Heteroatom Chemistry
Volume 27, Number 2, 2016

Straightforward Diastereoselective Synthesis of P-Chirogenic (1*R*)-1,8,8-Trimethyl-2,4-diaza-3-phosphabicyclo[3.2.1]octane 3-Oxides: Application as Chiral NMR Solvating Agents

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Received 29 September 2015; revised 2 December 2015; accepted 15 December 2015

ABSTRACT: *A direct route to enantio- and diastereopure nitrogen-substituted phosphine oxides has been developed. The desired P-stereogenic compounds were obtained in good yields and high purity. The starting point of the synthesis was (+)-camphor, which is a readily available compound from the chiral pool. The new nitrogen-substituted phosphine oxides could be transformed from their pentavalent state to their trivalent form with* N,O-*bis(trimethylsilyl)acetamide, which makes them potential chiral ligands. It was possible to apply these compounds as chiral-solvating agents in chiral recognition experiments with a racemic alcohol and acid.* © 2016 Wiley Periodicals, Inc. Heteroatom Chem. 27:121–134, 2016; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.21309

INTRODUCTION

Organophosphorus compounds are an important part of many research areas such as agrochemistry, medicinal chemistry, biochemistry, and organic synthesis [1]. The application of enantiopure compounds is especially interesting for the synthesis of biologically active compounds and for the preparation of reagents [2]. Furthermore, enantiopure phosphorus compounds have been applied as organocatalysts [3] and largely as ligands in metal-catalyzed asymmetric reactions [4].

A special challenge is the synthesis of chiral phosphorus compounds incorporating a chirogenic phosphorus atom. Examples of different compounds **1**–**6** are shown in Fig. 1. For the synthesis of these compounds, different strategies are possible. Next to a standard resolution [5], kinetic and dynamic resolution [6] can be applied. Furthermore, asymmetric catalytic reactions can directly form a new P-stereogenic center [7]. Another alternative is to start the synthesis of these compounds with a starting material from the chiral pool. In the latter case, an asymmetric phosphorus center will lead to the construction of enantiopure diastereomers [8]. An example is the menthyl hydrogen phosphinate **6**, which can also be further transformed to other chiral phosphorus compounds [9].

Especially structures containing phosphorus-heteroatom bonds [10], which can be abbreviated as SPO (secondary phosphine oxides) or according to the suggestion of Ackermann HASPO (heteroatom-substituted secondary phosphine oxides) like **4**, have recently received much attention [11]. The first heterocyclic compounds having both phosphorus and nitrogen atoms were prepared by Liebig and Wöhler

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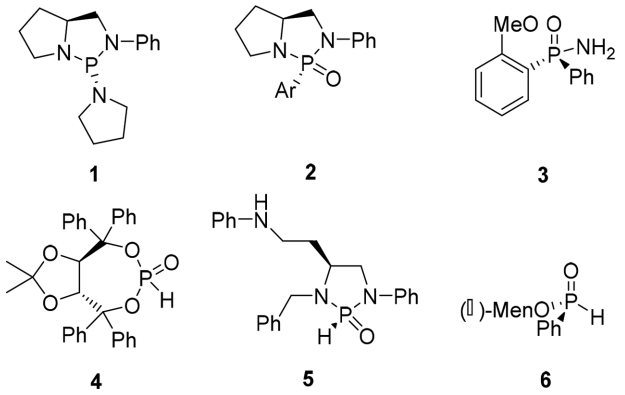


FIGURE 1 Examples of chiral organophosphorus compounds.

[12]. Enantiopure or enantioenriched heterocycles containing a trivalent or pentavalent P-stereogenic phosphorus atom can be easily generated by cyclization of diamines, amino alcohols, or diols around phosphorus moieties. Phosphorus-heteroatom heterocycles are extremely attractive compounds because in contrast to the classic phosphines they presented marked stability toward moisture and air and can be used as organocatalysts or as ligands in transition metal transformations [13].

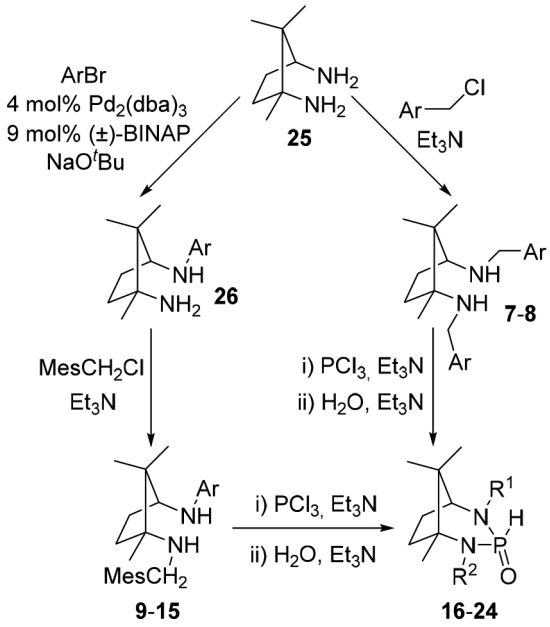
One relevant class of P-stereogenic diaminophosphine oxides was discovered by Hamada and co-workers. They synthesized a new class of P-chirogenic phosphine oxides based on a chiral asymmetric diamine framework, called P-stereogenic diaminophosphine oxides: DIAPHOXs **5** [14]. These chiral ligands with a stereogenic center on a phosphorus atom [15] have been prepared from (*S*)-aspartic acid [16].

Diaminophosphine oxides have been applied as preligands in cross-coupling reactions [17] and Ni-catalyzed asymmetric hydrocarbamoylations of alkenes [18]. In addition, diaminophosphine oxides and aminophosphonic acids analogues have a high potential as biological active compounds [19].

Here, we present the straightforward synthesis of new enantiopure C_1 symmetric nitrogen-substituted SPOs with a P-stereogenic center via a diastereoselective route from camphor. The chirogenic phosphorus atom is embedded in a rigid bicyclic system being part of a six- and seven-membered ring.

RESULTS AND DISCUSSION

To synthesize the desired chiral nitrogen-substituted phosphine oxides, the starting diamines **7**–**15** were prepared from (+)-*cis*-(1*R*,3*S*)-1,2,2-trimethylcyclopentane-1,3-diamine (**25**). The latter can be synthesized according to the literature [20]



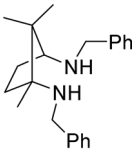
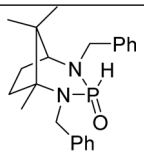
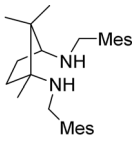
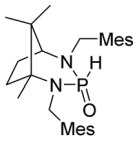
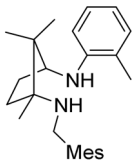
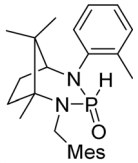
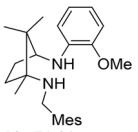
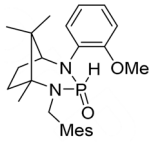
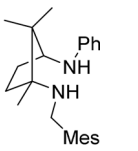
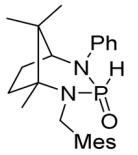
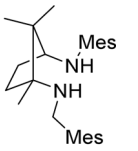
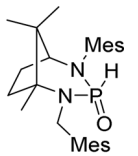
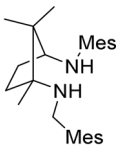
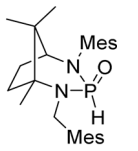
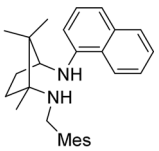
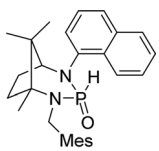
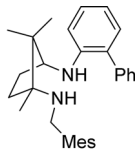
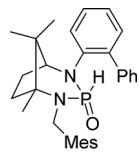
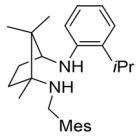
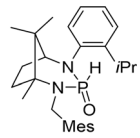
SCHEME 1 Synthesis of enantiopure camphor-based HASPOs **16**–**24**.

from (+)-camphoric acid, which was purchased from commercial sources. The symmetrical substituted diamines **7** and **8** were prepared according to a literature procedure [21]. Thereafter, a series of enantiopure secondary diamines **26** with two differently substituted nitrogen atoms were synthesized via an alkylation of monoarylated diamines [22] with mesitylmethylene chloride in the presence of triethylamine in acetonitrile under reflux (Scheme 1). The corresponding diamines **9**–**15** were obtained in yields between 50% and 70% as shown in Table 1. The use of the less sterically demanding benzyl bromide and chloride as electrophile with **9**–**15** in the reaction resulted in a mixture of products that could not be separated.

HASPOs are accessible from diamines [2a,13c, 23]. The new desired nitrogen-substituted SPOs were prepared in two steps from the diamines **7**–**15**, by treating these secondary diamines with PCl_3 and Et_3N at −60°C (Scheme 1). The temperature was slowly raised to room temperature in toluene. After filtration through $MgSO_4$, the heterocyclic chloride derivative was obtained. In the second step, H_2O and Et_3N were added to the chloride derivative at −60°C. The temperature was slowly raised to room temperature in toluene. After filtration through $MgSO_4$, the desired product was isolated. The presence of Et_3N as a base was required due to the formation of HCl, which can decompose the desired product [13h].

The products **16–24** were characterized by mass spectrometry and multinuclear NMR spectroscopy. ^{31}P NMR chemical shifts were, respectively, in the

TABLE 1 Synthesis of Diamines and SPOs

Entry	Diamine	Product[a]	^{31}P, δ (ppm)
1	 **7** [21]	 **16**, 94 %	10.1
2	 **8** [21]	 **17**, 73 %	9.6
3	 **9**, 64 %	 **18**, 89 %	3.9
4	 **10**, 71 %	 **19**, 97 %	3.9
5	 **11**, 62 %	 **20**, 88 %	3.9
6	 **12**, 61 %	 **21a**, 36 %	1.9
7	 **12**, 61 %	 **21b**, 16 %	−4.2
8	 **13**, 54 %	 **22**, 86 %	4.9
9	 **14**, 57 %	 **23**, 97 %	5.4
10	 **15**, 51 %	 **24**, 84 %	5.4

[a]Absolute configuration assigned by NOESY.

same range as those reported for related compounds [13c,13d]. The results with selected ^{31}P NMR data are shown in Table 1.

From Table 1, it is possible to conclude that excellent yields can be obtained for the synthesis of the secondary phosphine oxides. The products were obtained as one diastereomer. It is remarkable that the reactions carried out on a larger scale gave cleaner desired products, which did not need any purification. Only one product obtained from diamine **12** was achieved as two diastereomers **21a** (Table 1, entry 6) and **21b** (Table 1, entry 7), which were separated by column chromatography. Figure 2 shows a ^{31}P NMR of the diastereomers prior to separation and of **21b** after isolation. In general, ^{31}P NMR resonances for the compounds were in the range of $\delta =$ 1.9–10 ppm. **21b** appeared at $\delta = -4.2$ ppm. The reason of the formation of two diastereomers from **12** can be due to the sterically demanding mesityl substituent present in the diamine. In all other derivatives, one ortho-position incorporates a small hydrogen atom. When a rotation around the N-arly bond is possible, the sterical hindrance induced by these aryl substituents can be smaller than that of a mesityl substituent.

The absolute configuration of the new P-stereogenic centers in the obtained products was established by NOESY. It can be assumed from the spectra that substrates containing the same substituent on the nitrogen atoms have *S* configuration on the phosphorus atom whereas ligands with two different substituents on the nitrogen atoms have *R* configuration on the phosphorus atom.

The ^{1}H NMR spectra showed that the proton attached to the phosphorus appeared as a characteristic doublet with a coupling $J_{\text{P-H}} = 617.0$–649.9 Hz. Additionally, NOESY studies revealed that the P–H

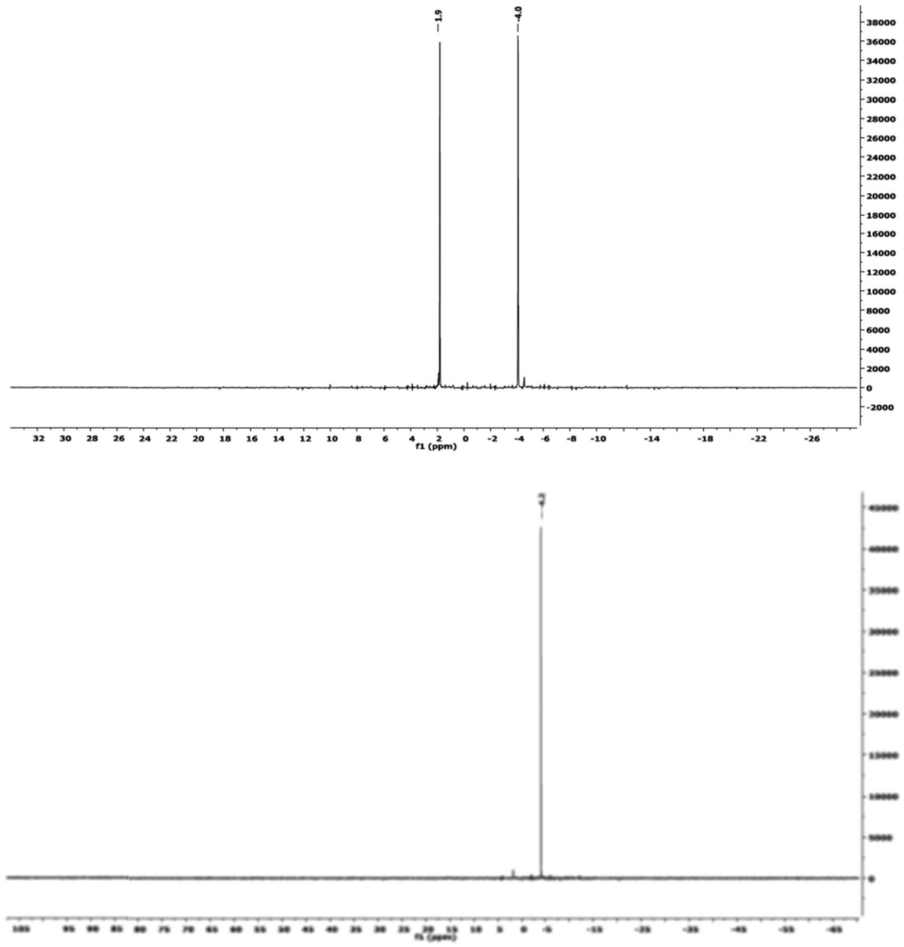


FIGURE 2 ^{31}P NMR of **21a** and **21b** before separation and of **21b** after separation.

bond in the ligands is on the same side as the Me_2C bridge. An example is given in Fig. 3 for compound **16**.

The exception is diastereomer **21b**, where the P–H bond is on the other side as the Me_2C bridge. The spectra are shown in Fig. 4.

Since just very few six- and seven-membered ring diaminophosphine oxides are known and for instance even seven-membered enantiopure binaphthyl-derived analogues are unknown, it was decided to study the behavior of the newly prepared compounds **16**–**24** in more detail. The pentavalent phosphorus species were activated in situ by *N*,*O*-bis(trimethylsilyl)acetamide (BSA) to induce P(V)–P(III) tautomerization to afford trivalent phosphorus compounds, trapped as TMS adducts (Scheme 2), which can be used as ligands in metal-catalyzed reactions. The generation of trivalent phosphorus compounds was monitored by ^{31}P NMR spectroscopy. The principal investigation was performed with symmetric secondary substituted compound **16** and the addition of 4 equiv BSA to toluene-D_8. The experiment was controlled at different times; however, the best result was obtained after 24 h. The reaction was much slower compared to five-membered ring diaminophosphine oxides like DIAPHOX **5** [14]. The ^{31}P NMR showed that pentavalent ligand **16** (chemical shift: 8.1 ppm, toluene-D_8) reacted with BSA to provide the formation of a trivalent phosphorus species (chemical shift: 117.4 ppm, toluene-D_8) (Fig. 5).

Further investigation revealed that when asymmetric compound **20** with a chemical shift of 2.4 ppm reacted with BSA in toluene-D_8, the generation of the trivalent phosphorus species, with a chemical shifted 104.9 ppm, could be performed faster than with compound **16** (Fig. 6).

A current research field is to develop efficient methods for the easy and fast measurement of the enantiomeric excess of chiral compounds [24]. The application of chiral-solvating reagents for NMR spectroscopy is a very useful method to achieve determination of the enantiomeric excesses of chiral organic molecules. The advantage of this convenient

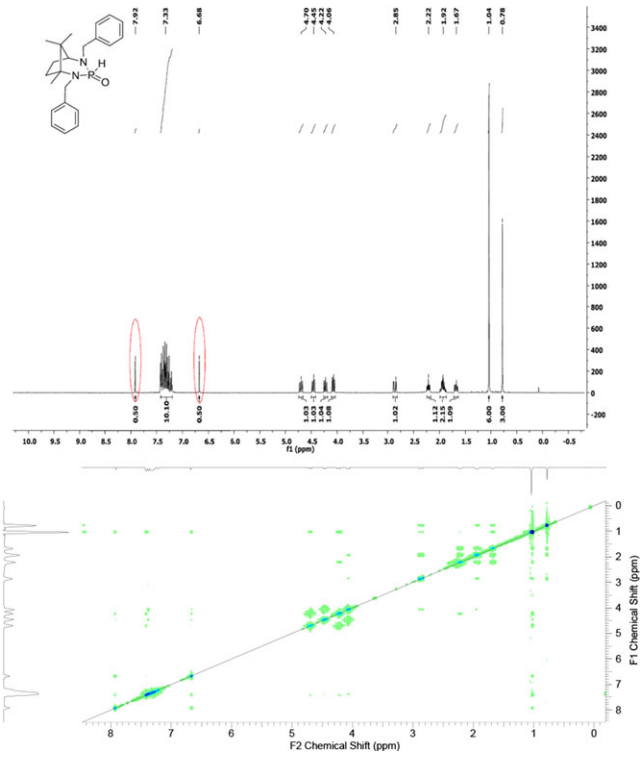


FIGURE 3 ^{1}H NMR and NOESY of compound **16**.

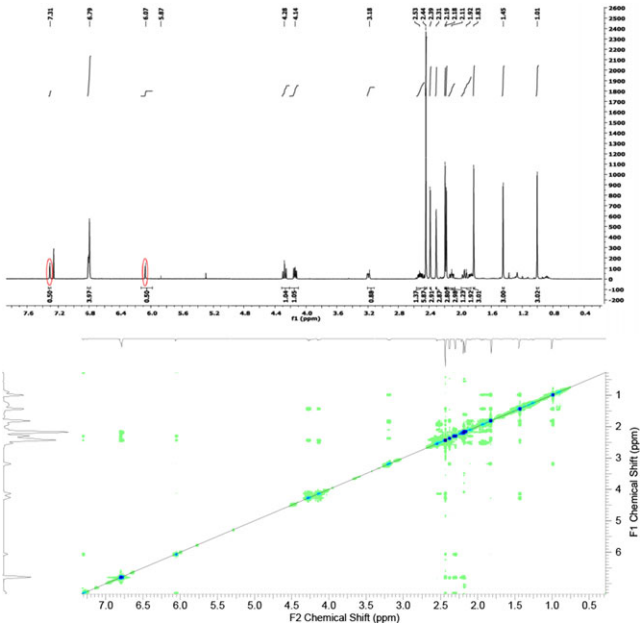
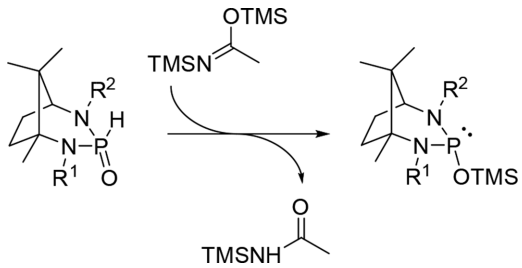


FIGURE 4 ^{1}H NMR and NOESY of diastereomer **21b**.

method is an easy performance without using any chiral derivatization of the analyte [25]. Many different kinds of chiral shift reagents, such as crown ethers, cyclodextrins, porphyrins, macrocycles, and others have been investigated [26].



SCHEME 2 BSA-induced P(V)-P(III) transformation.

Organophosphorus compounds derived from chiral C_2-symmetric diamines have been used as chiral-derivatizating reagents for NMR studies [27]. However, the potential of chiral HASPOs as chiral-solvating agents has not been investigated so far. Hence, the synthesized new compounds **16** and **18** were evaluated as chiral-solvating agents in dry toluene. The chiral shift experiments were carried out by measuring the ^{1}H NMR and ^{19}F NMR spectra of a mixture of α-(trifluoromethyl)benzyl alcohol and **16** or **18**, respectively, in a ratio of 1:1 in toluene at room temperature. While the symmetric substituted compound **16** showed no shift difference of the CF_3 group in the ^{19}F NMR, compound **18** resulted in a shift difference of 7 Hz (Fig. 7). The interaction of the two compounds is caused by the formation of a hydrogen bond of the alcohol with the oxygen atom of the phosphine oxide.

The ^{1}H NMR spectra were also recorded for the mixtures mentioned above. Compound **18** interacted with the methine proton of α-trifluoromethyl benzyl alcohol and showed a shift difference of 7 Hz, whereas no shift difference was observed with **16** (Fig. 8).

Furthermore, mandelic acid was investigated with **16** and **18** and the signal of the proton at the asymmetric center showed a shift difference of 1 Hz with **16** and 6 Hz with **18** (Fig. 9).

CONCLUSION

A new class of chiral HASPOs was prepared from inexpensive camphoric acid, by treating the secondary diamine with different substituents with PCl_3 and Et_3N, followed by H_2O which provided the desired compounds in pure diastereomeric and enantiomeric form. Preliminary experiments indicated that trivalent phosphorus compounds are formed in the presence of BSA. This is beneficial for their application as ligands in metal-catalyzed asymmetric transformations. Furthermore, the new compounds could also be of interest as chiral-starting material for further transformations like a hydrophosphorylation to prepare new P,C-stereogenic tertiary

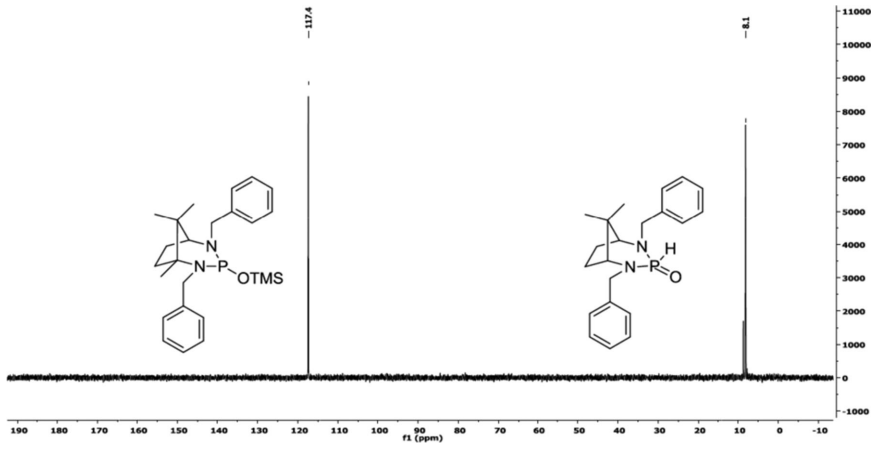


FIGURE 5 ^{31}P NMR of **16** with BSA after 24 h.

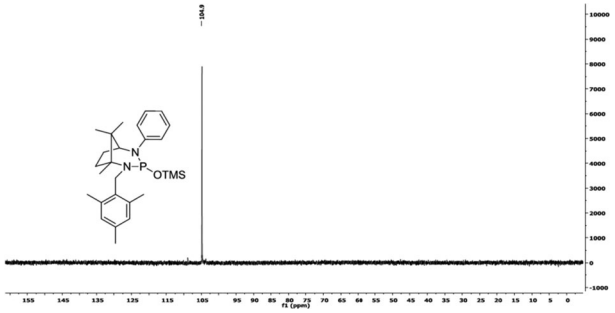


FIGURE 6 ^{31}P NMR of **20** with BSA after 24 h.

α-hydroxyl phosphinates [28]. Finally, it was possible to show that the new compounds **16** and **18** can be applied as chiral-solvating agents. The phosphorus compounds proved to be versatile chiral-discriminating agents for different types of racemic compounds such as alcohols and acids.

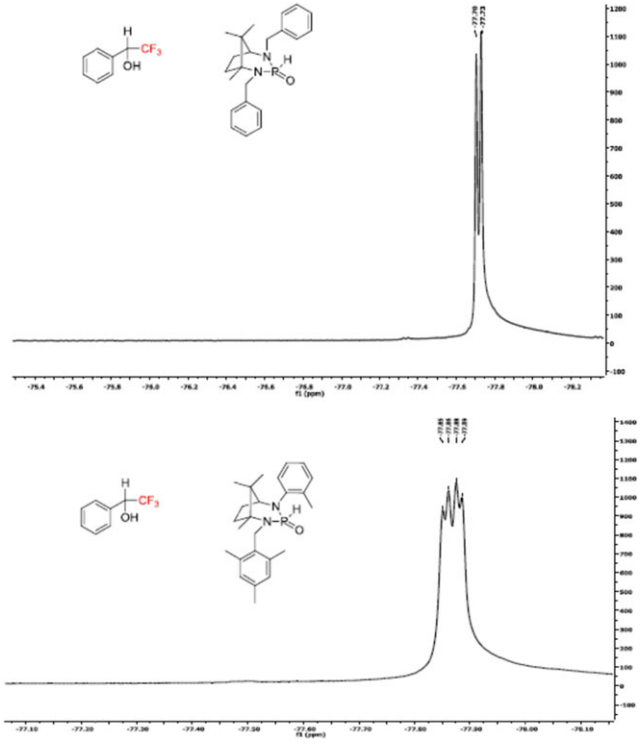


FIGURE 7 ^{19}F NMR of α-(trifluoromethyl)benzyl alcohol in the presence of **16** and **18**.

EXPERIMENTAL

General

All reactions were carried out using Schlenk line techniques. All reagents which are not described below were purchased from commercial sources. Reactions were monitored by TLC. Flash column chromatography was performed on Silica gel 60 (230–400 mesh). Nuclear magnetic resonance data were recorded on a Bruker Advance 500 (^{1}H NMR: 500 MHz, ^{13}C NMR: 126 MHz, ^{15}N NMR: 51 MHz) and Bruker Advance 300 (^{31}P NMR: 202 MHz, ^{19}F NMR: 125 MHz) spectrometers. NMR chemical shifts δ are reported in parts per million (ppm) and are referenced to the residual solvent signal as the internal standard. The coupling constants J are given in hertz (Hz). NMR signals were assigned via COSY, HSQC, and HMBC. Melting points were taken on a Dr. Tottoli apparatus and are uncorrected. Infrared IR data were recorded on a FT-IR spectrometer Vertex from Bruker. Mass spectra were recorded with a Hewlett Packard 5989B at 70 eV. Analytical data are given as relative mass (m/z), and the brackets indicate the intensity in percent (%) related to the basic peak. High-resolution mass spectra were recorded on a Waters Quadrupole-ToF Synapt 2G. Optical rotations were measured using a 1-dm path length

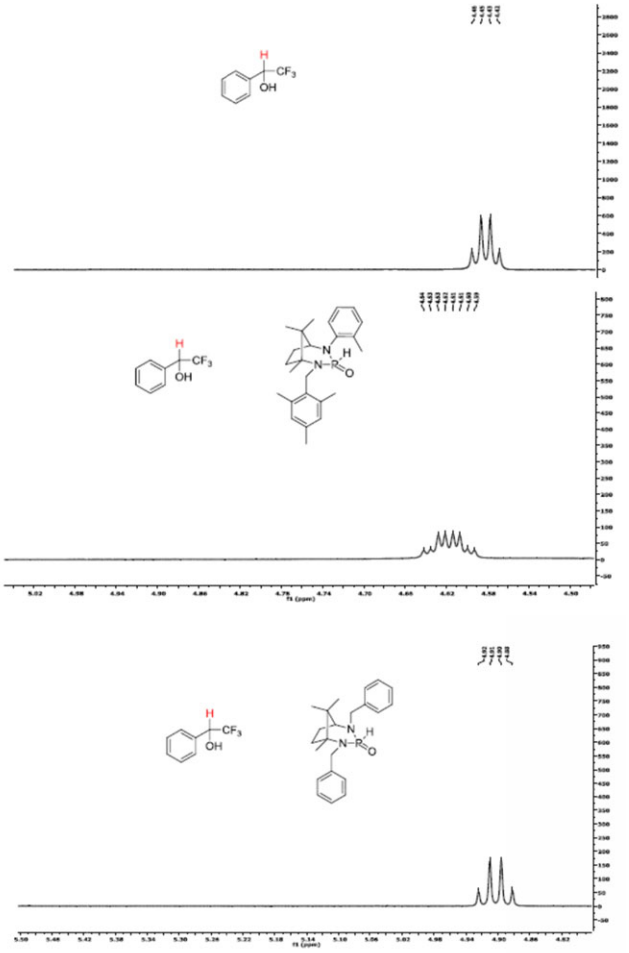


FIGURE 8 ^{1}H NMR of α-(trifluoromethyl)benzyl alcohol in the presence of **16** and **18**.

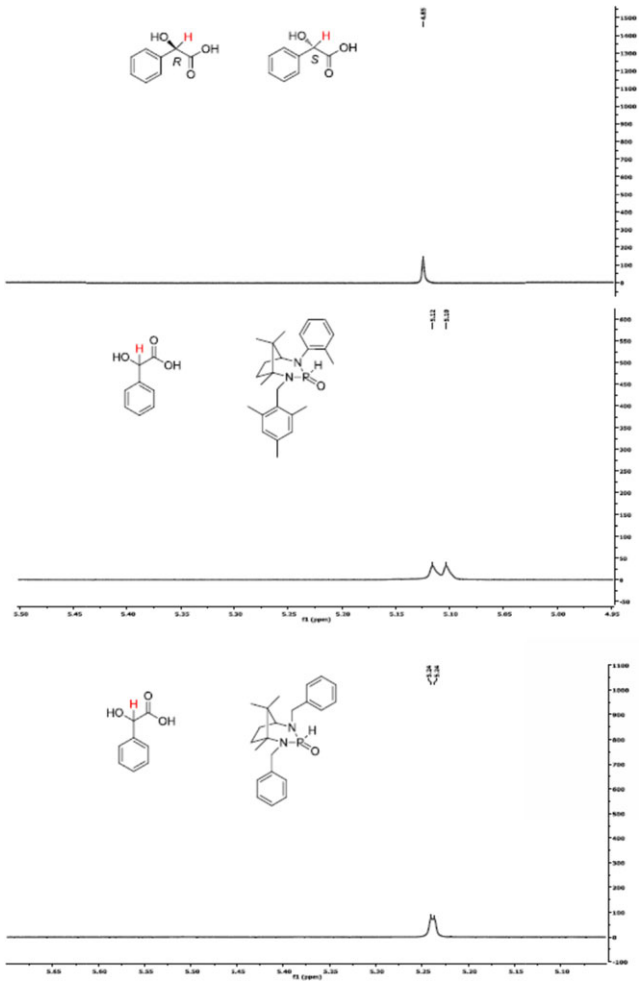


FIGURE 9 ^{1}H NMR of mandelic acid with **16** and **18**.

(*c* is given as g/100 mL) on a Perkin-Elmer 241 MC polarimeter in the reported solvent. (+)-*cis*-(1*R*,3*S*)-1,2,2-Trimethylcyclopentane-1,3-diamine (**25**) was synthesized according to the literature [20] from (+)-camphoric acid, which was purchased from commercial sources. Diamines **7** and **8** [21] and monoarylated diamines [22] were prepared according to the literature.

General Procedure for the Alkylation of Monoarylated Diamines **26** *by Mesitylmethyl Chloride*

To the stirred mixture of monoarylated diamine **26** (1 equiv) and triethylamine (1.2 equiv) in acetonitrile at room temperature, mesitylmethyl chloride (1.1 equiv) was added. The resulting solution was refluxed overnight. After refluxing, the reaction mixture was cooled down and filtered and the filtrate was evaporated under reduced pressure. The crude residue was purified by flash column chromatography.

(1R,3S)-1,2,2-Trimethyl-N^1-(2,4,6-trimethylbenzyl)-N^3-(o-tolyl)-1,3-cyclopentanediamine (**9**). Prepared from monoarylated diamine (0.30 g, 1.29 mmol), triethylamine (0.22 mL, 1.58 mmol), and 2,4,6-trimethylbenzyl chloride (0.24 g, 1.42 mmol) in acetonitrile (10 mL). The crude product was purified via column chromatography (CH_2Cl_2/MeOH, 95:5), and the secondary diamine **9** was obtained as colorless oil (0.30 g, 0.82 mmol, 64%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.18 – 7.14 (m, 1H, *H*-5′, *o*-tolyl), 7.06 (dd, J = 7.2, 0.6 Hz, 1H, *H*-6′), 6.96 (s, 2H, *H*-3″, *H*-5″, mesityl), 6.69 (d, J = 7.9 Hz, 1H, *H*-3′), 6.65 (td, J = 7.3, 1.0 Hz, 1H, *H*-4′), 4.97 (s, 1H, *H*-N1), 3.86 and 3.74 (two d, J = 10.7 Hz, 2H, NCH2, *H*-1‴), 3.82–3.77 (m, 1H, *H*-3), 2.46 (s, 6H, 2″-CH_3, 6″-CH_3), 2.39 (s, 3H, 4″-CH_3), 2.28–2.18 (m, 2H, *H*-4), 1.90 (s, 3H, 2′-CH_3), 1.80–1.71 (m, 2H, *H*-5), 1.36 (s, 3H, *H*-8), 1.14 and 1.02 (two s, 6H, *H*-6, *H*-7)

ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 146.6 (*C*-1′ in *o*-tolyl), 136.8 (*C*-2″, *C*-6″ in mesityl), 136.4 (*C*-4″), 134.1 (*C*-1″), 130.2 (*C*-6′), 129.2 (*C*-3″, *C*-5″), 126.9 (*C*-5′), 122.2 (*C*-2′), 115.6 (*C*- 4′), 109.5 (*C*-3′), 65.5 (*C*-1), 62.1 (*C*-3), 48.8 (*C*-2), 40.2 (*C*-1‴ in $NHCH_2$), 32.5 (*C*-4), 30.6 (*C*-5), 25.9 (*C*-6), 21.0 (4″-CH_3), 19.6 (2″-CH_3, 6″-CH_3), 19.0 (*C*-8), 17.5 (*C*-2′), 17.0 (*C*-7) ppm. ^{15}N NMR (51 MHz, $CDCl_3$) δ = 83.8 (1N, N^3), 53.5 (1N, N^1). IR (ATR) ν = 3360, 2958, 2914, 2865, 1601, 1576, 1507, 1477, 1448, 1384, 1370, 1316, 1257, 1217, 1158, 1070, 1051, 850, 742, 713 cm^{-1}. MS (ESI, + 3 kV): *m/z* (%) = 365 ([M + H]$^+$, 100%). HRMS (ESI): Calcd. for $C_{25}H_{37}N_2$: 365.2956, found: 365.2957. $[\alpha]^{20}_D$ = +24 (*c* = 0.5, CH_2Cl_2).

(1R,3S)-N^3-(2-Methoxyphenyl)-1,2,2-trimethyl-N^1-(2,4,6-trimethylbenzyl)-1,3-cyclopentanediamine (**10**). Prepared from monoarylated diamine (0.30 mg, 1.21 mmol), triethylamine (0.20 mL, 1.45 mmol, 1.2 equiv) and 2,4,6-trimethylbenzyl chloride (0.22 g, 1.33 mmol) in acetonitrile (10 mL). The crude product was purified via column chromatography (CH_2Cl_2/MeOH, 95:5), and the secondary diamine **10** was obtained as yellow oil (0.32 g, 0.85 mmol, 71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.95 (s, 2H, *H*-3″, *H*-5″), 6.91 – 6.87 (m, 1H, *H*-5′), 6.77 (dd, *J* = 7.9, 1.3 Hz, 1H, *H*-6′), 6.69 (dd, *J* = 8.0, 1.2 Hz, 1H, *H*-3′), 6.63 (td, *J* = 7.7, 1.5 Hz, 1H, *H*-4′), 3.84 (d, *J* = 10.6 Hz, 1H, *H*-1‴), 3.76 (dd, *J* = 8.4, 4.5 Hz, 1H, *H*-3), 3.72 (s, 3H, 2″-OCH_3), 3.70 (s, 1H, *H*-1‴) 2.46 (s, 6H, 2″-CH_3, 6″-CH_3), 2.36 (s, 3H, 4″-CH_3), 2.20 – 2.11 (m, 2H, *H*-4), 1.76 – 1.64 (m, 2H, *H*-5), 1.33 (s, 3H, *H*-8), 1.09 (s, 3H, *H*-6), 0.97 (s, 3H, *H*-7) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 146.9 (*C*-2′), 138.8 (*C*-1′), 137.2 (*C*-2″, *C*-6″), 136.3 (*C*-4″), 134.3 (*C*-1″), 129.0 (*C*-3″, *C*-5″), 121.2 (*C*-5′), 115.1 (*C*-4′), 109.5 (*C*- 6′, *C*-3′), 65.0 (*C*-1), 61.9 (*C*-3), 55.2 (2′-OCH_3), 48.6 (*C*-2), 40.5 (*C*-1‴), 32.8 (*C*-4), 30.3 (*C*-5), 25.5 (*C*-6), 21.0 (4″-CH_3), 20.2 (*C*-8), 19.5 (2″-CH_3), 19.4 (6″-CH_3), 17.0 (*C*-7) ppm. ^{15}N NMR (51 MHz, $CDCl_3$) δ = 74.1 (bs, 1N, N^1), 53.5 (bs, 1N, N^3) ppm. IR (ATR) ν = 3424, 2958, 2865, 1596, 1517, 1453, 1370, 1336, 1252, 1223, 1174, 1110, 1027, 850, 732 cm^{-1}. MS (ESI, +3 kV): *m/z* (%) = 381 ([M + H]$^+$, 100%). HRMS (ESI): Calcd. for $C_{25}H_{37}N_2O$: 381.2913, found: 381.2906. $[\alpha]^{20}_D$ = +12 (c = 0.49, CH_2Cl_2).

(1R,3S)-1,2,2-Trimethyl-N^1-(2,4,6-trimethylbenzyl)-N^3-phenyl-1,3-cyclopentanediamine (**11**). Prepared from monoarylated diamine (0.30 g, 1.37 mmol), triethylamine (0.23 mL, 1.65 mmol) and 2,4,6-trimethylbenzyl chloride (0.26 g, 1.51 mmol) in acetonitrile (10 mL). The crude product was purified *via* column chromatography (CH_2Cl_2/MeOH, 95:5) and the secondary diamine **11** was obtained as yellow oil (0.30 g, 0.85 mmol, 62%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.27 – 7.23 (m, 2H, *H*-3′, *H*-5′), 7.03 (s, 2H, *H*-3″, *H*- 5″), 6.75 – 6.71 (m, 1H, *H*-4′), 6.64 (dd, *J* = 8.6, 0.9 Hz, 2H, *H*-2′, *H*-6′), 3.88 (d, *J* = 10.6 Hz, 1H, *H*-1‴), 3.78 – 3.74 (m, 2H, *H*-1‴, *H*-3), 2.52 (s, 6H, 2″-CH_3, 6″-CH_3), 2.43 (s, 3H, 4″-CH_3), 2.30 – 2.21 (m, 2H, *H*-4), 1.81 – 1.72 (m, 2H, *H*-5), 1.38 (s, 3H, *H*-8), 1.14 (s, 3H, *H*-6), 1.05 (s, 3H, *H*-7) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 148.7 (*C*-1′), 137.1 (2′-CH_3, 6″-CH_3′), 136.6 (*C*- 1″), 134.1 (*C*-4″), 129.3 (*C*-3″, *C*-5″), 129.2 (*C*-3′, *C*-5′), 116.2 (*C*-4′), 113.0 (*C*-2′, *C*-6′), 65.5 (*C*-1), 62.7 (*C*-3), 48.7 (*C*-2), 40.6 (*C*-1‴), 32.3 (*C*-4), 30.1 (*C*-5), 26.1 (*C*- 6), 21.1 (4″-CH_3), 19.6 (2″-CH_3, 6″-CH_3), 19.4 (*C*-8), 17.1 (*C*-7) ppm. ^{15}N NMR (51 MHz, $CDCl_3$) δ = 53.46 (s, 1N, N^3) ppm. MS (ESI, +3 kV): *m/z* (%) = 351 ([M+H]$^+$, 100%). HRMS (ESI): Calcd. for $C_{24}H_{35}N_2$: 351.2808, found: 351.2800. $[\alpha]^{20}_D$ = +71 (*c* = 0.5, CH_2Cl_2).

(1R,3S)-N^3-Mesityl-1,2,2-trimethyl-N^1-(2,4,6-trimethylbenzyl)-1,3-cyclopentanediamine (**12**). Prepared from monoarylated diamine (0.30 g, 1.15 mmol), triethylamine (0.19 mL, 1.38 mmol) and 2,4,6-trimethylbenzyl chloride (0.21 g, 1.27 mmol) in acetonitrile (10 mL). The crude product was purified via column chromatography (CH_2Cl_2/MeOH, 95:5), and the secondary diamine **12** was obtained as colorless oil (0.28 g, 0.11 mmol, 61%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.94 (s, 2H, *H*-3″, *H*-5″), 6.84 (s, 2H, *H*-3′, *H*-5′), 3.89 (d, *J* = 10.9 Hz, 1H, *H*-1‴), 3.75 (d, *J* = 10.9 Hz, 1H, *H*-1‴), 3.58 (dd, *J* = 8.1, 6.3 Hz, 1H, *H*-3), 2.48 (s, 6H, 2″-CH_3, 6″-CH_3), 2.36 (s, 3H, 4″-CH_3), 2.29 (s, 3H, 4′-CH_3), 2.28 (s, 6H, 2′-CH_3, 6′-CH_3), 2.18–2.01 (m, 2H, *H*-4, *H*-5), 1.67 (dqd, *J* = 12.0, 10.1, 5.8 Hz, 2H, *H*-4, *H*-5), 1.32 (s, 3H, *H*-8), 1.12 (s, 3H, *H*-6), 1.10 (s, 3H, *H*-7) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 143.8 (*C*-1′), 136.9 (*C*-1″), 136.3 (*C*-2″, *C*-6″), 134.5 (*C*-4″), 129.8 (*C*-3′, *C*-5′), 129.3 (*C*-4′), 129.1 (*C*-3″, *C*-5″), 127.7 (*C*-2′, *C*-6′), 65.8 (*C*-3), 64.4 (*C*-1), 48.1 (*C*-2), 40.9 (*C*-1‴), 34.0 (*C*-5), 30.0 (*C*-4), 23.8 (*C*-7), 21.0 (4′-CH_3), 20.6 (4″-CH_3), 20.5 (*C*-8), 19.6 (2′-CH_3, 6′-CH_3), 19.5 (2″-CH_3, 6″-CH_3), 16.9 (*C*-6) ppm. ^{15}N NMR (51 MHz, $CDCl_3$) δ = 67.46 (1N, N^3), 54.62 (1N, N^1) ppm. IR (ATR) ν = 3379, 2962, 2864, 1610, 1583, 1477, 1368, 1297, 1226, 1156, 1121, 1085, 1023, 1004, 846, 737, 717, 686, 564 cm^{-1}. MS (ESI, +3 kV): *m/z* (%) = 393 ([M + H]$^+$, 100%). HRMS (ESI): Calcd. for $C_{27}H_{41}N_2$: 393.3268, found: 393.3270. $[\alpha]^{20}_D$ = −1 (*c* = 0.48, CH_2Cl_2).

(1R,3S)-1,2,2-Trimethyl-N^1-(2,4,6-trimethylbenzyl)-N^3-(naphthalen-1-yl)-1,3-cyclopentanediamine (**13**). Prepared from monoarylated diamine (0.30 g, 1.12 mmol), triethylamine (0.19 mL, 1.34 mmol), and 2,4,6-trimethylbenzyl chloride (0.21 g, 1.23 mmol) in acetonitrile (10 mL). The crude product was purified via column chromatography (CH_2Cl_2/MeOH, 95:5), and the secondary diamine **13** was obtained as brown oil (0.24 g, 0.61 mmol, 54%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.80 (d, J = 8.0 Hz, 1H, *H*-8′), 7.48–7.43 (m, 1H, *H*-5′), 7.39 (dd, J = 9.9, 5.9 Hz, 1H, *H*-4′), 7.29 (d, J = 8.4 Hz, 1H, *H*-7′), 7.18 (d, J = 8.1 Hz, 1H, *H*-6′), 7.11 (t, J = 7.5 Hz, 1H, *H*-3′), 7.01 (s, 2H, *H*-3″, *H*-5″), 6.64 (d, J = 7.6 Hz, 1H, *H*-2′), 3.91 (d, J = 10.6 Hz, 2H, *H*-1‴), 3.79 (d, J = 10.8 Hz, 1H, *H*-3), 2.48 (s, 3H, 4″-C*H*$_3$), 2.41 (d, J = 6.4 Hz, 6H, 2″-C*H*$_3$, 6″-C*H*$_3$), 2.23-2.09 (m, 2H, *H*-4), 1.91–1.75 (m, 2H, *H*-5), 1.40 (s, 3H, *H*-8), 1.18 (s, 3H, *H*-7), 1.09 (s, 3H, *H*-6) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 143.9 (*C*-1′), 137.6 (*C*-4″), 136.8 (*C*-1″), 136.5 (*C*-2″), 134.8 (*C*-6″), 134.0 (*C*-4′a), 129.5 (*C*-5′), 128.8 (*C*-3″, *C*-5″), 128.3 (*C*-3′), 126.9 (*C*-6′), 125.5 (*C*-7′), 123.9 (*C*-8′), 121.1 (*C*-8′a), 115.4 (*C*-4′), 103.0 (*C*-2′), 66.0 (*C*-1), 62.9 (*C*-3), 49.2 (*C*-2), 40.0 (*C*-1″), 31.9 (*C*-5), 30.2 (*C*-4), 26.5 (4″-*C*H$_3$), 21.1 (*C*-11), 20.0 (2″-*C*H$_3$), 19.7 (6″-*C*H$_3$), 18.8 (*C*-7), 17.0 (*C*-6) ppm. IR (ATR) ν = 3326, 2958, 2867, 1579, 1524, 1482, 1405, 1385, 1371, 1230, 1074, 849, 764, 720 cm^{-1}. MS (ESI, +3 kV): *m/z* (%) = 400 ([M + H]$^+$, 10%). HRMS (ESI): Calcd. for $C_{28}H_{37}N_2$: 400.2878, found: 400.3000. $[\alpha]^{20}_D = -12$ (c = 0.47, CH_2Cl_2).

(1R,3S)-N^3-([1,1′-Biphenyl]-2-yl)-1,2,2-trimethyl-N^1-(2,4,6-trimethylbenzyl)-1,3-cyclopentanediamine (**14**). Prepared from monoarylated diamine (0.30 g, 1.02 mmol), triethylamine (0.17 mL, 1.22 mmol) and 2,4,6-trimethylbenzyl chloride (0.19 g, 1.12 mmol) in acetonitrile (10 mL). The crude product was purified via column chromatography (CH_2Cl_2/MeOH, 95:5), and the secondary diamine **14** was obtained as yellow oil (0.25 g, 0.58 mmol, 57%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.46–7.43 (m, 2H, *H*-6′, *H*-4″), 7.36–7.28 (m, 4H, *H*-3″, *H*-5″, *H*-3′, *H*-4′), 7.17 (dd, J = 7.4, 1.6 Hz, 1H, *H*-5′), 6.91 (s, 2H, *H*-3″, *H*-5″), 6.81 (ddd, J = 8.4, 6.2, 2.6 Hz, 2H, *H*-2″, *H*-6″), 4.49 (br s, 1H, *H*-N$_3$), 3.79 (d, J = 10.7 Hz, 2H, *H*-1‴′), 3.62 (d, J = 10.7 Hz, 1H, *H*-3), 2.39 (s, 3H, 4″-C*H*$_3$), 2.35 (s, 6H, 2″-C*H*$_3$, 6″-C*H*$_3$), 2.18–2.11 (m, 1H, *H*-4), 2.07–1.99 (m, 1H, *H*-5), 1.73 (ddd, J = 13.4, 9.7, 7.4 Hz, 1H, *H*-5), 1.56–1.47 (m, 1H, *H*-4), 1.33 (s, 3H, *H*-8), 1.08 (s, 3H, *H*-7), 0.85 (s, 3H, *H*-6) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 145.5 (*C*-2′), 139.8 (*C*-1″), 137.1 (*C*-4″), 136.2 (*C*- 2″, *C*-6″), 134.2 (*C*-3″, *C*-5″), 130.5 (*C*-4′), 129.3 (*C*-2″, *C*-6″), 129.1 (*C*-4″), 128.7 (*C*-3″, *C*-5″), 127.8 (*C*-6′), 127.0 (*C*-5′), 116.2 (*C*-1′), 110.7 (*C*-3′), 64.4 (*C*- 1), 62.0 (*C*-3), 48.2 (*C*-2), 40.7 (*C*-1″), 33.4 (*C*-5), 30.1 (*C*-4), 24.8 (4″-*C*H$_3$), 21.0 (*C*-8), 19.9 (2″-*C*H$_3$, 6″-*C*H$_3$), 19.5 (*C*-7), 16.9 (*C*-6) ppm. IR (ATR) ν = 3424, 2958, 2860, 1600, 1578, 1508, 1435, 1317, 849, 768, 739, 702 cm^{-1}. MS (ESI, +3 kV): *m/z* (%) = 427 ([M + H]$^+$, 100%). HRMS (ESI): Calcd. for $C_{30}H_{39}N_2$: 427.3116, found: 427.3113. $[\alpha]^{20}_D = -50$ (c = 0.48, CH_2Cl_2).

(1R,3S)-N^3-(2-Isopropylphenyl)-1,2,2-trimethyl-N^1-(2,4,6-trimethylbenzyl)-1,3-cyclopentanediamine (**15**). Prepared from monoarylated diamine (0.30 g, 1.15 mmol), triethylamine (0.19 mL, 1.40 mmol), and 2,4,6-trimethylbenzyl chloride (0.21 g, 1.27 mmol) in acetonitrile (10 mL). The crude product was purified via column chromatography (CH_2Cl_2/MeOH, 95:5), and the secondary diamine **15** was obtained as yellow oil (0.23 g, 0.59 mmol, 51%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.15–7.09 (m, 2H, *H*-3′, H-5′), 6.95 (s, 2H, H-3″, H- 5″), 6.69 (dd, J = 7.8, 5.1 Hz, 2H, *H*-4′, H-6′), 5.20 (br s, 1H, N^3*H*), 3.92–3.63 (m, 4H, *H*-1″, *H*-3, 2′-C*H*), 2.44 (s, 6H, 2″-C*H*$_3$, 6″-C*H*$_3$), 2.38 (s, 3H, 4″-C*H*$_3$), 2.23 (ddd, J = 18.2, 13.7, 10.5 Hz, 2H, *H*-5), 1.78–1.68 (m, 2H, *H*-4), 1.35 (s, 3H, *H*-8), 1.16 (d, J = 6.7 Hz, 3H, 2′-C-C*H*$_3$), 1.13 (s, J = 5.9 Hz, 3H, 2′-C-C*H*$_3$), 1.01 (s, 3H, *H*-7), 0.93 (s, 3H, *H*-6) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 146.3 (*C*-1′), 136.6 (*C*-4″), 136.3 (*C*-2″), 134.1 (*C*-″), 132.1 (*C*-2″), 129.2 (*C*-3″), 126.6 (*C*-5″), 125.5 (*C*-3′), 124.9 (*C*-5′), 115.7 (*C*-4′), 109.7 (*C*-6′), 65.5 (*C*-1), 62.2 (*C*-3), 49.0 (*C*-2), 40.2 (*C*-1″), 32.5 (*C*-5), 30.6 (2′- *C*H), 27.3 (2′-CH-*C*H$_3$), 26.0 (2′-CH-*C*H$_3$), 22.1 (4″-*C*H$_3$), 21.9 (*C*-8), 21.0 (2″-*C*H$_3$), 19.5 (6″-*C*H$_3$), 18.8 (*C*-6), 17.1 (*C*-7) ppm. IR (ATR) ν = 3370, 2963, 2870, 1601, 1579, 1508, 1453, 1386, 1369, 1312, 1258, 1219, 1160, 1084, 1037, 850, 739 cm^{-1}. MS (ESI, +3 kV): *m/z* (%) = 393 ([M + H]$^+$, 100%). HRMS (ESI): Calcd. for $C_{27}H_{41}N_2$: 393.3280, found: 393.3270. $[\alpha]^{20}_D = -16$ (c = 0.48, CH_2Cl_2).

General Procedure for the Preparation of Pentavalent Nitrogen-Substituted SPOs **16–24**. A solution of the suitable diamine (1 equiv) in toluene was added to the mixture of phosphorus trichloride (1.1 equiv) and triethylamine (2.5 equiv) in toluene at −60°C over 30 min. The solution was warmed to room temperature. After 2 h, the mixture was filtered through $MgSO_4$ and the filtrate was again cooled to −60°C. Triethylamine (1.1 equiv) and water (1 equiv) were added, and the cooling bath was removed. After 1 h, the reaction mixture was filtered again through $MgSO_4$ and the filtrate was concentrated under

reduced pressure. The method of filtration for each compounds are given below.

*(1R,3S,5S)-2,4-Dibenzyl-1,8,8-trimethyl-2,4-diaza-3-phosphabicyclo[3.2.1]octane 3-oxide (***16***).* Prepared from diamine **7** (0.60 g, 1.86 mmol), phosphorus trichloride (0.18 mL, 2.05 mmol), and triethylamine (0.66 mL, 4.65 mmol) in toluene (10 mL), and water (34.00 μL, 1.86 mmol) and triethylamine (0.28 mL, 2.05 mmol) after filtration. After evaporation, product **16** was obtained as a yellow solid (0.68 g, 1.75 mmol, 94%). mp: 118.3°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.44–7.13 (m, 10H, Ar*H*), 7.30 (d, J = 619.9 Hz, 1H, *H*-3, P-*H*), 4.69 (dd, J = 12.4, 4.9 Hz, 1H, *H*-1″), 4.47 (dd, J = 15.4, 10.3 Hz, 1H, *H*-1″), 4.23 (dd, J = 17.3, 10.5 Hz, 1H, *H*-1″, NCH_2), and 4.08 (dd, J = 15.4, 7.3 Hz, 1H, *H*-1″, NCH_2), 2.86 (dd, J = 15.6, 6.7 Hz, 1H, *H*- 5), 2.22 (ddd, J = 13.9, 10.1, 5.8 Hz, 1H, *H*-6,), 1.99–1.86 (m, 2H, *H*-6, *H*-7), 1.68 (ddd, J = 13.8, 11.0, 5.5 Hz, 1H, *H*-7), 1.04 (s, 6H, *H*-11, *H*-9, 2×CH_3), 0.78 (s, 3H, *H*-10, CH_3) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 141.2 (*C*-1′), 138.1 (*C*-1″), 128.6 (*C*-3′, *C*-5′), 128.5 (*C*-3″, *C*-5″), 128.4 (*C*-2′, *C*-6′), 127.4 (*C*-2″, *C*-6″), 127.0 (*C*-4′), 126.7 (*C*-4″), 71.4 (*C*-1″), 67.7 (*C*-1″), 50.1 (*C*-1), 47.3 (*C*-5), 45.6 (*C*-8), 36.6 (*C*-7), 29.2 (*C*-6), 24.4 (*C*-9), 19.5 (*C*-11), 18.4 (*C*-10) ppm. ^{31}P NMR (202 MHz, $CDCl_3$) δ = 10.1 ppm. IR (ATR) ν = 3429, 3056, 3022, 2949, 2336, 1604, 1493, 1453, 1373, 1201, 1113, 1092, 1066, 1027, 908, 876, 739, 698, 520, 481, 454 cm^{-1}. MS (ESI, +3 kV): *m/z* (%) = 391 [M + Na]+, 100%). HRMS (ESI): Calcd. for $C_{22}H_{29}N_2ONaP$: 391.1930, found: 391.1915. $[\alpha]^{20}{}_D$ = +19 (c = 0.60, EtOH).

*(1R,3S,5S)-1,8,8-Trimethyl-2,4-bis(2,4,6-trimethylbenzyl)-2,4-diaza-3-phosphabicyclo[3.2.1]octane 3-oxide (***17***).* Prepared from diamine **8** (0.20 g, 0.49 mmol), phosphorus trichloride (0.05 mL, 0.54 mmol), and triethylamine (0.17 mL, 1.23 mmol) in toluene (10 mL), and water (8.90 μL, 0.49 mmol) and triethylamine (0.08 mL, 0.54 mmol) after filtration. After evaporation, product **17** was obtained as a yellow solid (0.16 g, 0.35 mmol, 73%). mp: 99.7°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.83 (d, J = 7.4 Hz, 4H, *H*-3′, *H*-5′, *H*-3″, *H*-5″), 6.32 (d, J = 629.4 Hz, 1H, P-*H*), 4.28 (dd, J = 11.5, 3.0 Hz, 1H, *H*-1″), 4.11 (dt, J = 21.3, 9.4 Hz, 2H, *H*-1″, *H*-1″), 3.96 (dd, J = 14.2, 7.4 Hz, 1H, *H*-1″), 2.59–2.50 (m, 1H, *H*-5), 2.46 (s, 6H, 4′-C*H*3, 4″-CH_3), 2.34 (m, 1H, *H*-7), 2.25 (d, J = 3.1 Hz, 12H, 2′-CH_3, 6′-CH_3, 2″-CH_3, 6″-CH_3), 2.00–1.81 (m, 3H, *H*-6, *H*-7, *H*-6), 1.32 (s, 3H, *H*-9), 0.92 (s, 3H, *H*-11), 0.80 (s, 3H, *H*-10) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 139.1 (*C*-4′), 138.2 (*C*-4″), 137.5 (*C*-1′), 136.9 (*C*- 1″), 130.1 (*C*-2′), 130.0 (*C*-2″), 129.1 (*C*-3′, *C*-5′ *C*-3″, *C*-5″), 128.6 (*C*-6′), 128.5 (*C*-6″), 69.7 (*C*-1), 65.2 (*C*-5), 47.1 (*C*-8), 43.1 (*C*-1″), 42.3 (*C*-1″), 35.4 (*C*-7), 28.0 (*C*-6), 24.9 (*C*-10), 21.0 (4′-CH_3), 20.9 (4″-CH_3), 20.4 (2′-CH_3), 20.0 (2″-CH_3), 18.9 (6′-CH_3, 6″-CH_3), 18.0 (*C*-9), 17.9 (*C*-11) ppm. ^{31}P NMR (202 MHz, CDCl3) δ = 9.6 ppm. IR (ATR) ν = 2949, 2379, 1610, 1468, 1370, 1305, 1257, 1194, 1164, 1115, 1017, 894, 841, 747, 531 cm^{-1}. MS (ESI, +3 kV): *m/z* (%) = 453 ([M + H]$^+$, 100%); 475 ([M + Na]$^+$, 100%). HRMS (ESI): Calcd. for $C_{28}H_{42}N_2OP$: 453.3032, found: 453.3035; $C_{28}H_{41}N_2ONaP$: 475.2853, found: 475.2854. $[\alpha]^{20}{}_D$ = −12 (c = 0.50, EtOH).

*(1R,3R,5S)-1,8,8-Trimethyl-4-(o-tolyl)-2-(2,4,6-trimethylbenzyl)-2,4-diaza-3-phosphabicyclo[3.2.1]octane 3-oxide (***18***).* Prepared from diamine **9** (0.26 g, 0.72 mmol), phosphorus trichloride (0.07 mL, 0.79 mmol), triethylamine (0.25 mL, 1.80 mmol) in toluene (10 mL), and water (13.00 μL, 0.72 mmol) and triethylamine (0.11 mL, 0.79 mmol) after filtration. After evaporation, product **18** was obtained as a white solid (0.26 g, 0.64 mmol, 89%). mp: 170.5 °C. ^{1}HNMR (500 MHz, $CDCl_3$) δ = 7.15–7.04 (m, 3H, *H*-4′, *H*-5′, *H*-6′), 6.31 (d, *J* 637.2 Hz, P-*H*), 6.91 (s, 1H, *H*-3′), 6.79 (s, 2H, *H*-3″, *H*-5″), 4.33 (dd, J = 11.7, 3.3 Hz, 1H, *H*-1″), 4.21–4.10 (m, 1H, *H*-1″), 3.08 (dd, J = 20.4, 5.5 Hz, 1H, *H*-5), 2.72 (ddd, J = 14.2, 9.7, 4.9 Hz, 1H, *H*-6), 2.59 (ddd, J = 14.0, 9.7, 4.1 Hz, 1H, *H*-7), 2.48 (s, 6H, 2″-C*H*3, 6″-CH_3), 2.31 (s, 3H, 2′-CH_3), 2.20 (s, 3H, 4″-CH_3), 2.15–1.91 (m, 2H, *H*-6, *H*-7), 1.42 (s, 3H, *H*-9), 1.37 (s, 3H, *H*-11), 0.97 (s, 3H, *H*-10) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 141.8 (C-1′), 139.0 (C-2′), 137.4 (C-4″), 131.1 (C-3′), 129.1 (C-3″, C-5″), 128.7 (C-1″), 128.6 (C-2″, C-6″), 126.9 (C-4′, C-5′), 126.7 (C-6′), 73.4 (C-11), 70.2 (C-5), 47.4 (C-8), 42.2 (C-1″), 35.4 (C-7), 30.0 (C-6), 24.9 (4″-CH_3), 20.9 (6″-CH_3), 20.5 (4″-CH_3), 20.2 (C-11), 19.4 (2′-CH_3), 18.2 (C-9), 18.1 (C-10) ppm. ^{31}P NMR (202 MHz, $CDCl_3$) δ = 3.9 ppm. IR (ATR) ν = 3414, 2953, 2409, 1610, 1488, 1458, 1389, 1345, 1207, 1192, 1154, 1110, 1080, 1018, 976, 890, 852, 759, 724, 544, 454 cm^{-1}. MS (ESI, +3 kV): *m/z* (%) = 411 ([M + H]$^+$, 58%); 433 ([M + Na]$^+$, 100%). HRMS (ESI): Calcd. for $C_{25}H_{36}N_2OP$: 411.2565, found: 411.2563; $C_{25}H_{35}N_2ONaP$: 433.2385, found: 433.2391. $[\alpha]^{20}{}_D$ = +73 (c = 0.52, EtOH).

*(1R,3R,5S)-4-(2-Methoxyphenyl)-1,8,8-trimethyl-2-(2,4,6-trimethylbenzyl)-2,4-diaza-3-phosphabicyclo[3.2.1]octane 3-oxide (***19***).* Prepared from diamine **10** (0.15 g, 0.39 mmol), phosphorus trichloride (0.04 mL, 0.43 mmol), triethylamine (0.14 mL, 0.98 mmol) in toluene (10 mL), and

water (7.00 μL, 0.39 mmol) and triethylamine (0.06 mL, 0.43 mmol) after filtration. After evaporation, product **19** was obtained as yellow oil (0.16 g, 0.38 mmol, 97%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.86 (s, 2H, 2″-C*H*$_3$, 6″-C*H*$_3$), 6.80 (m, 1H, *H*-3′), 6.69 (d, J = 7.7 Hz, 1H, *H*-6′), 6.60 (dd, J = 7.9, 1.2 Hz, 1H, *H*-4′), 6.55 (d, J = 7.1 Hz, 1H, *H*-5′), 6.36 (d, J = 645.2 Hz, 1H, P*H*), 3.81–3.58 (m, 5H, *H*-1″, 2′-O-C*H*$_3$), 2.52–2.44 (m, 1H, *H*-5), 2.38 (s, 6H, 2″-C*H*$_3$, 6″-C*H*$_3$), 2.28 (s, 3H, 4″-C*H*$_3$), 2.09 (dd, J = 25.7, 12.1 Hz, 2H, *H*-7, *H*-6), 1.62 (dd, J = 19.9, 10.9 Hz, 2H, *H*-7, *H*-6), 1.25 (s, 3H, *H*-9), 1.01 (s, 3H, *H*-11), 0.89 (s, 3H, *H*-10) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 146.8 (*C*-2′), 138.9 (*C*-4″), 137.2 (*C*-1″), 136.1 (*C*-2″, *C*-6″), 134.3(*C*-1′), 128.9 (*C*-3″), 128.1 (*C*-5″), 125.3 (*C*-5′), 121.3 (*C*-4′), 115 (*C*-6′), 109.4 (*C*-2′), 64.9, (*C*-1), 61.8 (*C*-5), 55.1 (2′-O*C*H$_3$), 48.6 (*C*-8), 40.5 (*C*-1″), 32.8 (*C*-7), 30.2 (*C*-6), 25.4 (4″-*C*H$_3$), 20.9 (2″-*C*H$_3$, 6″-*C*H$_3$), 19.5 (*C*-9), 19.3 (*C*-10), 16.9 (*C*-11) ppm. ^{31}P NMR (202 MHz, $CDCl_3$) δ = 3.9 ppm. IR (ATR) ν = 3424, 2958, 1599, 1515, 1455, 1371, 1224, 1113, 1029, 909, 850, 730 cm^{-1}. MS (ESI, +3 kV): *m/z* (%) = 427 ([M + H]$^+$, 62%); 449 ([M + Na]$^+$, 100%). HRMS (ESI): Calcd. for $C_{25}H_{36}N_2O_2P$: 427.2514, found: 427.2525; $C_{25}H_{35}N_2O_2NaP$: 449.2334, found: 449.2343. $[\alpha]^{20}_D$ = +11 (c = 0.45, EtOH).

*(1R,3R,5S)-1,8,8-Trimethyl-2-(2,4,6-trimethylbenzyl)-4-phenyl-2,4-diaza-3-phosphabicyclo[3.2.1]octane 3-oxide (***20***).* Prepared from diamine **11** (0.27 g, 0.77 mmol), phosphorus trichloride (0.07 mL, 0.80 mmol), triethylamine (0.27 mL, 1.94 mmol) in toluene (10 mL), and water (14.00 μL, 0.78 mmol) and triethylamine (0.12 mL, 0.86 mmol) after filtration. After evaporation, product **20** was obtained as a white solid (0.27 g, 0.68 mmol, 88%). mp: 154.3°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.28–7.18 (m, 4H, *H*-2′, *H*-6′, *H*-3″, *H*-5″), 6.84 (s, 2H, *H*-3′, *H*-5′), 6.37 (d, J = 649.9, 1H, P-*H*), 4.34 (dd, J = 11.7, 2.9 Hz, 1H, *H*-1″), 4.23–4.11 (m, 1H, *H*-1″), 3.63 (dd, J = 18.6, 6.0 Hz, 1H, *H*-5), 2.73–2.64 (m, 1H, *H*-6), 2.49 (s, 6H, 2″-C*H*$_3$, 6″-C*H*$_3$), 2.45–2.36 (m, 2H, *H*-7), 2.25 (s, 3H, 4″-C*H*$_3$), 1.95–1.87 (m, 1H, *H*-6), 1.44 (s, 3H, *H*-9), 1.24 (s, 3H, *H*-11), 1.06 (s, 3H, *H*-10) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 146.1 (*C*-1′), 139.1 (*C*-4″), 137.5 (*C*-1″), 129.3 (*C*- 3′), 129.1 (*C*-5′), 128.3 (*C*-3″, *C*-5″), 125.4 (*C*-2″, *C*-6″), 123.4 (*C*-4′), 122.2 (*C*-2″, *C*-6″), 71.5 (*C*-5), 70.7 (*C*-1), 46.9 (*C*-8), 42.4 (*C*-1″), 35.4 (*C*-7), 30.5 (*C*-6), 24.7 (4″-*C*H$_3$), 21.0 (2″-*C*H$_3$), 20.5 (6″-*C*H$_3$), 19.4 (*C*-11), 18.0 (*C*-9, *C*-10) ppm. ^{31}P NMR (202 MHz, $CDCl_3$) δ = 3.9 ppm. IR (ATR) ν = 3424, 2943, 2375, 1595, 1493, 1464, 1391, 1360, 1278, 1249, 1224, 1205, 1154, 1114, 1087, 1058, 1016, 963, 889, 850, 747, 693, 524, 464 cm^{-1}. MS (ESI, +3 kV): *m/z* (%) = 397 ([M + H]$^+$, 50%); 419 ([M + Na]$^+$, 100%). HRMS (ESI): Calcd. for $C_{24}H_{34}N_2OP$: 397.2409, found: 397.2408; $C_{24}H_{33}N_2ONaP$: 419.2228, found: 419.2232. $[\alpha]^{20}_D$ = +39 (c = 0.46, EtOH).

*4-Mesityl-1,8,8-trimethyl-2-(2,4,6-trimethylbenzyl)-2,4-diaza-3-phosphabicyclo[3.2.1]octane 3-oxide (***21a/21b***).* Prepared from diamine **12** (0.35 g, 0.89 mmol), phosphorus trichloride (0.09 mL, 0.98 mmol), triethylamine (0.31 mL, 2.22 mmol) in toluene (10 mL), and water (16.00 μL, 0.89 mmol) and triethylamine (0.14 mL, 1.00 mmol) after filtration. After evaporation, product **21** was obtained as a yellow solid of two diastereoisomers, which were separated by column chromatography (*n*-hexane/EtOAc, 7:3).

*(1R,3R,5S)-4-Mesityl-1,8,8-trimethyl-2-(2,4,6-trimethylbenzyl)-2,4-diaza-3-phosphabicyclo[3.2.1]octane 3-oxide (***21a***).* The product was obtained as a yellow solid (0.14 g, 0.32 mmol, 36%). mp: 144.7°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.79 (t, J = 20.3 Hz, 4H, *H*-3′, *H*-5′, *H*-3″, *H*-5″), 6.62 (d, J = 627.9 Hz, 1H, P-*H*), 4.49 (dd, J = 12.8, 5.9 Hz, 1H, *H*-1″), 4.29–4.12 (m, 1H, *H*-1″), 3.09 (dd, J = 17.9, 5.0 Hz, 1H, *H*-5), 2.67–2.60 (m, 2H, *H*-6, *H*-7), 2.54 (s, 3H, 4′-C*H*$_3$), 2.47 (s, 6H, 2′-C*H*$_3$, 6′-C*H*$_3$), 2.26 (s, 3H, 4″-C*H*$_3$), 2.20 (d, J = 9.3 Hz, 6H, 2″-C*H*$_3$, 6″-C*H*$_3$), 2.09–2.01 (m, 1H, *H*-6), 1.91–1.85 (m, 1H, *H*-7), 1.37 (s, 3H, *H*-9), 1.29 (m, 3H, *H*-11), 0.94 (s, 3H, *H*-10) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 139.7 (*C*-1′), 138.3 (*C*-4″), 137.6 (*C*-1″), 137.1 (*C*-6″), 136.9 (*C*-1″), 136.6 (*C*-6′), 130.8 (*C*-3′, *C*-5′), 130.5 (*C*-4′), 129.9 (*C*-3″), 129.2 (*C*-5″), 73.4 (*C*-5), 70.6 (*C*-1), 48.5 (*C*-8), 42.3 (*C*-1″), 35.8 (*C*-6), 30.6 (*C*-7), 25.9 (4′-*C*H$_3$), 22.1 (4″-*C*H$_3$), 21.5 (*C*-9), 20.9 (2″-*C*H$_3$), 20.7 (6″-*C*H$_3$), 20.7 (6′-*C*H$_3$), 20.6 (2′-*C*H$_3$), 18.9 (*C*-11), 18.8 (*C*-10) ppm. ^{31}P NMR (202 MHz, $CDCl_3$) δ = 1.9 ppm. IR (ATR) ν = 3424, 2924, 2345, 2212, 1605, 1468, 1341, 1212, 1144, 1081, 1031, 968, 850, 728, 565 cm^{-1}. MS (ESI, +3 kV): *m/z* (%) = 439 ([M + H]$^+$, 100%). HRMS (ESI): Calcd. for $C_{27}H_{40}N_2OP$: 439.2878, found: 439.2874. $[\alpha]^{20}_D$ = +54 (c = 0.56, EtOH).

(1R,3S,5S)-4-Mesityl-1,8,8-trimethyl-2-(2,4,6-trimethylbenzyl)-2,4-diaza-3-phosphabicyclo[3.2.1]octane 3-oxide (**21b***).* The product was obtained as a white solid (0.06 g, 0.14 mmol, 16%). mp: 139.5°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.79 (m, 4H, *H*-3, *H*-5, *H*-3″, *H*-5″), 6.69 (d, J = 617.0 Hz, 1H, P-*H*), 4.28 (t, J = 10.7 Hz, 1H, *H*-1″), 4.14 (dd, J = 11.1, 7.1 Hz, 1H, *H*- 1″), 3.19 (ddd, J = 11.2, 3.5, 1.9 Hz, 1H, *H*-5), 2.58–2.45 (m, 1H, *H*-6), 2.44 (s, 6H, 2′-C*H*$_3$, 6′-C*H*$_3$), 2.39

(s, 3H, 4′-CH_3), 2.31 (s, 3H, 4″-CH_3), 2.19 (s, 3H, 2″-CH_3), 2.18 (s, 3H, 6″-CH_3), 2.13–2.08 (m, 1H, *H*-7), 1.98–1.85 (m, 2H, *H*-6, *H*-7), 1.83 (s, 1H, *H*-10), 1.45 (s, 1H, *H*-9), 1.01 (s, 1H, *H*-11) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 139.9 (*C*-1′), 139.1 (*C*-4″), 137.9 (*C*-1″), 136.9 (*C*- 2″), 136.7 (*C*-6″), 136.4 (*C*-4′), 130.3 (*C*-3′), 129.7 (*C*-5′), 129.0 (*C*-3″, *C*-5″), 127.8 (*C*-2′), 127.7 (*C*-6′), 73.2 (*C*-5), 70.0 (*C*-1), 48.5 (*C*-8), 43.3 (*C*-1″), 36.9 (*C*-6), 30.3 (*C*-7), 26.9 (4′-*C*H_3), 21.0 (4″-*C*H_3), 20.7 (*C*-11), 20.4 (2″-*C*H_3), 20.0 (6″-*C*H_3), 19.9 (6′-*C*H_3), 19.6 (2′-*C*H_3), 18.6 (*C*-9), 18.5 (*C*-10) ppm. ^{31}P NMR (202 MHz, $CDCl_3$) δ = −4.2 ppm. IR (ATR) ν = 3424, 2924, 2345, 2212, 1605, 1468, 1341, 1212, 1144, 1081, 1031, 968, 850, 728, 565 cm^{-1}. MS (ESI, +3 kV): *m/z* (%) = 439 ([M + H]$^+$, 100%). HRMS (ESI): Calcd. for $C_{27}H_{40}N_2OP$: 439.2878, found: 439.2872. $[\alpha]^{20}{}_D$ = +40 (*c* = 0.57, EtOH).

*(1R,3R,5S)-1,8,8-Trimethyl-2-(2,4,6-trimethylbenzyl)-4-(naphthalen-1-yl)-2,4-diaza-3-phosphabicyclo[3.2.1]octane 3-oxide (***22***).* Prepared from diamine **13** (0.17 g, 0.42 mmol), phosphorus trichloride (0.04 mL, 0.46 mmol), triethylamine (0.15 mL, 1.07 mmol) in toluene (10 mL), and water (7.60 μL, 0.42 mmol) and triethylamine (0.06 mL, 0.43 mmol) after filtration. After evaporation, product **22** was obtained as brown oil (0.16 g, 0.36 mmol, 86 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.29 (s, 1H, *H*-8′), 8.01 (s, 1H, *H*-5′), 7.83 (d, *J* = 8.1 Hz, 1H, *H*-6′), 7.73 (d, *J* = 6.6 Hz, 1H, *H*-7′), 7.48 (m, 1H, *H*-4′), 7.31–7.26 (m, 1H, *H*-3′), 7.22–7.19 (m, 1H, *H*-2′), 6.81 (s, 2H, *H*- 3″, *H*-5″), 6.38 (d, *J* = 644.7 Hz, 1H, P-*H*), 4.41 (d, *J* = 10.4 Hz, 1H, *H*-1″), 4.29–4.20 (m, 1H, *H*-1″), 3.27 (d, *J* = 19.6 Hz, 1H, *H*-5), 2.55 (s, 6H, 2′-CH_3, 6′-CH_3), 2.20 (s, 3H, 4′-CH_3), 2.01 (m, 4H, *H*-6, *H*-7), 1.66 (s, 3H, *H*-9), 1.50 (s, 3H, *H*-11), 1.01 (s, 3H, *H*-10) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 139.1 (*C*-1′), 138.8 (*C*-4″), 137.2 (*C*-1″), 135.0 (*C*-2″, *C*-6″), 131.9 (*C*-4′a, *C*-8′a), 129.1 (*C*-5′), 128.8 (*C*-3″, *C*-5″), 128.5 (*C*-3′), 127.2 (*C*-6′), 126.1 (*C*-7′), 125.0 (*C*-8′), 125.7 (*C*-4′), 122.9 (*C*-2′), 73.9 (*C*-5), 70.2 (*C*-1), 53.4 (*C*-8), 42.7 (*C*-1″), 36.0 (*C*-7), 29.7 (*C*-6), 24.9 (4′-*C*H_3), 20.9 (*C*-11), 20.5 (2′-*C*H_3, 6′-*C*H_3), 18.3 (*C*-9), 18.1 (*C*-10) ppm. ^{31}P NMR (202 MHz, CDCl3) δ = 4.9 ppm. IR (ATR) ν = 3429, 2949, 2390, 2218, 1725, 1610, 1592, 1573, 1464, 1392, 1267, 1197, 1150, 1113, 1079, 1052, 1014, 950, 885, 848, 796, 775, 726, 641, 571, 546, 519, 461, 429 cm^{-1}. MS (ESI, +3 kV): *m/z* (%) = 447 ([M + H]$^+$, 81%); 469 ([M + Na]$^+$, 100%). HRMS (ESI): Calcd. for $C_{28}H_{36}N_2OP$: 447.2565, found: 447.2574; $C_{28}H_{35}N_2ONaP$: 469.2385, found: 469.2388. $[\alpha]^{20}{}_D$ = +48 (*c* = 0.45, EtOH).

*(1R,3R,5S)-1,8,8-Trimethyl-2-(2,4,6-trimethylbenzyl)-4-([1,1′-biphenyl]-2-yl)-2,4-diaza-3-phosphabicyclo[3.2.1]octane 3-oxide (***23***).* Prepared from diamine **14** (0.15 g, 0.35 mmol), phosphorus trichloride (0.03 mL, 0.34 mmol), triethylamine (0.12 mL, 0.86 mmol) in toluene (10 mL), and water (6.00 μL, 0.33 mmol) and triethylamine (0.05 mL, 0.36 mmol) after filtration. After evaporation, product **23** was obtained as a yellow solid (0.16 g, 0.34 mmol, 97%). mp: 139.1°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.64 (d, *J* = 8.0 Hz, 1H, *H*-6′), 7.39–7.33 (m, 2H, *H*- 3″, *H*-5″), 7.29–7.24 (m, 3H, *H*-2″, *H*-4″, *H*-3″), 7.21–7.16 (m, 3H, *H*-3′, *H*-4′, *H*-5′), 6.81 (s, 2H, *H*-3″, *H*-5″), 6.23 (d, *J* = 642.7 Hz, 1H, P-*H*), 4.26 (dd, *J* = 11.7, 3.7 Hz, 1H, *H*-1″), 4.06 (dd, *J* = 20.8, 11.7 Hz, 1H, *H*-1″), 3.03–2.95 (m, 1H, *H*-5), 2.59 (ddd, *J* = 14.0, 9.7, 4.4 Hz, 1H, *H*-6), 2.40 (s, 6H, 2″-CH_3, 6″-CH_3), 2.26 (s, 3H, 4″-CH_3), 2.21 – 2.13 (m, 1H, *H*-7), 1.85 (dddd, *J* = 15.9, 13.5, 11.9, 4.5 Hz, 2H, *H*-6, *H*-7), 1.28 (s, 3H, *H*-9), 0.77 (s, 3H, *H*-11), 0.61 (s, 3H, *H*-10) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 141.5 (*C*-2′), 141.3 (*C*-1″), 140.8 (*C*-4″), 139.0 (*C*- 1″), 137.9 (*C*-2″), 137.4 (*C*-6″), 131.6 (*C*-3″), 130.4 (*C*-5″), 129.8 (*C*-4′), 129.1 (*C*-2′), 129.1 (*C*-6′), 128.5 (*C*-3″), 128.3 (*C*-5″), 128.2 (*C*-4″), 127.9 (*C*-6′), 127.1 (*C*-5′), 126.0 (*C*-1′), 125.3 (*C*-3′), 74.0 (*C*-1), 70.0 (*C*-1″), 47.3 (*C*-5), 42.5 (*C*-8), 35.7 (*C*-7), 29.3 (4″-*C*H_3), 24.7 (*C*-6), 21.5 (*C*-11), 21.0 (2″-*C*H_3), 20.5 (6″-*C*H_3), 18.5 (*C*-9), 18.0 (*C*-10) ppm. ^{31}P NMR (202 MHz, $CDCl_3$) δ = 5.4 ppm. IR (ATR) ν = 3444, 2933, 2399, 1473, 1345, 1193, 1153, 1108, 1077, 1018, 976, 894, 850, 762, 749, 703, 559, 528 cm^{-1}. MS (ESI, +3 kV): *m/z* (%) = 473 ([M + H]$^+$, 24%); 495 ([M + Na]$^+$, 52%). HRMS (ESI): Calcd. for $C_{30}H_{38}N_2OP$: 473.2722, found: 473.2737; $C_{30}H_{37}N_2ONaP$: 495.2541, found: 495.2559. $[\alpha]^{20}{}_D$ = +41 (*c* = 0.45, EtOH).

*(1R,3R,5S)-4-(2-Isopropylphenyl)-1,8,8-trimethyl-2-(2,4,6-trimethylbenzyl)-2,4-diaza-3-phosphabicyclo[3.2.1]octane 3-oxide (***24***).* Prepared from diamine **15** (0.15 g, 0.38 mmol), phosphorus trichloride (0.04 mL, 0.46 mmol), triethylamine (0.13 mL, 0.93 mmol) in toluene (10 mL), and water (6.70 μL, 0.37 mmol) and triethylamine (0.06 mL, 0.43 mmol) after filtration. After evaporation, product **24** was obtained as a brown solid (0.14 g, 0.32 mmol, 84%). mp: 157.2°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.23–7.04 (m, 3H, *H*-3′, *H*-4′, *H*-5′), 6.81 (d, *J* = 33.2 Hz, 3H, *H*-6′, *H*-3″, *H*-5″), 6.23 (d, *J* = 638.8 Hz, 1H, P*H*), 4.40–4.06 (m, 2H, *H*-1″), 3.45 (s, 1H, 2′-C*H*), 3.07 (dd, *J* = 20.7, 5.3 Hz, 1H, *H*-5), 2.81–2.53 (m, 2H, *H*-7), 2.47 (s, 6H, 2″-CH_3, 6″-CH_3), 2.19 (s, 3H, 4″-CH_3), 1.96 (dd, *J* = 43.6, 32.4 Hz, 2H, *H*-6), 1.47–1.32 (m, 6H, *H*-9, *H*-11),

1.31–1.13 (m, 6H, 2× 2′-CH-CH_3), 0.97 (s, 3H, *H*-10) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 147.6 (*C*-1′), 139.9 (*C*-4″), 138.9 (*C*-1″), 137.5 (*C*-2″, *C*-6″), 132.2 (*C*-3″, *C*-5″), 129.1 (*C*-6′), 128.5 (*C*-2′), 127.4 (*C*-4′), 126.5 (*C*-3′), 126.3 (*C*-5′), 74.5 (*C*-5), 70.0 (*C*-1), 53.4 (2′-*C*), 47.8 (*C*-8), 42.6 (*C*-1″), 35.7 (*C*-6), 29.9 (*C*-7), 26.6 (2′-C-*C*H_3), 25.0 (2′-C-*C*H_3), 24.5 (4″-*C*H_3), 23.9 (*C*-9), 20.9 (2″-*C*H_3), 20.5 (6[″-*C*H_3), 19.7 (*C*-10), 18.2 (*C*-11) ppm. ^{31}P NMR (202 MHz, $CDCl_3$) δ = 5.4 ppm. IR (ATR) ν = 3438, 2958, 2384, 1612, 1582, 1483, 1443, 1387, 1349, 1308, 1217, 1151, 1112, 1079, 1055, 1016, 973, 890, 848, 754, 688, 548, 526, 506, 473, 446, 407 cm^{-1}. MS (ESI, +3 kV): *m/z* (%) = 439 ([M + H]$^+$, 63%); 461 ([M + Na]$^+$, 100%). HRMS (ESI): Calcd. for $C_{27}H_{40}N_2OP$: 439.2878, found: 439.2880; $C_{27}H_{39}N_2ONaP$: 461.2698, found: 461.2700. $[\alpha]^{20}_D$ = + 51 (c = 0.46, EtOH).

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