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# Hydrophosphonylation of chiral hexahydroquinoxalin-2(1*H*)-one derivatives as an effective route to new bicyclic compounds: Aminophosphonates, enamines and imines

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ABSTRACT

A series of new aminophosphonate and phosphonic acid derivatives of hexahydroquinoxalin-2(1*H*)-ones and tetrahydroquinoxalin-2(1*H*)-ones were synthesised via hydrophosphonylation of the corresponding bicyclic imines with various dialkyl or diaryl *H*-phosphonates, *H*-phosphinates or *H*-phosphine oxides as phosphorus nucleophiles. The utility of the obtained compounds was demonstrated by their application as a source of phosphonate carbanion in the Horner-Wadsworth-Emmons (HWE) reaction leading to new bicyclic amines with an exocyclic, and unexpectedly, also endocyclic double bond depending on the structure of the aldehyde used.



## 1. Introduction

Due to their unique chemical and physical properties and very interesting biological activity, the chemistry of organophosphorus compounds continuously attracts attention of organic and medicinal chemists [1]. A special emphasis is placed on phosphorus-substituted heterocycles which can be found in many bioactive molecules such as selective inhibitors of hepatitis C virus (HCV) [2], antibiotics and new therapeutics for malaria and tuberculosis [3]. The development of straightforward and efficient methods for the formation of C–P bonds is the key step in the construction of such derivatives. Classical synthetic methods rely on the application of *H*-phosphonates as phosphorus nucleophiles in the reaction with C=O or C=N bonds present in the substrate and usually require addition of an acid, base or metal catalyst [4,5]. However, the search for new, atom-economic and transition-metal free methods leading to effective introduction of the phosphonate group into the organic molecule, and the synthesis of new phosphorus-containing compounds is still needed in order to expand possible applications of the molecules obtained that way.

In the course of our previous studies, we have reported on the preparation of enantiomerically pure, chiral bicyclic imine and its application in the diastereoselective Mannich reaction with phenols and other nucleophiles (furan, pyrrole, indole) to give products exhibiting interesting antiproliferative activities (Fig. 1) [6]. Herein in line with our interest in organophosphorus chemistry and especially in the synthesis of new phosphorus-containing

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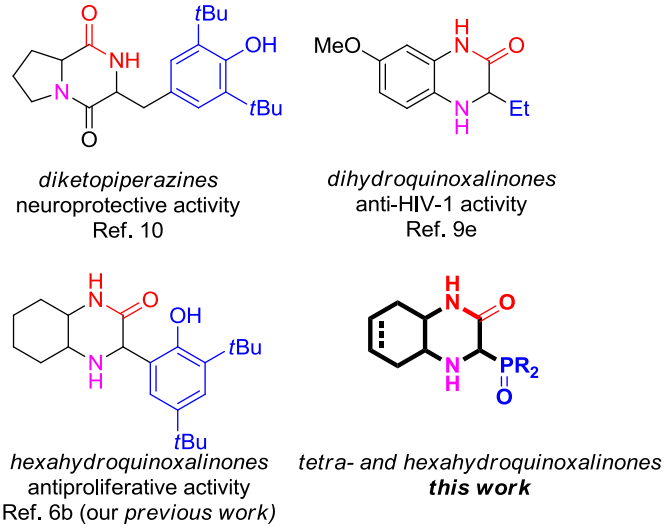


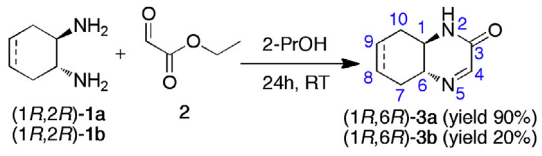

**Fig. 1.** Examples of biologically active hexahydroquinoxalinones as analogues of dihydroquinoxalin-2(1*H*)-one and diketopiperazines.

heterocycles [7], we present the results on the direct hydrophosphonylation of such chiral imines, hexahydroquinoxalin-2(1*H*)-one derivatives, with various phosphorus nucleophiles, leading to new bicyclic aminophosphonates. Although the stereoselective nucleophilic addition to imines provides an efficient and convenient route for the preparation of cyclic phosphonates [8], the phosphorus derivatives of hexahydroquinoxalin-2(1*H*)-ones have not been reported in the literature in spite of the potential application of such compounds as analogues of quinoxalin-2(1*H*)-one [9] and diketopiperazines [10] in medicinal chemistry (Fig. 1).

## 2. Results and discussion

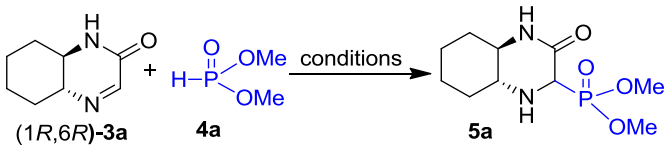
In continuation of our research on nucleophilic addition to bicyclic chiral imines, we studied their reaction with phosphorus nucleophiles (two-component phospha-Mannich or Pudovik reaction [11]). Previously, a highly diastereoselective addition of substituted phenols or indole leading to derivatives exhibiting biological activity was observed [6]. The chiral bicyclic imines **3a,b** were prepared via a modification of a method described in our previous publications [6]. Enantiopure diamines, (1*R*,2*R*)-cyclohexane-1,2-diamine (**1a**) or (1*R*,2*R*)-cyclohex-4-ene-1,2-diamine (**1b**), were reacted with ethyl glyoxylate (**2**). After 24 h of stirring at room temperature in isopropanol, the desired imines were isolated in 90% (**3a**) and 20% yield (**3b,** lower yield resulted from side reactions; Scheme 1). The synthesis of imine **3a** could be performed on 5 g scale of the final, pure product.

Our initial study on hydrophosphonylation focused on the reaction of (*R*,*R*)-hexahydroquinoxalinone (3-oxa-2,5-diazabicyclo [4.4.0]dec-4-ene **3a**) with dimethyl *H*-phosphonate (**4a**), used as a model phosphorus nucleophile, under various conditions (Table 1). The phosphorylated product **5a** was formed in 72% yield (*dr* 56:44) when the reaction was performed in toluene at 80 °C for 1 h and in




**Scheme 1.** Preparation of bicyclic imines **3a** and **3b**.

**Table 1**
Screening of reaction conditions for phosphorylation of imine **3a** with dimethyl *H*-phosphonate (**4a**).[a]



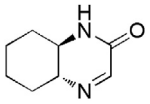
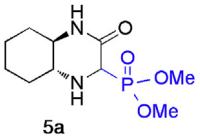
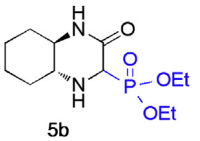
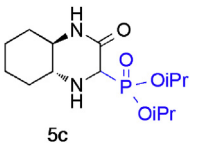
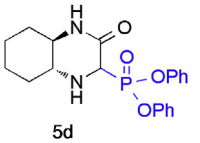
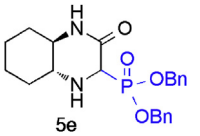
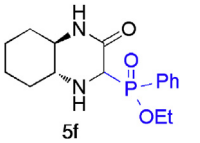
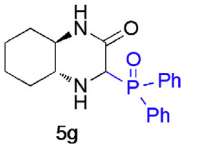
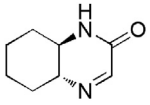
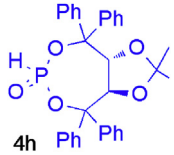
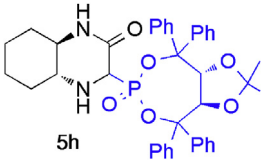
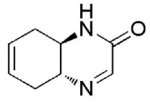
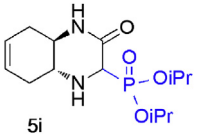
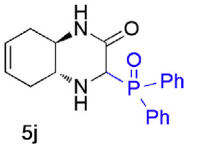

| Entry | Reaction conditions | Yield (%)/*dr* |
|---|---|---|
| 1. | $CH_2Cl_2$, r.t., 24 h | 43/54:46 |
| 2. | $CH_2Cl_2$, $Et_3N$, r.t., 24 h | 52/52:48 |
| 3. | Toluene, r.t., 24 h | 40/51:49 |
| 4. | Toluene, $Et_3N$, r.t., 24 h | 67/55:45 |
| 5. | Toluene, 80 °C, 1 h | 50/54:46 |
| **6.** | **Toluene, $Et_3N$, 80 °C, 1 h** | **72/56:44** |
| 7. | neat, 80 °C, 1 h | 30/58:42 |
| 8. | neat, $Et_3N$, 80 °C, 1 h | 43/57:43 |
| 9. | Toluene, TMEDA, r.t., 24 h | 10/57:43 |
| 10. | Toluene, DIPA, r.t., 24 h | 25/55:45 |
| 11. | Toluene, DMAP, r.t., 24 h | 10/56:44 |
| 12. | Toluene, pyridine, r.t., 24 h | 53/55:45 |
| 13. | Toluene, DABCO, r.t., 24 h | 10/57:43 |
| 14. | Toluene, L-proline, r.t., 24 h | 65/51:49 |
| 15. | Toluene, quinuclidine, r.t., 24 h | 15/56:44 |
| 16. | Toluene, quinine, r.t., 24 h | 15/54:46 |

[a] Reaction conditions: Imine **3a** (0.7 mmol), *H*-phosphonate **4a** (0.7 mmol), base (0.7 mmol), and solvent (10 mL) were stirred at 80 °C or at room temperature, after 1 h or 24 h the solvent was evaporated under vacuum and a crude product was analysed by $^{31}P$ and $^{1}H$ NMR spectroscopy.

the presence of $Et_3N$ (Table 1, entry 6). Longer reaction time did not result in improving reaction yield, instead we observed formation of undesired by-products (as seen in $^{31}P$ NMR when monitoring the reaction progress). It is noticeable that 67% yield (*dr* 55:45) of **5a** was achieved at room temperature after 24 h (Table 1, entry 4), while 50% yield (*dr* 55:45) could be observed in the absence of $Et_3N$ at 80 °C (Table 1, entry 5), indicating that both the presence of a base and elevated temperature are prerequisites for a high reaction yield and fast transformation.

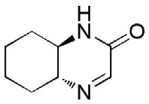
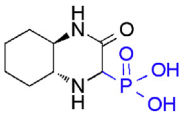
During solvent optimization, toluene was found superior to dichloromethane (Table 1, entries 1–2) and neat conditions (Table 1, entries 7–8). In all cases the phosphorylated product **5a** was formed as an inseparable mixture of diastereoisomers with diastereoisomeric ratio (*dr*) roughly 55:45 (Table 1, entries 1–8). In each case, the signal in the $^{31}P$ NMR spectra corresponding to the major diastereoisomer was situated at a lower value of chemical shift. Additionally, we have tested several amines in order to examine the influence of base on the outcome of the reaction (Table 1, entries 9–16). Reactions with classical bases such as *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), diisopropylamine (DIPA), 4-(dimethylamino)pyridine (DMAP) or pyridine did not lead to the desired product with better diastereoselectivity. Similarly, utilisation of more complex or chiral bases, *e.g.* 1,4-diazabicyclo [2.2.2]octane (DABCO), L-proline, quinuclidine or quinine did not have a positive impact on the asymmetric induction. Therefore, we concluded that the optimal conditions required reacting imine **3a** with *H*-phosphonate **4a** during 1 h in toluene at 80 °C and in the presence of $Et_3N$ (Table 1, entry 6). With the optimal reaction conditions in hand we have examined the scope of phosphorus nucleophiles (Table 2). Structurally diverse *H*-phosphonates **4a-e**, *H*-phosphinate **4f** and phosphine oxide **4g** reacted cleanly with hexahydroquinoxalinone **3a** and its unsaturated analogue **3b**, affording the corresponding phosphorylated products **5a**–**j** in good yields. Importantly, the yields of isolated phosphonates were not dependent on the steric bulk of the dialkyl or diaryl *H*-

**Table 2**
Synthesis of bicyclic aminophosphonates **5a-j** and phosphonic acid **6**.[a]

| Imine | Phosphorus nucleophile | Product | Yield (%)/*dr* |
|---|---|---|---|
|  (1*R*,6*R*)-3a | HP(O)(OMe)$_2$ (**4a**) |  **5a** | 72/56:44 |
| | HP(O)(OEt)$_2$ (**4b**) |  **5b** | 32/53:47 |
| | HP(O)(OiPr)$_2$ (**4c**) |  **5c** | 87/52:48 |
| | HP(O)(OPh)$_2$ (**4d**) |  **5d** | 69/50:50 |
| | HP(O)(OBn)$_2$ (**4e**) |  **5e** | 69/50:50 |
| | HP(O)Ph(OEt) (**4f**) |  **5f** | 54/50:50 |
| | HP(O)Ph$_2$ (**4g**) |  **5g** | 64/55:45 |
|  (1*R*,6*R*)-3a |  **4h** |  **5h** | 72/60:40 |
|  (1*R*,6*R*)-3b | HP(O)(OiPr)$_2$ (**4c**) |  **5i** | 73/55:45 |
| | HP(O)Ph$_2$ (**4g**) |  **5j** | 95/57:43 |

(*continued on next page*)

**Table 2** (*continued*)

| Imine | Phosphorus nucleophile | Product | Yield (%)/*dr* |
|---|---|---|---|
|  (1*R*,6*R*)-**3a** | $P(OSiMe_3)_3$[b] |  **6** | 76/70:30 |

[a] Reaction conditions: imine (1.0 mmol), phosphorus nucleophile (1.0 mmol), $Et_3N$ (1.0 mmol), toluene (25 mL), 80 °C, 1 h.
[b] Reaction conditions: imine (1.0 mmol), $P(OSiMe_3)_3$ (1.0 mmol), $CH_2Cl_2$ (15 mL), r.t., 24 h then MeOH (15 mL), r.t. 12 h, crystallization.

phosphonates used and ranged from 54% to 95%. The only exception was found in the case of product **5b** which was prepared in only 32% yield (conversion 51% based on the $^{31}P$ NMR of the crude reaction mixture) due to difficulties with its separation from unreacted imine and *H*-phosphonate **4b** during chromatographic purification. In addition, *H*-phosphinate **4f**, diphenylphosphine oxide **4g**, and chiral *H*-phosphonate derivative of TADDOL **4h** could be also used as phosphorus nucleophiles under optimized reaction conditions and produced desired addition products **5f**, **5g**, **5h** and **5j** with good overall yields despite the structural rigidity and steric hindrance of the phosphorus nucleophiles.

The bicyclic aminophosphonates **5a-j** were purified by column chromatography and isolated as crystalline, non-hygroscopic solids. Pure single diasteroisomers were isolated only in the case of **5h** (via column chromatography, pure diasteroisomer **5h′**) and **5j** (through crystallization, pure diasteroisomer **5j′**) (see Supporting Information for details). However, after storage in solution of distereomerically pure **5h′** and **5j′** we observed a stepwise epimerisation on the carbon atom directly attached to the phosphorus substituent, resulting in changes in ratio of diastereoisomers as seen in $^{31}P$ NMR. For **5h′** after 72 h in dichloromethane at room temperature the *dr* changed from 97:3 to 58:42, and in the case of **5j′** under similar conditions *dr* changed from 99:1 to 56:44.

Additionally, we have performed a reaction of imine **3a** with tris(trimethylsilyl) phosphite followed by methanolysis of the formed silylated ester to obtain the desired bicyclic aminophosphonic acid **6** (76% yield, *dr* 70:30) after crystallization (Table 2). Finally, we have also tested the possibility of performing the synthesis of bicyclic aminophosphonate **5a**, as model reaction, in one-pot (see Supporting information for details). Unfortunately, the obtained overall yields were much lower than in the case of standard procedure presented in Table 1. Although products **5a-j** were isolated as mixtures of diastereoisomers, we were able to distinguish the signals in the $^{1}H$ and $^{13}P$ NMR spectra corresponding to each diastereoisomer and to assign the absolute configuration on the carbon atom directly attached to the phosphorus substituent, based on the $^{1}H$ NMR and NOESY experiments (See Supporting information).

Isolation of a pure major diasteroisomer of aminophosphonate **5h** by a careful chromatography on silica column followed by crystallization enabled single crystal X-ray diffraction analysis for this compound (**5h′**) (Fig. 2). Four chiral centers present in the molecule of aminophosphonate **5h**, obtained with the use of enantiopure TADDOL-derived *H*-phosphonate (**4h**) as a nucleophile, originated from enantiopure substrate and reagent. These are bridging carbon atoms of enantiopure imine **3a** and TADDOL reactants and all possess *R* configuration. The analysis of molecular structure of **5h′** reveals that a new chiral center at 4-C atom has *R* configuration as well (see Supporting information for details concerning X-ray analysis).

Overall the diastereoselectivity of the investigated nucleophilic addition to enantiopure imine **3a** was relatively low: the

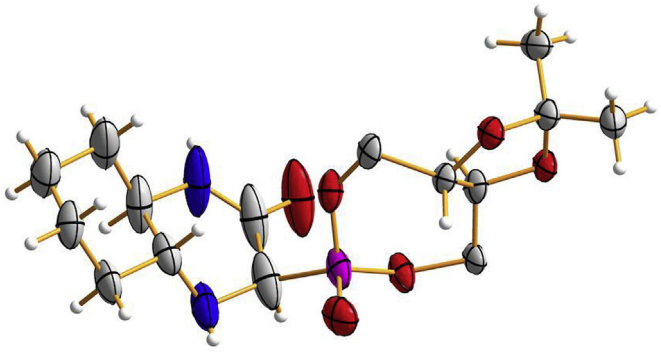
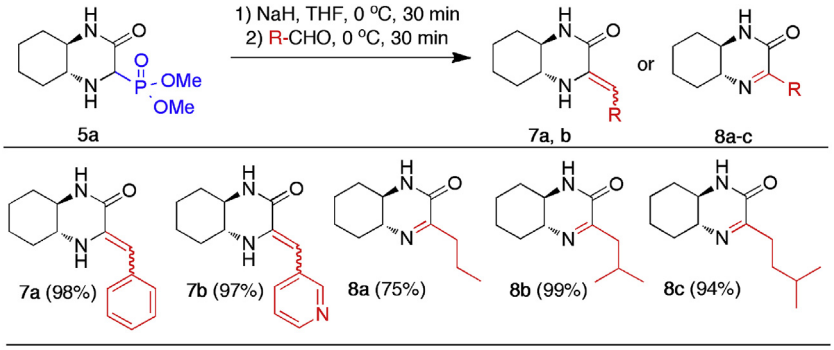


**Fig. 2.** Molecular structure of aminophosphonate **5h′**. Four phenyl groups are omitted for clarity.

diastereomer ratios did not exceed 70:30 which is in contrast to our previous findings concerning phenol additions to **3a** [6]. However, the conditions of hydrophosphonylation (the use of triethylamine as a base) and the presence of both carbonyl and phosphonate functions render the 4-H proton prone to dissociation which can lead to epimerisation on 4-C. DFT calculations (see Supporting Information for details) performed for the reaction of **3a** with **4a** suggest that energies of two epimers of **5a** are essentially the same (within the range of the accuracy of the method) which is in agreement with the observed diastereomeric ratio (ca. 1:1). From the data obtained, it seems very likely that the two phosphonate epimers readily interconvert under the reaction conditions and this would preclude their formation in high dastereoselectivity via the presented methodology. The DFT calculations do, however, support the notion that the kinetic diastereoselectivity of the process (ratio of the two rate constants defining reaction on the two diastereotopic faces of the reactant) may also be relatively low (and in fact close in value to the equilibrium position of about 55:45) due to the small energy differences in calculated transition state energies. The equilibrium may be reached very rapidly as suggested by our observation in the case of formation of **5a**, we found that the diastereoselectivity of the reaction does not depend on conversion (reaction progress was monitored be means of $^{31}P$ NMR).

Finally, in order to demonstrate the synthetic utility of the obtained bicyclic aminophosphonates, we tested compound **5a** (a diastereomeric mixture) as a source of phosphonate carbanion in Horner-Wadsworth-Emmons (HWE) reaction. This transformation is well established as a powerful and versatile tool used for the formation of new C=C bond [12]. Previously, selective reaction of aldehydes with potassium salt of diketopiperazine phosphonate served as an important step in the synthesis of various natural products [13]. In our case, the use of bicyclic aminophosphonate **5a** in HWE reaction with aromatic and heteroaromatic aldehydes, under mild reaction conditions, led to the desired alkenes **7a,b** in excellent yields (98 and 97% respectively), as 1:1 mixture of *E:Z* isomers (Scheme 2). This was documented by the presence of two




**Scheme 2.** HWE reaction of the synthesised aminophosphonate **5a.**

singlets of equal intensity in 6.5–6.8 ppm region in $^{1}$H NMR spectra of **7a** and **7b**. Unexpectedly, the use of aliphatic aldehydes such as propionaldehyde, isobutyraldehyde and isovaleraldehyde produced chiral imines **8a-c**, as more stable tautomers, in very good yields (75–99%). Formation of the latter products in good yields is very interesting since they cannot be accessed by standard synthetic protocols [14]; the presence of a reactive C=N bond opens a new possibility for their further functionalization. Among the HWE products, only racemic compound **8b** has been described in the literature [14c]. It is worth to mention that formation of pure substituted bicyclic imines **8a-8c** does not require separation of diastereomeric aminophosphonates obtained in the previous stage from enantiomerically and diastereomerically pure cyclic imine.

## 3. Conclusions

In summary, a transition-metal-free and atomeconomic method for effective hydrophosphonylation of enantiomerically pure hexahydroquinoxalin-2(1*H*)-one and tetrahydroquinoxalin-2(1*H*)-one with a wide range of phosphorus nucleophiles under mild reaction conditions was presented. The desired new bicyclic aminophosphonates were obtained in good overall yields albeit with low diastereoselectivity. Based on the DFT calculations and monitoring the progress of the reaction be means of $^{31}$P NMR we postulate that the two phosphonate epimers readily interconvert which precludes their formation in high dastereoselectivity. Additionally, kinetic diastereoselectivity of the process may also be relatively low and equilibrium may be reached very rapidly. Finally, we have presented the application of one of the obtained bicyclic aminophosphonates in the HWE reaction. In this way, novel, and difficult to obtained by standard procedures, heterobicyclic compounds with an exocyclic, and unexpectedly also endocyclic, double bond depending on the aldehyde used were obtained. Further extensive research on the biological activity of the obtained bicyclic aminophosphonates and their utility as useful synthetic intermediates is currently being carried out in our laboratory and the results will be published in due course.

## 4. Experimental section

Melting points were determined on the Schmelzpunkt Bestimmer Apotec melting-point apparatus using the standard open capillary method and are uncorrected. $^{1}$H, $^{13}$C and $^{31}$P NMR spectra were collected on Jeol 400yh, Bruker Avance III 500 and Bruker Avance II 600 instruments. NMR spectra recorded in $CDCl_3$, $D_2O$ and DMSO-$d_6$ were referenced to the respective residual $^{1}$H or $^{13}$C signals of the solvents. The reported *J* values are those observed from the splitting patterns in the spectrum and may not reflect the true coupling constant values. NOESY experiments were carried out at 293 K. Infrared spectra (4000-400 $cm^{-1}$) were collected on a Perkin Elmer 2000 FTIR spectrophotometer. High resolution mass spectra were collected using electrospray ionization on Waters LCT Premier XE TOF instrument. Optical rotations were measured using an Optical Activity Ltd. Model AA-5 automatic polarimeter; $[\alpha]_D$ values are given in $10^{-1}$ deg $cm^2$ $g^{-1}$. Chromatographic separations were performed on silica gel 60 (70–230 mesh). Thin layer chromatography was carried out using silica gel 60 precoated plates.

### 4.1. Synthesis of cyclic imines

1,2-Diamine **1a** or **1b** (4.00 mmol, 456 mg or 448 mg respectively, 2.00 equiv) was dissolved in 2-PrOH (8 mL). To the stirred solution ethyl glyoxalate solution (50% solution in toluene, 2.00 mmol, 0.420 mL, 1.00 equiv) was added and the mixture was stirred for 24 h at room temperature (293 K). The solvent was removed in vacuo and the product was purified by silica gel column chromatography (eluent: $CH_2Cl_2$/MeOH 97:3 v/v).

#### 4.1.1. (1R,6R)-3-oxo-2,5-diazabicyclo[4.4.0]dec-4-ene (3a)

Colorless solid; 5.46 g, 90% yield (20.0 times enlarged scale); mp. 172–175 °C; $[\alpha]_D^{20}$ -238 (c 0.78, $CH_2Cl_2$); IR (KBr): 488, 736, 774, 1361, 1416, 1446, 1622, 1665, 1710, 2854, 2935, 3104, 3184 $cm^{-1}$; $^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.70 (t, $J = 2.8$ Hz, 1H), 7.13 (br. s, 1H), 3.05–3.14 (m, 2H), 2.34–2.36 (m, 1H), 1.76–1.95 (m, 3H), 1.31–1.45 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 158.1, 156.4, 63.1, 54.2, 31.6, 31.1, 25.3, 23.7; HRMS (ESI-TOF) calcd. for $C_8H_{13}N_2O$ $[M+H]^+$ *m/z*: 153.1022 found: 153.1019.

#### 4.1.2. (1R,6R)-3-oxo-2,5-diazabicyclo[4.4.0]deca-4,8-diene (3b)

Brown solid; 117 mg; 20% yield; mp. 200–202 °C; $[\alpha]_D^{20}$ -435 (c 0.40, $CH_2Cl_2$); IR (KBr): 488, 736, 773, 1360, 1416, 1446, 1622, 1665, 1709, 2854, 2935, 3104, 3184 $cm^{-1}$; $^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.75 (t, $J = 2.8$ Hz, 1H), 6.99 (br. s, 1H), 5.74–5.78 (m, 1H), 5.61–5.65 (m, 1H), 3.36–3.49 (m, 2H), 2.77–2.82 (m, 1H), 2.41–2.47 (m, 1H), 2.14–2.26 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 157.6, 156.2, 126.4, 123.2, 58.9, 50.4, 32.0, 31.9; HRMS (ESI-TOF) calcd. for $C_8H_{11}N_2O$ $[M+H]^+$ *m/z*: 151.0871 found: 151.0872.

### 4.2. Synthesis of aminophosphonates and aminophosphine oxides

Imine **3a** or **3b** (1.00 mmol, 152 mg or 150 mg respectively, 1.00 equiv) was dissolved in toluene (5 mL) and appropriate *H*-phosphonate or diphenylphosphine oxide (1.00 mmol, 1.00 equiv) was added followed by addition of $Et_3N$ (1.00 mmol, 0.140 mL, 1.00 equiv). The resulting mixture was stirred for 1 h at 80 °C. After that time the solvent was evaporated under vacuum, and the resulting crude product was purified by column chromatography (eluent: $CH_2Cl_2$/MeOH 97:3 v/v).

*4.2.1. Dimethyl-[(1R,6R)-3-oxo-2,5-diazabicyclo[4.4.0]dec-4-yl] phosphonate (5a)*

Light yellow solid; 189 mg; 72% yield; mixture of diastereoisomers *dr* 56:44; IR (KBr): 771, 823, 1030, 1066, 1251, 1367, 1416, 1452, 1666, 1714, 2858, 2936, 3072, 3192, 3298 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 6.76 (br. s, 1H), 6.68 (br. s, 1H), 4.12 (d, $J = 19.8$ Hz, 1H), 4.04 (d, $J = 21.7$ Hz, 1H), 3.89 (d, $J = 10.7$ Hz, 3H), 3.85 (d, $J = 10.7$ Hz, 6H), 3.84 (d, $J = 11.1$ Hz, 3H), 3.08–3.12 (m, 1H), 2.99–3.03 (m, 1H), 2.88–2.92 (m, 1H), 2.44–2.48 (m, 1H), 1.99–2.04 (m, 2H), 1.74–1.87 (m, 8H), 1.18–1.42 (m, 8H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 165.8, 165.7 (d, $J = 5.5$ Hz), 58.8, 58.5, 58.4, 58.1, 57.8, 57.5, 57.4, 57.0, 55.8, 55.0, 54.5 (d, $J = 6.4$ Hz), 53.8 (d, $J = 7.3$ Hz), 53.5 (t, $J = 7.3$ Hz), 30.9 (d, $J = 16.4$ Hz), 30.5 (d, $J = 28.2$ Hz), 24.4 (d, $J = 10.9$ Hz), 23.7 (d, $J = 10.0$ Hz), 23.4; $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ 23.7, 21.8; HRMS (ESI-TOF) calcd. for $C_{10}H_{20}N_2O_4P$ $[M+H]^+$ *m/z*: 263.1161 found: 263.1155.

*4.2.2. Diethyl-[(1R,6R)-3-oxo-2,5-diazabicyclo[4.4.0]dec-4-yl] phosphonate (5b)*

Off-white solid; 93 mg; 32% yield; mixture of diastereoisomers *dr* 53:47; IR (KBr): 976, 1031, 1238, 1671, 2933, 3181, 3278 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 6.48 (br. s, 1H), 6.43 (br. s, 1H), 4.12–4.29 (m, 8H), 4.06 (d, $J = 19.6$ Hz, 1H), 3.97 (d, $J = 20.8$ Hz, 1 Hz), 2.97–3.09 (m, 2H), 2.87–2.93 (m, 1H), 2.40–2.45 (m, 1H), 2.11 (br. s, 2H), 1.70–1.82 (m, 8H), 1.16–1.39 (m, 20H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 165.8, 165.7, 63.9 (d, $J = 6.3$ Hz), 63.4 (d, $J = 7.5$ Hz), 63.1, 63.0, 62.9, 59.3, 58.7, 58.68, 58.5, 57.8, 57.7, 57.4, 55.0, 31.1, 31.0, 30.6, 30.4, 24.5 (d, $J = 10.3$ Hz), 23.8 (d, $J = 7.5$ Hz), 16.6, 16.5, 16.47; $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 21.8, 19.8; HRMS (ESI-TOF) calcd. for $C_{12}H_{24}N_2O_4P$ $[M+H]^+$ *m/z*: 291.1474 found: 291.1487.

*4.2.3. Diisopropyl-[(1R,6R)-3-oxo-2,5-diazabicyclo[4.4.0]dec-4-yl] phosphonate (5c)*

Colorless solid; 277 mg; 87% yield; mixture of diastereoisomers *dr* 52:48; IR (KBr): 992, 1240, 1370, 1670, 2938, 2979, 3184, 3291 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 6.45–6.30 (m, 2H), 4.90–4.70 (m, 4H), 4.01 (d, $J = 20$ Hz, 1H), 3.94 (d, $J = 21$ Hz, 1H), 3.17–2.87 (m, 3H), 2.50–2.37 (m, 1H), 2.35–2.00 (m, 2H), 1.85–1.60 (m, 8H), 1.50–1.10 (m, 32H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 166.0, 165.9, 72.5 (d, $J = 6.9$ Hz), 72.3 (d, $J = 7.5$ Hz), 72.0 (d, $J = 6.9$ Hz), 71.7 (d, $J = 7.5$ Hz), 59.2 (d, $J = 92.5$ Hz), 59.0 (d, $J = 68.4$ Hz), 58.1 (d, $J = 6.9$ Hz), 57.7, 57.4, 54.9, 31.2, 31.1, 30.6, 30.3, 24.6–23.6 (12C); $^{31}P$ NMR (162 MHz, $CDCl_3$): 19.85 (dt, $J_1 = 20.6$ Hz, $J_2 = 7.5$ Hz), 17.48 (dt, $J_1 = 19.6$ Hz, $J_2 = 6.5$ Hz); HRMS (ESI-TOF) calcd. for $C_{14}H_{27}N_2O_4P$ $[M+H]^+$ *m/z*: 319.1787, found: 319.1790.

*4.2.4. Diphenyl-[(1R,6R)-3-oxo-2,5-diazabicyclo[4.4.0]dec-4-yl] phosphonate (5d)*

Colorless solid; 266 mg; 69% yield; mixture of diastereoisomers *dr* 50:50; IR (KBr): 505, 690, 765, 776, 932, 945, 1191, 1215, 1263, 1492, 1592, 1668, 1874, 1946, 2859, 2937, 3072, 3187, 3306, 3317, 3430 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 8.15 (br. s, 1H), 8.13 (br. s, 1H), 7.31–7.37 (m, 8H), 7.14–7.20 (m, 12H), 4.34 (d, $J = 17.7$ Hz, 1H, **4*S***), 4.25 (d, $J = 25.1$ Hz, 1H, **4*R***), 2.95 (br. s, 2H), 2.83–2.89 (m, 2H), 2.58–2.63 (m, 1H, **4*R***), 2.36–2.40 (m, 1H, **4*S***), 1.77–1.80 (m, 3H), 1.59–1.63 (m, 5H), 0.98–1.28 (m, 8H); $^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ 164.7 (d, $J = 4.8$ Hz), 164.3 (d, $J = 4.8$ Hz), 151.4 (d, $J = 9.6$ Hz), 150.9 (d, $J = 3.9$ Hz, 2C overlapped), 150.8 (d, $J = 3.9$ Hz, 2C overlapped), 150.7 (d, $J = 10.1$ Hz), 130.2 (4C overlapped), 130.2 (2C overlapped), 130.1 (2C overlapped), 125.6 (3C overlapped), 125.4, 121.4 (4C overlapped), 121.2 (2C overlapped), 121.1 (2C overlapped), 59.0, 58.1, 58.0, 57.3, 56.6, 56.3, 31.3, 30.8, 30.5 (d, $J = 7.7$ Hz), 25.2, 24.5, 23.9; $^{31}P$ NMR$\{^1H\}$ (162 MHz, DMSO-$d_6$): δ 15.6, 14.6; HRMS (ESI-TOF) calcd. for $C_{20}H_{24}N_2O_4P$ $[M+H]^+$ *m/z*: 387.1474 found: 387.1457.

*4.2.5. Dibenzyl-[(1R,6R)-3-oxo-2,5-diazabicyclo[4.4.0]dec-4-yl] phosphonate (5e)*

Light yellow solid; 286 mg; 69% yield; mixture of diastereoisomers *dr* 50:50; IR (KBr): 458, 696, 738, 997, 1045, 1241, 1369, 1419, 1458, 1668, 2859, 2934, 3034, 3169, 3287, 3334, 3435 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.27–7.38 (m, 20H), 6.16 (br. s, 1H), 6.10 (br. s, 1H), 5.03–5.28 (m, 8H), 4.13 (d, $J = 19.6$ Hz, 1H), 4.06 (d, $J = 20.8$ Hz, 1H), 2.94–2.99 (m, 2H), 2.82–2.88 (m, 1H), 2.35–2.42 (m, 1H), 1.87 (br. s, 2H), 1.62–1.79 (m, 8H), 1.08–1.39 (m, 8H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 166.0, 165.9, 158.2, 156,6, 136.3–136.7 (m, 4C), 128.0–128.6 (m, 20C), 69.1 (d, $J = 6.3$ Hz), 68.5 (d, $J = 6.7$ Hz), 68.3 (d, $J = 6.7$ Hz, 2C overlapped), 59.5, 58.9, 58.4, 58.3, 57.9, 57.7, 57.6, 57.1, 54.8, 30.6 (q, $J = 15.4$ Hz), 24.4 (d, $J = 10.6$ Hz), 23.7 (d, $J = 4.8$ Hz); $^{31}P$ NMR$\{^1H\}$ (162 MHz, $CDCl_3$): δ 22.8, 20.6; HRMS (ESI-TOF) calcd. for $C_{22}H_{28}N_2O_4P$ $[M+H]^+$ *m/z*: 415.1787, found: 415.1796.

*4.2.6. Ethyl-[(1R,6R)-3-oxo-2,5-diazabicyclo[4.4.0]dec-4-yl](phenyl)phosphinate (5f)*

Colorless solid; 174 mg; 54% yield; mixture of diastereoisomers *dr* 50:50; IR (KBr): 696, 752, 959, 1036, 1122, 1213, 1351, 1366, 1439, 1592, 1668, 2862, 2934, 3080, 3209, 3441 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.87–7.92 (m, 4H), 7.76–7.85 (m, 4H), 7.37–7.52 (m, 12H), 6.76 (br. s, 1H), 6.65 (br. s, 1H), 6.60 (br. s, 1H), 6.38 (br. s, 1H), 4.05–4.27 (m, 10H), 3.91–4.01 (m, 2H), 2.88–3.14 (m, 4H), 2.57–2.75 (m, 2H), 2.55 (br. s, 4H), 2.38–2.42 (m, 2H), 1.57–1.77 (m, 16H), 1.20–1.36 (m, 28H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 166.4, 166.24, 166.20, 166.1, 133.1, 133.0, 132.9, 132.8, 132.76, 132.71 (2C overlapped), 132.64, 132.62, 132.54, 132.51, 132.48, 130.7 (2C overlapped), 130.38, 130.35, 129.5, 129.3, 129.1, 129.0, 128.6 (d, $J = 3.9$ Hz), 128.4 (d, $J = 2.9$ Hz), 128.2 (d, $J = 6.7$ Hz), 128.1 (d, $J = 6.7$ Hz), 62.2 (d, $J = 6.7$ Hz), 62.0 (d, $J = 6.7$ Hz), 61.9 (d, $J = 6.7$ Hz), 61.6, 61.1 (d, $J = 10.6$ Hz), 60.5 (2C overlapped), 60.3 (d, $J = 10.6$ Hz), 59.4, 58.5 (d, $J = 10.6$ Hz), 58.2 (d, $J = 11.6$ Hz), 57.6, 57.3 (d, $J = 6.7$ Hz), 56.9, 55.3, 55.2, 31.1, 30.9, 30.85, 30.83, 30.6 (2C overlapped), 30.5, 30.4, 24.5, 24.46, 24.42, 24.3, 23.9, 23.73, 23.70, 23.6, 16.7, 16.67, 16.63, 16.6; $^{31}P$ NMR$\{^1H\}$ (162 MHz, $CDCl_3$): δ 39.0, 38.0, 35.8, 35.3; HRMS (ESI-TOF) calcd. for $C_{16}H_{24}N_2O_3P$ $[M+H]^+$ *m/z*: 323.1525 found: 323.1526.

*4.2.7. 4-(diphenylphosphoryl)-(1R,6R)-3-Oxo-2,5-diazabicyclo [4.4.0]decane (5g)*

Colorless solid; 227 mg; 64% yield; mixture of diastereoisomers *dr* 55:45; IR (KBr): 697, 1119, 1166, 1368, 1437, 1692, 2861, 2935, 3093, 3197, 3432; $^1H$ NMR (600 MHz, $CDCl_3$): δ 8.00–8.07 (m, 4H), 7.77–7.86 (m, 4H), 7.37–7.51 (m, 12H), 7.04 (br. s, 1H), 7.02 (br. s, 1H), 4.58 (d, $J = 13.8$ Hz, 1H), 4.50 (d, $J = 11.4$ Hz, 1H), 2.90–2.94 (m, 1H), 2.85 (br. s, 2H), 2.75–2.83 (m, 1H), 2.56–2.62 (m, 1H), 2.41–2.45 (m, 1H), 1.51–1.80 (m, 8H), 1.10–1.27 (m, 8H); $^{13}C$ NMR (151 MHz, $CDCl_3$): δ 166.8 (d, $J = 4.2$ Hz), 166.7 (d, $J = 2.1$ Hz), 132.8, 132.4 (d, $J = 9.0$ Hz, 2C overlapped), 132.2 (d, $J = 9.7$ Hz, 2C overlapped), 132.0 (d, $J = 9.7$ Hz, 2C overlapped), 131.9 (2C overlapped), 131.79, 131.77, 131.6 (d, $J = 9.7$ Hz, 2C overlapped), 131.4, 131.2, 130.0, 128.5 (d, $J = 12.5$ Hz, 2C overlapped), 128.2 (d, $J = 12.5$ Hz, 2C overlapped), 128.1 (2C overlapped), 128.0 (2C overlapped), 61.6, 61.1 (d, $J = 27.1$ Hz), 60.5, 58.6 (d, $J = 10.4$ Hz), 57.1 (d, $J = 29.1$ Hz), 55.3, 30.7 (2C overlapped), 30.3 (d, $J = 19.4$ Hz, 2C overlapped), 24.4 (d, $J = 20.1$ Hz, 2C overlapped), 23.7 (d, $J = 10.4$ Hz, 2C overlapped); $^{31}P$ NMR$\{^1H\}$ (243 MHz, $CDCl_3$): δ 31.6, 29.0; HRMS (ESI-TOF) calcd. for $C_{20}H_{24}N_2O_2P$ $[M+H]^+$ *m/z*: 355.1575 found: 355.1580.

*4.2.8. (4-((3aR,8aR)-2,2-Dimethyl-6-oxido-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl))-(1R,6R)-3-oxo-2,5-diazabicyclo[4.4.0]decan (5 h)*

Colorless solid; 478 mg; 72% yield; mixture of diastereoisomers

*dr* 60:40; IR (KBr): 697, 726, 743, 924, 939, 995, 1021, 1040, 1054, 1090, 1166, 1216, 1256, 1351, 1372, 1383, 1448, 1496, 1676, 1816, 1904, 1958, 2859, 2934, 2991, 3062, 3204, 3394 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.43–7.72 (m, 16H), 7.22–7.38 (m, 24H), 7.13 (br. s, 1H, **4*R***), 5.97 (br. s, 1H, **4*S***), 5.68 (d, *J* = 8.0 Hz, 1H, **4*S***), 5.47 (d, *J* = 7.6 Hz, 1H, **4*R***), 5.38 (d, *J* = 8.0 Hz, 1H), 5.09 (d, *J* = 8.3 Hz, 1H), 4.26 (d, *J* = 18.0 Hz, 1H, **4*S***), 4.12 (d, *J* = 19.9 Hz, 1H, **4*R***), 2.96–3.00 (m, 1H, **4*S***), 2.82–2.87 (m, 2H), 2.35–2.39 (m, 1H), 2.13 (br. s, 2H), 1.58–1.70 (m, 8H), 1.21–1.33 (m, 8H), 1.07 (s, 3H), 0.77 (s, 3H), 0.47 (s, 3H), 0.38 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 165.5 (d, *J* = 2.4 Hz), 165.1 (d, *J* = 7.7 Hz), 144.4 (d, *J* = 7.7 Hz), 144.2 (d, *J* = 4.8 Hz), 144.1, 143.9, 140.3 (d, *J* = 9.6 Hz), 140.1 (d, *J* = 10.6 Hz), 139.9, 139.8, 129.8, 129.4, 129.3, 129.1, 128.3, 128.25 (2C overlapped), 128.2 (2C overlapped), 128.1, 128.0 (2C overlapped), 127.9, 127.8 (2C overlapped), 127.7 (4C overlapped), 127.6, 127.5 (8C overlapped), 127.4 (8C overlapped), 127.38 (2C overlapped), 127.3 (2C overlapped), 127.2 (2C overlapped), 127.0 (2C overlapped), 114.2, 113.4, 90.7 (d, *J* = 13.5 Hz), 89.4 (d, *J* = 13.0 Hz), 88.2 (d, *J* = 9.2 Hz), 87.8 (d, *J* = 10.6 Hz), 81.0, 79.7, 79.0, 78.8, 60.1, 58.8, 58.7, 58.6, 58.3, 57.4, 55.1, 53.6, 31.0 (d, *J* = 22.2 Hz), 30.3 (d, *J* = 24.6 Hz), 27.3 (d, *J* = 14.9 Hz), 26.2 (d, *J* = 30.3 Hz), 24.5, 23.9; $^{31}P$ NMR{$^1H$} (162 MHz, $CDCl_3$): δ 17.4 (**4*S***), 11.3 (**4*R***); HRMS (ESI-TOF) calcd. for $C_{39}H_{42}N_2O_6P$ $[M+H]^+$ *m*/*z*: 665.2781, found: 665.2787.

#### 4.2.9. (4-((3aR,8aR)-2,2-Dimethyl-6-oxido-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl))-(1R,4R,6R)-3-oxo-2,5-diazabicyclo[4.4.0]decan (5 h′) –

Colorless solid; 239 mg; 36% yield; single diastereoisomer separated from 5 h by column chromatography (eluent: $CH_2Cl_2$/MeOH 97:3 v/v), 97% purity; mp. 176–178 °C; $[\alpha]_D^{20}$ −128 (c 0.64, $CH_2Cl_2$); IR (KBr): 698, 726, 742, 940, 1040, 1054, 1090, 1256, 1351, 1383, 1448, 1675, 2858, 2933, 3396 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.46–7.64 (m, 8H), 7.22–7.37 (m, 13H), 5.46 (d, *J* = 7.6 Hz, 1H), 5.36 (d, *J* = 7.6 Hz, 1H), 5.09 (d, *J* = 8.0 Hz, 1H), 4.14 (d, *J* = 20.0 Hz, 1H), 2.82–2.87 (m, 1H), 2.25–2.28 (m, 1H), 1.52–1.72 (m, 4H), 1.22–1.32 (m, 4H), 0.75 (s, 3H), 0.43 (s, 3H); $^1C$ NMR (100 MHz, $CDCl_3$): δ 165.5 (d, *J* = 2.4 Hz), 144.1 (d, *J* = 4.6 Hz), 143.9, 140.1 (d, *J* = 10.6 Hz), 139.7, 129.8, 129.4, 128.3 (2C overlapped), 127.9 (2C overlapped), 127.8 (2C overlapped), 127.8 (4C overlapped), 127.8 (4C overlapped), 127.3 (2C overlapped), 127.2 (2C overlapped), 127.0 (2C overlapped), 114.2, 91.1 (d, *J* = 13.5 Hz), 88.4 (d, *J* = 9.2 Hz), 79.5, 78.6, 58.6 (d, *J* = 15.5 Hz), 31.1, 29.8, 27.2, 26.4, 24.4, 23.7; $^{31}P$ NMR{$^1H$} (162 MHz, $CDCl_3$): δ 10.8; HRMS (ESI-TOF) calcd. for $C_{39}H_{41}N_2O_6P$ $[M+H]^+$ *m*/*z*: 665.2781, found: 665.2787.

#### 4.2.10. Diisopropyl-[(1R,6R)-3-oxo-2,5-diazabicyclo[4.4.0]dec-4-yl-8-ene]phosphonate (5i)

Orange solid; 231 mg; 73% yield; mixture of diastereoisomers *dr* 55:45; IR (KBr): 664, 1006, 1108, 1243, 1371, 1669, 2977, 3182, 3291 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 6.63–6.45 (m, 2H), 5.66–5.60 (m, 2H), 5.59–5.52 (m, 2H), 4.93–4.70 (m, 4H), 4.00 (d, *J* = 20 Hz, 1H), 3.93 (d, *J* = 21 Hz, 1H), 3.40–3.22 (m, 3H), 2.79–2.69 (m, 1H), 2.37–1.86 (m, 10H), 1.39–1.29 (m, 24H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 166.1 (d, *J* = 3.4 Hz), 165.9, 125.4, 125.4, 123.9, 123.7, 62.5 (d, *J* = 7.1 Hz), 72.2 (d, *J* = 7.8 Hz), 72.0 (d, *J* = 7.1 Hz), 71.8 (d, *J* = 7.5 Hz), 59.4 (d, *J* = 29.5 Hz), 57.9, 54.4 (d, *J* = 14.7 Hz), 54.1, 54.0, 50.6, 31.8, 31.8, 31.2, 30.8, 24.5–23.6 (8C); $^{31}P$ NMR (162 MHz, $CDCl_3$): δ 19.9 (dt, $J_1$ = 20.6 Hz, $J_2$ = 7.5 Hz), 17.3 (dt, $J_1$ = 19.6 Hz, $J_2$ = 7.5 Hz); HRMS (ESI-TOF) calcd. for $C_{14}H_{26}N_2O_4P$ $[M+H]^+$ *m*/*z*: 317.1630, found: 317.1636.

#### 4.2.11. 4-(diphenylphosphoryl)-(1R,6R)-3-Oxo-2,5-diazabicyclo[4.4.0]dec-8-ene (5j)

Orange solid; 334 mg; 95% yield; mixture of diastereoisomers *dr* 57:43; IR (KBr): 692, 725, 753, 1122, 1174, 1375, 1437, 1683, 2851, 2928, 3105, 3206, 3336 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 8.03–8.11 (m, 4H), 7.78–7.86 (m, 4H), 7.40–7.53 (m, 12H), 6.29 (br. s, 1H, **4*S***), 6.23 (br. s, 1H, **4*R***), 5.46–5.60 (m, 4H), 4.57 (d, 1H, *J* = 13.3 Hz, **4*S***), 4.53 (d, 1H, *J* = 12.2 Hz, **4*R***), 3.15–3.26 (m, 2H), 2.99–3.01 (m, 1H, **4*R***), 2.76–2.82 (m, 1H, **4*S***), 1.84–2.35 (m, 10H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 166.6 (d, *J* = 2.3 Hz), 166.5, 132.6, 132.7, 132.6, 132.2–131.9 (6C overlapped), 131.2 (d, *J* = 80.4 Hz), 131.1 (d, *J* = 44.8 Hz), 131.0 (d, *J* = 46.0 Hz), 130.2 (d, *J* = 78.1 Hz), 128.8, 128.7, 128.5–128.1 (4C overlapped), 125.5, 125.5, 123.5, 125.4, 61.7 (d, *J* = 50.0 Hz), 60.8 (d, *J* = 81.0 Hz), 54.7 (d, *J* = 10.9 Hz), 54.1, 53.6, 51.1, 31.8, 31.7, 31.1, 30.8; $^{31}P$ NMR (162 MHz, $CDCl_3$): δ 32.2 (m, **4*S***), 28.9 (m, **4*R***); HRMS (ESI-TOF) calcd. for $C_{20}H_{22}N_2O_2P$ $[M+H]^+$ *m*/*z*: 353.1419, found: 353.1433.

#### 4.2.12. 4-(diphenylphosphoryl)-(1R,4S,6R)-3-Oxo-2,5-diazabicyclo[4.4.0]dec-8-ene (5j′) –

Orange solid; 144 mg; 43% yield; single diastereoisomer separated by crystallization of 5j, solvents ($CHCl_3$ 2.5 mL + cyclohexane 6 mL)**;** IR (KBr): 754, 1123, 1149, 1350, 1415, 1659, 2900, 3034, 3146, 3266 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 8.01–8.09 (m, 2H), 7.77–7.85 (m, 2H), 7.37–7.56 (m, 6H), 6.22 (s, 1H), 5.59–5.66 (m, 1H), 5.50–5.57 (m, 1H), 4.57 (d, 1H, *J* = 13.3 Hz), 3.22–3.24 (m, 1H), 2.74–2.83 (m, 1H), 1.84–2.35 (m, 5H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 166.6 (d, *J* = 3.4 Hz), 128.1 (d, 2C, *J* = 9.7 Hz), 132.4 (d, 2C, *J* = 9.4 Hz), 132.2 (d, *J* = 2.9 Hz), 132.1 (d, *J* = 2.6 Hz), 131.1 (d, *J* = 103.4 Hz), 130.3 (d, *J* = 101.1 Hz), 125.5, 123.5, 60.8 (d, *J* = 81.0 Hz), 54.6 (d, *J* = 10.9 Hz), 54.1, 31.7, 30.8; $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 32.2; HRMS (ESI-TOF) calcd. for $C_{20}H_{22}N_2O_2P$ $[M+H]^+$ *m*/*z*: 353.1419, found: 353.1433.

### 4.3. Synthesis of phosphonic acid 6

To the solution of imine **3a** (1.00 mmol, 152 mg, 1.00 equiv) in $CH_2Cl_2$ (15 mL) the tris(trimethylsilyl) phosphite (1.00 mmol, 0.334 mL, 1.00 equiv) was added. The resulting reaction mixture was stirred for 24 h at room temperature and subsequently the solvent was removed under reduced pressure. The resulting residue was dissolved in methanol (10 mL) and stirred for 12 h at room temperature. After that time solvent was removed under reduced pressure, and the product was purified by crystallization (abs. EtOH/$Et_2O$ 1:5 v/v) yielding the desired product as a white solid.

#### 4.3.1. [(1R,6R)-3-oxo-2,5-diazabicyclo[4.4.0]dec-4-yl]-phosphonic acid (6)

Colorless solid; 178 mg; 76% yield; mixture of diastereoisomers *dr* 70:30; IR (KBr): 932, 1068, 1191, 1346, 1453, 1668, 2942, 3419 $cm^{-1}$; $^1H$ NMR (600 MHz, $D_2O$): δ 4.10 (d, *J* = 19.2 Hz, 1H), 4.06 (d, *J* = 18.9 Hz, 1H), 3.35–3.32 (m, 1H), 3.29–3.27 (m, 1H), 3.04–2.99 (m, 1H), 2.04–2.02 (m, 1H), 1.96–85 (m, 4H), 1.71–1.69 (m, 2H), 1.63–1.60 (m, 2H), 1.43–1.18 (m, 8H); $^{13}C$ NMR (151 MHz, $D_2O$): δ 164.9 (d, *J* = 3.5 Hz), 164.5 (d, *J* = 3.4 Hz), 57.5, 54.9, 53.0 (d, *J* = 121 Hz), 30.3, 26.7, 23.5, 22.4; $^{31}P$ NMR{$^1H$} (243 MHz, $D_2O$): δ 5.3, 5.0; HRMS (ESI-TOF) calcd. for $C_8H_{16}N_2O_4P$ [M+H]+ *m*/*z*: 235.0848; found: 235.0851.

$C_8H_{16}N_2O_4P$ [M+H]+ *m*/*z*: 235.0848; found: 235.0851.

### 4.4. HWE reaction

Sodium hydride (60% dispersion in mineral oil, 1.20 mmol, 48.0 mg, 1.20 equiv) was dissolved in anhydrous THF (10 mL) under argon atmosphere. A mixture was cooled to 273 K in an ice bath and then **5a** (1.00 mmol, 262 mg, 1.00 equiv) was added. The mixture was stirred for 30 min. The aldehyde was added (1.00 mmol, 1.00 equiv) and the reaction continued for 30 min in 273 K and then for 30 min in room temperature. Reaction mixture was washed with

$Et_2O$ (20 mL) and saturated $NaHCO_3$ solution (20 mL). The organic layer was dried ($Na_2SO_4$), filtered and evaporated under reduced pressure.

#### 4.4.1. 4-(benzylidene)-[(1R,6R)-3-oxo-2,5-diazabicyclo[4.4.0] decan] (7a)

Yellow solid; 238 mg; 98% yield; a mixture of (*E*/*Z*) isomers in 1:1 ratio; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.16–7.40 (m, 10H), 6.63 (br. s, 1H), 6.55 (br. s, 1H), 6.45 (br. s, 1H), 4.49 (br. s, 1H), 4.11 (dd, $J$ = 13.45, 1.83 Hz, 1H), 3.68 (d, $J$ = 13.45 Hz, 1H), 3.22–3.29 (m, 1H), 3.03–3.09 (m, 2H), 2.83–2.90 (m, 1H), 1.75–1.90 (m, 8H), 1.27–1.47 (m, 8H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 164.5, 163.6, 158.3 (2C overlapped), 136.7, 136.3, 135.4, 129.4, 128.9 (2C overlapped), 128.5 (2C overlapped), 128.3 (2C overlapped), 126.6, 126.5, 107.5 (2C overlapped), 68.0, 56.5, 56.1, 54.3, 40.2, 31.8, 31.0, 30.3, 25.3, 23.9, 23.7, 23.6; HRMS (ESI-TOF) calcd. for $C_{15}H_{18}N_2O$ $[M+H]^+$ *m*/*z*: 243.1497, found: 243.1494.

#### 4.4.2. 4-(Pyrid-3-ylmethylene)-[(1R,6R)-3-oxo-2,5-diazabicyclo [4.4.0]decan] (7b)

Yellow solid; 237 mg; 97% yield; a mixture of (*E*/*Z*) isomers in 1:1 ratio; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.68 (d, $J$ = 2.5 Hz, 1H), 8.55 (d, $J$ = 1.8 Hz, 1H), 8.44 (dd, $J$ = 4.9, 1.8 Hz, 1H), 8.39 (dd, $J$ = 4.7, 1.8 Hz, 1H), 7.66 (t, $J$ = 1.5 Hz, 1H), 7.65 (t, $J$ = 1.5 Hz, 1H), 7.27 (ddd, $J$ = 8.0, 4.9, 0.6 Hz, 1H), 7.20 (ddd, $J$ = 8.0, 4.9, 0.9 Hz, 1H), 6.60 (br. s, 1H), 6.51 (s, 1H), 6.50 (br. s, 1H), 4.48 (s, 1H), 4.03 (d, $J$ = 14.4 Hz, 1H), 3.75 (d, $J$ = 14.1 Hz, 1H), 3.23–3.30 (m, 1H), 3.02–3.08 (m, 2H), 2.89–2.95 (m, 1H), 2.29–2.31 (m, 1H), 1.74–1.91 (m, 7H), 1.24–1.44 (m, 8H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 163.5, 163.0, 158.0, 150.5, 149.1, 147.7, 146.8, 137.3, 136.9, 135.3, 132.6, 132.5, 123.7, 123.6, 123.5, 102.9, 62.9, 56.4, 55.9, 54.4, 37.4, 31.7, 31.0, 30.3, 25.2, 23.9, 23.7, 23.6; HRMS (ESI-TOF) calcd. for $C_{14}H_{18}N_3O$ $[M+H]^+$ *m*/*z*: 244.1450, found: 244.1449.

#### 4.4.3. 4-Propyl-[(1R,6R)-3-oxo-2,5-diazabicyclo[4.4.0]dec-4-ene] (8a)

Yellow solid; 146 mg; 75% yield; mp. 108–109 °C; $[\alpha]_D^{20}$ -168 (c 0.22, $CH_2Cl_2$); IR (KBr): 1085, 1362, 1456, 1652, 1683, 2859, 2925, 3208 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): δ 6.39 (br. s, 1H), 2.95–3.15 (m, 2H), 2.58–2.66 (m, 1H), 2.41–2.48 (m, 1H), 2.27–2.31 (m, 1H), 1.75–1.87 (m, 3H), 1.54–1.73 (m, 2H), 1.22–1.41 (m, 4H), 0.93 (t, $J$ = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 165.9, 158.7, 62.5, 54.4, 35.7, 31.9, 31.1, 25.3, 23.8, 20.3, 13.9; HRMS (ESI-TOF) calcd. for $C_{11}H_{19}N_2O$ $[M+H]^+$ *m*/*z*: 195.1497, found: 195.1505.

#### 4.4.4. 4-Isobutyl-[(1R,6R)-3-oxo-2,5-diazabicyclo[4.4.0]dec-4-ene] (8b)

Yellow solid; 207 mg; 99% yield; mp. 97–99 °C; $[\alpha]_D^{20}$ -134 (c 0.32, $CH_2Cl_2$); IR (KBr): 1063, 1363, 1455, 1652, 1683, 2859, 2924, 3209 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): δ 6.47 (br. s, 1H), 3.03–3.10 (m, 2H), 2.67 (ddd, $J$ = 13.4, 7.0, 1.8 Hz, 1H), 2.30–2.32 (m, 1H), 2.21 (dd, $J$ = 13.3, 8.0 Hz, 1H), 2.03 (dq, $J$ = 6.7, 1.2 Hz, 1H), 1.33–1.44 (m, 3H), 1.27–1.44 (m, 4H), 0.92 (d, $J$ = 6.7 Hz, 3H), 0.88 (d, $J$ = 6.7 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 165.6, 158.9, 62.5, 54.5, 42.3, 31.9, 31.1, 26.7, 25.3, 23.7, 22.8, 22.3; HRMS (ESI-TOF) calcd. for $C_{12}H_{21}N_2O$ $[M+H]^+$ *m*/*z*: 209.1654, found: 209.1662.

#### 4.4.5. 4-Isopentyl-[(1R,6R)-3-oxo-2,5-diazabicyclo[4.4.0]dec-4-ene] (8c)

Yellow solid; 210 mg; 94% yield; mp. 98–101 °C; $[\alpha]_D^{20}$ -36 (c 0.22, $CH_2Cl_2$); IR (nujol): 1093, 1367, 1456, 1652, 1683, 2924, 3208 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): δ 6.00 (br. s, 1H), 3.04–3.08 (m, 2H), 2.59–2.65 (m, 1H), 2.45–2.53 (m, 1H), 2.27–2.31 (m, 1H), 1.75–1.89 (m, 3H), 1.59 (sept., $J$ = 6.72, 1H), 1.20–1.47 (m, 6H), 0.89 (d, $J$ = 6.72, 6H), $^{13}$C NMR (100 MHz, $CDCl_3$): δ 166.3, 158.9, 62.4, 54.3, 35.7, 31.8, 31.0, 29.7, 28.2, 25.3, 23.8, 22.6, 22.4; HRMS (ESI-TOF) calcd. for $C_{13}H_{23}N_2O$ $[M+H]^+$ *m*/*z*: 223.1810, found: 223.1805.

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## Appendix A. Supplementary data

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