.37–1.05 (bm, 3H), 1.18 (d, $J_{H\text{-}P}$ = 14.82 Hz, 1H), 5.10 (dq, $J_{H\text{-}P}$ = 140.67 Hz, 1H), 7.44–7.47 (m, 2H), 7.51–7.56 (m, 1H), 7.62–7.66 (m, 2H); ^{31}P NMR (202 MHz, $CDCl_3$): δ 30.49 (bm); $[\alpha]_D$ = −2.0 (c 1.03, $CHCl_3$). These data are consistent with previously reported [32].

*((S_P)-(6,6-Dimethylbicyclo[3.1.1]heptan-2-yl)(hydroxy)methyl)(methyl)(phenyl)phosphine-borane (S_P)-****12c***. Yield 94% (0.0812 g). White solid, m.p. = 77.8–78.8 °C. R_f = 0.40 (hexane/AcOEt = 4:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.39–1.02 (bm, 3H), 0.76 (s, 3H), 1.11 (s, 3H), 11.38 (d, J = 10.09 Hz, 1H), 1.50–1.58 (m, 2H), 1.66 (d, $^{1}J_{P\text{-}H}$ = 10.09 Hz, 3H), 1.70 (bs, 1H), 1.73–1.81 (m, 4H), 1.97–2.01 (m, 1H), 2.26–2.33 (m, 1H), 3.90 (dd, $J_{H\text{-}H}$ = 1.89 Hz, $J_{P\text{-}H}$ = 6.31 Hz, 1H), 7.47–7.50 (m, 2H), 7.51–7.55 (m, 1H), 7.76–7.80 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 8.4 (d, $^{1}J_{P\text{-}C}$ = 39.1 Hz), 19.6 (d, $J_{P\text{-}C}$ = 5.5 Hz), 19.9, 23.3, 24.1, 26.6, 37.8 (d, $J_{P\text{-}C}$ = 4.5 Hz), 39.3, 40.5, 40.7 (d, $J_{P\text{-}C}$ = 5.5 Hz), 74.3 (d, $^{1}J_{P\text{-}C}$ = 36.3 Hz), 127.5 (d, $^{1}J_{P\text{-}C}$ = 50.9 Hz), 128.7 (d, $^{3}J_{P\text{-}C}$ = 9.1 Hz), 131.5 (d, $^{4}J_{P\text{-}C}$ = 1.8 Hz),

132.5 (d, $^{2}J_{P\text{-}C}$ = 8.2 Hz), ^{31}P NMR (202 MHz, $CDCl_3$): δ 17.01 (bm); Anal. Calcd for $C_{17}H_{28}BOP$: C, 70.36; H, 9.73; Found: C, 70.46; H, 9.90. $[\alpha]_D$ = +10.9 (c 1.0, $CHCl_3$). HRMS (ESI-LTQ) m/z calcd for $C_{17}H_{29}BOP$ $[M+H]^+$: 291.20491, found: 291.20487.

4.7. Procedure of the Reduction of (3a-I) Using BH_3-SMe_2

In a two-necked round-bottom flask (25 mL) equipped with magnetic stirrer and argon inlet was placed phosphine oxide S_P-**3a-I** (0.0996 g, 0.3 mmol) in anhydrous THF (5 mL). Then, BH_3-SMe_2 (284.6 µL, 3 mmol), was added slowly to avoid uncontrolled bubbling. After addition of BH_3 complex, the reaction mixture was stirred at 60 °C for 72 h. Then, the saturated solution of $NaHCO_3$ was added to quench the reaction mixture and extracted with $CHCl_3$ (3 × 30 mL). The collected organic phases were evaporated to dryness and the residue was purified on silica gel using AcOEt/MeOH (v/v = 10:1) as eluent.

*trans-(S_P,1S,2R,3S,5R)-t-Butyl-2-(hydroxymethyl)-6,6-dimethylbicyclo[3.1.1]heptan-3-yl) (phenyl)phosphine oxide S_P-**13***. Oil. Yield 60% (0.0601 g). R_f = 0.19 (AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$): δ −0.09 (d, $J_{P\text{-}H}$ = 9.71 Hz, 1H), 0.99 (s, 3H), 1.09 (s, 3H), 1.33 (d, $J_{P\text{-}H}$ = 14.23 Hz, 9H), 1.72–1.76 (m, 1H), 1.80–1.86 (m, 1H), 1.87–1.92 (m, 1H), 2.24–2.29 (m, 2H), 2.40–2.48 (m, 1H), 2.88–2.98 (m, 1H), 3.50–3.56 (m, 1H), 3.64–3.69 (m, 1H), 5.93 (bs, 1H), 7.46–7.51 (m, 2H), 7.51–7.57 (m, 1H), 7.91–7.95 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.1, 25.8, 27.2, 28.2, 29.9, 31.4 (d, $J_{P\text{-}C}$ = 1.2 Hz), 32.15 (d, $J_{P\text{-}C}$ = 1.2 Hz), 33.96 (d, $^{1}J_{P\text{-}C}$ = 65.5 Hz), 38.17 (d, $^{4}J_{P\text{-}C}$ = 1.15 Hz), 40.5 (d, $J_{P\text{-}C}$ = 5.2 Hz), 44.2 (d, $J_{P\text{-}C}$ = 5.75 Hz), 44.3 (d, $J_{P\text{-}C}$ = 4.0 Hz), 67.9 (d, $^{3}J_{P\text{-}C}$ = 1.2 Hz), 128.2 (d, $^{3}J_{P\text{-}C}$ = 9.8 Hz), 128.54 (d, $^{1}J_{P\text{-}C}$ = 81.6 Hz), 131.87 (d, $^{4}J_{P\text{-}C}$ = 2.9 Hz), 133.3 (d, $^{3}J_{P\text{-}C}$ = 6.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 53.10 (s); Anal. Calcd for $C_{20}H_{31}O_2P$: C, 71.83; H, 9.34; Found: C, 71.90; H, 9.40.

5. Conclusions

In summary, we have evaluated syntheses of P,C-stereogenic hydroxyphosphine oxides based on 1,4- and 1,2-addition of secondary phosphine oxides to (1*R*)-myrtenal and (2*R*/2*S*)-myrtanal, respectively. Reactions involving racemic secondary phosphine oxides as substrates showed only moderate selectivity; however, using an enantiomerically pure secondary phosphine oxide creates a doubly asymmetric process that is highly selective and ready for practical use. In most cases, isolation of at least one or two diastereoisomerically pure P,C stereogenic adducts formed in the addition reaction was possible. 1,2-Additions of P-stereogenic secondary phosphine oxides to myrtanal produced α-hydroxyphosphine oxides having five densely distributed chirality centers, four of which were contiguous. The absolute configurations of isolated pure diastereoisomers were established using a single crystal crystallographic analysis and 2D NMR techniques. The stereochemical course of the studied addition reactions has been presented. A convenient and fully stereoselective reduction of enantiomerically pure P,C-stereogenic α-hydroxyphosphine oxides by BH_3 yielding the corresponding α-hydroxyphosphine-boranes with inversion of configuration at the P-center has been accomplished. Attempted similar reduction of a γ-hydroxyphosphine oxide by BH_3 did not take place. Further tuning of those addition processes as well as application of synthesized α-hydroxyphosphines as ligands is currently underway in our laboratory.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/sym15061172/s1, ^{1}H, ^{31}P{^{1}H}, ^{13}C{^{1}H} NMR spectra of isolated compounds, Table S1. Optimisation of the hydrogenation of (1*R*)-myrtenal (**2**). Table S2. The attempts of the hydrogenation of acetal derived from (1*R*)-myrtenal (**2**). Scheme S1. Separation of diastereoisomers of **9c** on silica gel. Refs. [40,41] are cited in Supplementary Materials.

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Data Availability Statement: The presented data (both in the ms and SI) are openly available.

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