EurJOC
European Journal of Organic Chemistry

Full Papers
doi.org/10.1002/ejoc.202100581

Chemistry Europe
European Chemical Societies Publishing

VIP *Very Important Paper*

Heteroaliphatic Dimethylphosphine Oxide Building Blocks: Synthesis and Physico-Chemical Properties

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Scalable synthesis of saturated heterocyclic dimethyl phosphine oxides (derivatives of azetidine, pyrrolidine, piperidine, and morpholine) is disclosed. The key steps of the synthesis relied on the reactions of $HP(O)Me_2$, i.e. the *phospha*-Mannich (the Kabachnik-Fields-type) condensation with cyclic imines or monoprotected diamines, palladium-catalyzed reactions of alkenyl halides or trifltates (generated from cyclic ketones), as well as base-mediated nucleophilic substitution, Michael addition, or oxirane ring opening. It was shown that introducing the $P(O)Me_2$ group into the saturated heterocyclic core had very strong impact on the compound's basicity: the corresponding α-, β-, and γ-isomeric derivatives were by ca. 4, 2, and 1.6 pK_a units less basic, respectively, as compared to the parent saturated heterocycle. Meanwhile, the $P(O)Me_2$-substituted compound was more basic than its SO_2i-Pr and SO_2NMe_2-containing isosteres (by ca. 1.2 and 0.4 pK_a units, respectively). It was also demonstrated that the $P(O)Me_2$ group typically increased the compound's hydrophilicity and aqueous solubility. In particular, the Log*P* values for the corresponding derivatives were by *ca.* 1.4–1.7 and 0.6 units lower than for the non-substituted counterpart and sulfonamide/sulfone isosteres, respectively. Finally, a potential of the synthesized building blocks to generate lead-like three-dimensional compound libraries was confirmed using the Nelson's LLAMA tool.

Introduction

Organic compounds containing phosphorus, i.e. phosphates, phosphonates, and phosphoramides, have an outstanding roles in life sciences varying from biomolecules having vital functions in living organisms to numerous commercial agricultural and pharmaceutical agents.[1–7] Meanwhile, phosphine oxides have been largely infamous as annoying by-products in organic synthesis (formed, for example, in Wittig, Appel, and Mitsunobu reactions) that are challenging to separate from the target compounds.[8] Nevertheless, this page in the $R_3P{=}O$ history was turned in 2017, when the first drug containing a phosphine oxide motif, brigatinib (used for the treatment of advanced anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer) was approved by FDA (Figure 1).[9,10] One of the key features in the successful design of this kinase inhibitor was related to hydrogen bond acceptor properties of the P=O group providing an efficient interaction with the biological target. Further studies revealed that the uncharged phosphine oxide moiety can be related to lower toxicities, improved cell permeability and oral bioavailability as compared to their more acidic organophosphorus counterparts, e.g. phosphates, phosphonates, or phosphinates charged at physiological pH.[11–13] This resulted in revision of the common medicinal chemistry filters that have been swiping out phosphine oxides. Additionally, $R_3P{=}O$ are more polar than dialkyl phosphonates, amides, or sulfonamides, being comparable to sulfoxides and

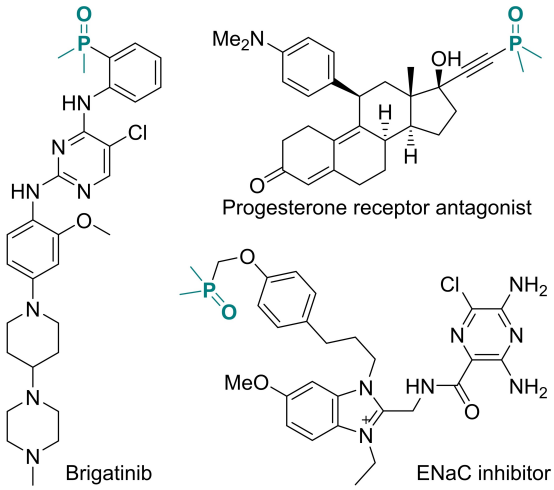

Figure 1. Pharmaceutically relevant dimethylphosphine oxides.

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejoc.202100581

sulfoximines.[14] Other fruitful physico-chemical features of phosphine oxides include higher aqueous solubility, stability upon both acidic and basic conditions, and microsomal stability in human liver.[9,14] The aforementioned favorable properties of phosphine oxides resulted in an increased interest of scientific and industrial chemists towards novel building blocks containing the dimethylphosphine moiety.

While most known compounds of this class contain the P(O)Me_2 moiety attached to the aromatic ring[15–22] or alkenes,[23–25] some examples of *sp*- and sp^3-hybridized derivatives have been studied as progesterone receptor agonist and epithelial Na^+ channel (ENaC) inhibitor, respectively (Figure 1).[26] Meanwhile, introducing the dimethylphosphine oxide fragment into low-molecular-weight saturated heterocyclic amines (such as azetidine, pyrrolidine, piperidine, or morpholine) was not explored in the literature to date. Taking into account recent interest in sp^3-enriched building blocks in early drug discovery,[27–29] in this work, we have aimed at the efficient synthesis of saturated P(O)Me_2-containing nitrogen heterocycles (Figure 2), as well as at evaluation of their physico-chemical properties in order to establish the impact of the dimethylphosphine oxide moiety on their potential to generate lead-like compound libraries.

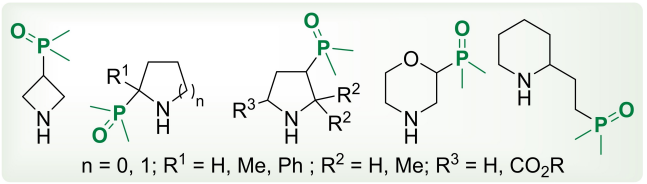


Figure 2. P(O)Me_2-substituted saturated heterocyclic amines – target compounds of this work.

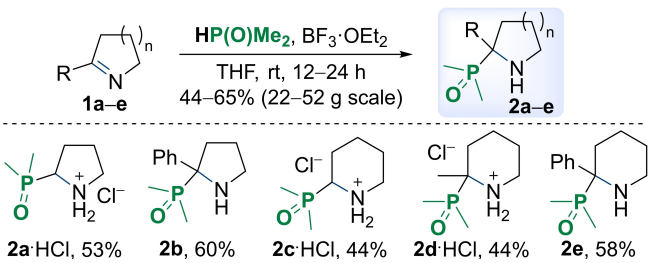
Results and Discussion

Synthesis. The known approaches to the preparation of P(O)Me_2-containing amines relied on the *phospha*-Mannich (the Kabachnik-Fields-type) reaction of the parent dimethyl phosphine oxide (HP(O)Me_2) with trimeric imines, which was used for the synthesis of two simplest acyclic (*N*-alkylaminomethyl)dimethylphosphine oxides (*i.e. N*-methyl- and *N*-benzyl).[30,31] Other literature methods involved reactions of HP(O)Me_2 with tetrasubstituted 2,5-dihydrooxazoles or 5,6-dihydro-2*H*-1,3-oxazines,[32] aromatic imines,[33,34] or dipeptide-derived aldehydes,[35] reactions of alkyl methylphosphonochloridates with the Grignard reagents,[36] as well as radical addition to the double bonds of enamides,[37] allyl amines/amides,[37,38] etc.[39]

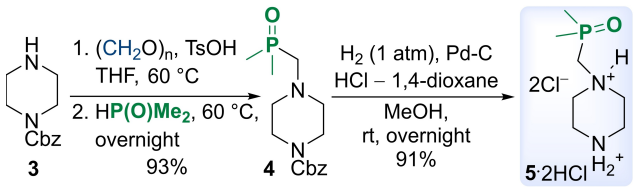
Prof. Dr. Dmitriy M. Volochnyuk got his Ph.D. (2005) and Dr.Sci. (2011) degrees from Institute of Organic Chemistry, NAS of Ukraine. At the moment, he shares his time as Head of Biologically Active Compounds Department at this institute, Professor at Taras Shevchenko National University of Kyiv, and senior scientific advisor at Enamine Ltd. Dr. Volochnyuk is an expert in organic synthesis, organofluorine, organophosphorus, heterocyclic, combinatorial, and medicinal chemistry. He is a co-author of more than 155 papers and 3 monograph chapters. Prof. Volochnyuk supervises and consults many research groups at Enamine Ltd. and Ukraininan academic institutions. This paper is a result of such collaboration with Dr. Evgeniy Y. Slobodyanyuk, Dr. Oleksandr O. Grygorenko, and their teams focusing on synthesis of advanced building blocks for drug discovery. On the photo (from left to right): Dr. Evgeniy Y. Slobodyanyuk, Prof. Dr. Dmitriy M. Volochnyuk, Olha Stotska, Dr. Oleksandr Grygorenko, and Andrii Fedyk.

Firstly, we took an advantage of the *phospha*-Mannich reaction that was tested with cyclic imines **1a**–**e** (typically existing as their trimers). Thus, refluxing of HP(O)Me_2 and trimeric **1a** in toluene gave the target product **2a** (ca. 50% by ^{1}H NMR), but its isolation and purification were complicated. Performing the same reaction with pre-mixed HP(O)Me_2 and Et_2Zn in toluene at −15 °C gave a complex mixture of products. Further optimization showed that **1a**–**e** reacted with HP(O)Me_2 in the presence of the Lewis acid ($BF_3 \cdot H_2O$), and gave 2-susbtituted pyrrolidines **2a** and **2b**, as well as piperidines **2c**–**e** in moderate to good isolated yields (44–60%, Scheme 1). Notably, the method was suitable for the preparation of more than 50 g of the target building blocks in one run. 2-Phenyl-substituted derivatives **2c** and **2e** were isolated as free bases, while products **2a**, **2b**, and **2d** were obtained as hydrochlorides.

The *phospha*-Mannich strategy was also implemented to monoprotected piperazine **3**, which reacted with paraformaldehyde and dimethylphosphine oxide in the presence of TsOH in THF at 60 °C to give *N*-Cbz-protected piperazin-1-ylmethyl derivative **4** in 93% yield (Scheme 2). Hydrogenolysis of **4** in the presence of Pd–C and HCl-1,4-dioxane in MeOH resulted in piperazine-containing dimethylphosphine oxide **5**, isolated as a dihydrochloride in 91% yield. Notably, previously reported



Scheme 1. The *phospha*-Mannich reaction of cyclic imines **1a**–**e**.



Scheme 2. Synthesis of **5**·2HCl.

methods for the preparation of similar derivatives relied on the alkylation of *N*-arylpiperazines with (chloromethyl) dimethylphosphine oxide.[40]

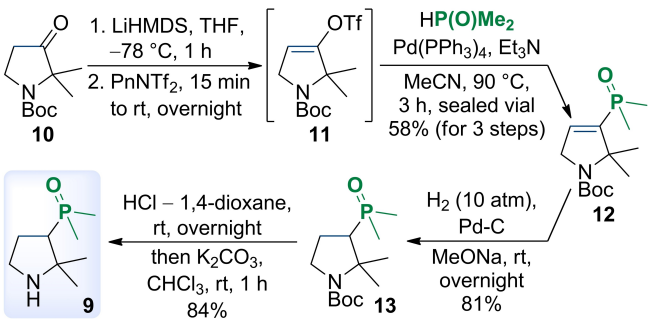
Nevertheless, it was obvious that the *phospha*-Mannich-based approach could not be easily extended for the selective preparation of other isomeric heteroaliphatic phosphine oxides; therefore, alternative synthetic sequences were designed. In particular, straightforward preparation of dimethyl(pyrrolidin-3-yl)phosphine oxide (**6**), an isomer of the product **2a** bearing no additional substituents, relied on the construction of the pyrrolidine ring by 1,3-dipolar cycloaddition of azomethyne ylides that demonstrated very good efficiency in our previous works.[41–44] For this purpose, a robust and scalable approach to the synthesis of dimethyl(vinyl)phosphine oxide (**7**) was developed, which included treatment of vinyl bromide with the parent dimethylphosphine oxide in the presence of $Pd(PPh_3)_4$ and Et_3N in MeCN (68% yield) (Scheme 3).

It should be stressed out that the known protocols for the synthesis of alkene **7** were based on β-elimination reactions[45,46] and were poorly scalable. The current method allowed for the preparation of **7** on up to 75 g scale; further studies of this valuable reagent are ongoing in our lab. Compound **7** was involved into 1,3-dipolar cycloaddition with *in situ* generated azomethine ylide for the synthesis of *N*-benzyl pyrrolidine **8** in 72% yield (Scheme 4).

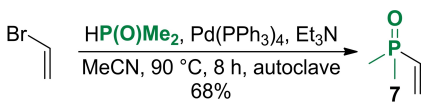
Further removal of *N*-protecting group of **8** required Pd–C-mediated hydrogenolysis in an autoclave under high pressure of H_2 (50 atm) at 50 °C; notably, the $P(O)Me_2$ moiety did not interfere with these relatively harsh conditions. The target compound was isolated from the reaction mixture as a hydrochloride **6**·HCl after work-up with HCl-1,4-dioxane (76% yield).

Synthesis of a close analog of **6**, (2,2-dimethylpyrrolidin-3-yl) dimethylphosphine oxide (**9**), commenced from ketone **10** that was transformed into the corresponding vinyl triflate **11** upon reaction with LiHDMS and then – $PhNTf_2$. Without additional purification, the derivative **11** was immediately involved in the reaction with dimethylphosphine similarly to vinyl bromide, which provided 2,5-dihydro-1*H*-pyrrole **12** in 58% yield over three steps (Scheme 5). Further reduction of the double bond in **12** was performed with H_2 (10 atm) in the presence of MeONa. *N*-Protected pyrrolidine **13** thus obtained was treated with HCl-1,4-dioxane to give pyrrolidine **9**·HCl, which was isolated as a free base in 84% yield.

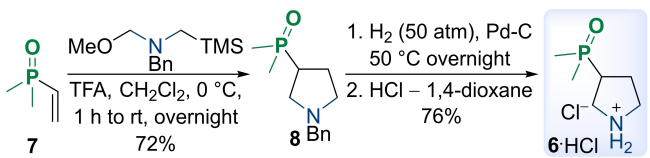
This approach was extended to 4-oxoproline derivative **14** for the preparation of proline-derived phosphine oxides **15** and **16** (Scheme 6). The reaction sequence included enolyzation-triflation of **14** into **17** followed by dimethylphosphine oxide group incorporation for the synthesis of **18** (80% yield over three steps). Further hydrogenation of **18** under mild conditions provided protected 4-$P(O)Me_2$-proline **19** in 91% yield. The *N*-



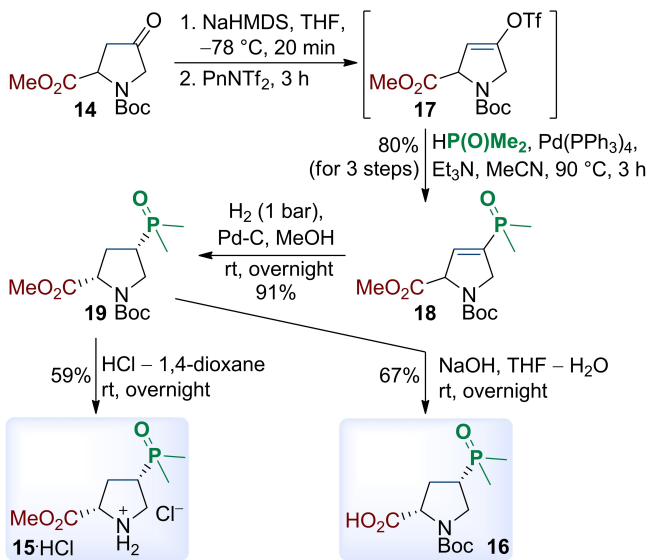
Scheme 5. Synthesis of 2,2-disubstituted pyrrolidine-3-ylphosphine oxide **9**.



Scheme 3. Synthesis of dimethyl(vinyl)phosphine oxide (**7**).



Scheme 4. 1,3-Dipolar cycloaddition approach to pyrrolidine derivative **6**·HCl.



Scheme 6. Synthesis of $P(O)Me_2$-substitited proline derivatives **15** and **16** (relative configurations are shown).

Boc group cleavage of **19** was used for the preparation of amino ester **15**·HCl (59% yield), while alkaline hydrolysis in THF-H_2O media at rt provided *N*-Boc proline **16** (67% yield). Notably, hydrogenation of **18** proceeded diastereoselectively; relative configuration of the products obtained was confirmed by NOE experiments with compounds **15**·HCl and **16** (Figure 3).

Another approach towards heteroaliphatic phosphine oxides was designed to obtain azetidine derivative. Since the corresponding vinyl triflate is challenging to be obtained, our attention turned to the reaction of alkyl halides with phosphinite nucleophile.[47] Thus, iodide **20** was used directly in the NaHMDS-mediated reaction with the $HP(O)Me_2$, which provided 3-$P(O)Me_2$ substituted derivative **21** in 48% yield (Scheme 7). Typical *N*-deprotection of **21** proceeded smoothly to give azetidin-3-yldimethylphosphine oxide (**22**·HCl) as a hydrochloride in high yield. The product **22**·HCl was obtained on up to 25 g scale in a single run.

Next, we have aimed at the preparation of morpholine-derived dimethylphosphine oxide **23**. It was envisaged that the three-atom *CCO* fragment of the morhpoline core could be introduced *via* oxirane ring opening with *N*-nucleophiles. For this purpose, hereto unknown dimethyl(oxiran-2-yl)phosphine oxide (**24**) was obtained in two steps from 2-chloroacetaldehyde (**25**) *via* an addition of $HP(O)Me_2$ to the carbonyl group providing 2-chloro-1-hydroxyethyl derivative **26** in 52% yield (Scheme 8).

Cyclization of **26** in the presence of MeONa in MeOH resulted in oxirane **24** in 85% yield. Notably, this very promising reagent was obtained on up to 70 g scale in a single run. Further steps relied on the epoxide ring opening with $BnNH_2$, followed by acylation with 2-chloroacetyl chloride in the presence of *i*-Pr_2NEt. The corresponding 2-chloro-*N*-(2-hydroxyethyl)acetamide **27** thus formed was immediately involved in the *t*-BuONa-mediated cyclization into morpholinone **28**, that was obtained in 62% yield over three steps (Scheme 9).

Amide reduction in **28** proceeded smoothly with borane (generated from $NaBH_4$ and I_2) in THF and gave *N*-benzyl morpholine **29** in 84% yield. The debenzylation of **29** was performed successfully under high pressure of H_2 (100 atm), and target morpholine **23** was obtained in 87% yield as a hydrochloride after action of HCl-1,4-dioxane.

Finally, ethylene homologue of **2c**, compound **30**, was obtained via the base-mediated Michael addition of dimethylphosphine oxide to 2-vinylpyridine (**31**), followed by catalytic hydrogenation of dimethyl(2-(pyridin-2-yl)ethyl)phosphine oxide (**32**) with H_2 (50 atm) in the presence of HOAc and treatment with HCl-1,4-dioxane, which gave piperidine **30**·HCl as a hydrochloride in 58% yield (Scheme 10).

Being inspired by the aforementioned results, we have also tested ethenesulfonyl fluoride (a good connective hub to explore the SuFFEx-type click chemistry[48]) was also tested as the Michael acceptor under analogous reaction conditions. It was successfully transformed into 2-$P(O)Me_2$-substituted ethane-1-sulfonyl fluoride **33** (68% yield), which reacted with

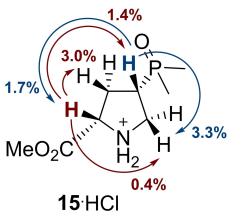
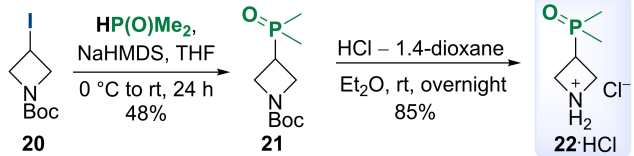
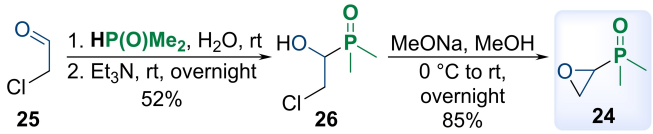


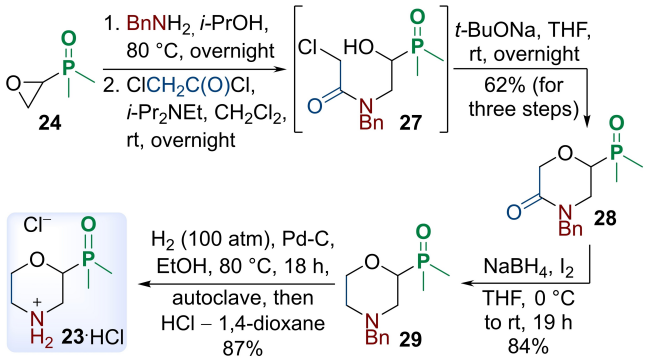
Figure 3. Significant NOEs observed for compounds **15**·HCl and **16**.



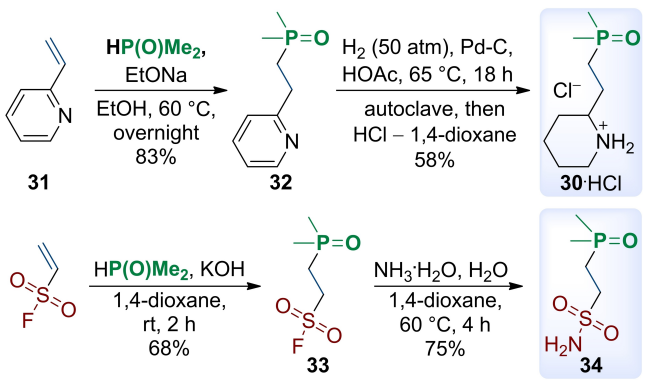
Scheme 7. An approach to azetidin-3-yldimethylphosphine oxide (**22**·HCl).



Scheme 8. Preparation of dimethyl(oxiran-2-yl)phosphine oxide (**24**).



Scheme 9. Synthesis of dimethyl(morpholin-2-yl)phosphine oxide (**23**·HCl).



Scheme 10. Synthesis of phosphine oxides **30**·HCl, **33**, and **34** via the Michael addition of $HPOMe_2$.

aq ammonia in 1,4-dioxane to give the corresponding sulfonamide **34** in 75% yield.

Physico-chemical properties. The next part of this work was devoted to evaluation of basicity (pK_a), lipophilicity (log*P*), and aqueous solubility (S_w) of P(O)Me_2-containing saturated heterocyclic amines. Isosteric sulfone **35** and sulfonamide **36** bearing SO_2*i*-Pr and SO_2NMe_2 groups, respectively, were also prepared for comparison of their physico-chemical properties to that of P(O)Me_2-substituted counterparts. The compound **35** was obtained from 3-bromopyridine (**37**) by nucleophilic substitution with *i*-PrSH–NaH, oxidation of sulfide **38** thus obtained into sulfone **39** with $RuCl_3$–$NaIO_4$, and further Pd–C-catalyzed hydrogenation with H_2 (45 atm) in aq HOAc (Scheme 11). In turn, synthesis of sulfonamide **36** relied of amination of known *N*-Cbz-protected sulfonyl chloride **40** into piperidine **41** bearing SO_2NMe_2 moiety, which was involved in hydrogenative cleave of Cbz-group to give **36**. Finally, isomeric piperidine derivatives **42** and **43** were also added to the series of compounds studied.

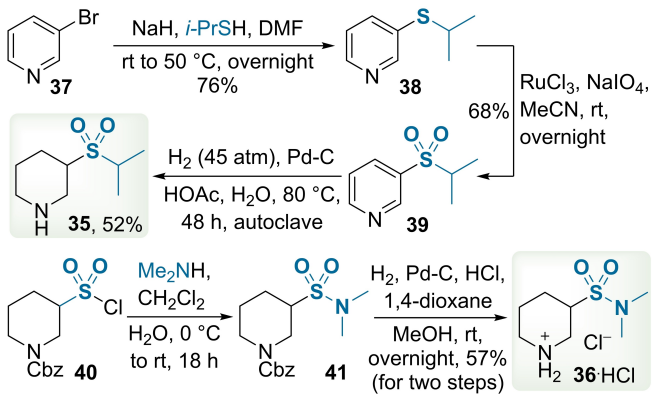
Measuring the dissociation constants revealed that introducing the dimethylphosphine oxide group into the α-position (**2a** and **2c**) decreased the values by more than 4 pK_a units as compared to the parent piperidine; the size of the ring (5- or 6-membered) showing no significant effect (Figure 4). Expectedly, moving the PO_2Me group further from the secondary amino function diminished this effect: for β-isomeric derivatives **6** and **42**, the pK_a values were by ca. 2 units lower than for piperidine, whereas for the γ-isomer – by 1.6 units.

For azeditine and morpholine derivatives **22** and **23**, the pK_a values were 8.68 and 7.13, which can be totally expected for these heterocycles. Further comparison of **42**, **35**, and **36** revealed that the P(O)Me_2 group has less pronounced effect on the basicity as compared to the SO_2*i*-Pr and SO_2NMe_2 moieties: the pK_a values for **35** and **36** were by 1.13 and 0.44 units, respectively, lower than for **42**.

To evaluate lipophilicity (Log*P*) and aqueous solubility (S_w) of the heterocycles studied in this work, *N*-benzoylated derivatives **44a–i** were synthesized from the corresponding amines **2a**, **2c**, **6**, **23**, **35**, **36**, **42**, and **43** (Scheme 12). It was found that for azetidine **44b**, pyrrolidines **44c** and **44c**, and γ-substituted piperidine **44g**, negative Log*P* values were observed. Moreover, α- and β-substituted piperidines **44e** and **44f** were also quite hydrophilic (Log*P* = 0.32 and 0.21). In all cases, the Log*P* values increased within the following series: γ < β < α. Comparison of the obtained values within the piperidine series (including parent piperidine **44a**, log*P* = 1.71) showed that introducing the P(O)Me_2 group decreased lipophilicity by 1.4–1.7 Log*P* units. This is higher than for the SO_2*i*-Pr- and SO_2NMe_2-substituted derivatives (**44h** and **44i**, respectively) by ca. 0.7 units.

Analysis of S_w values showed that over a 10-fold increase in aqueous solubility was observed for P(O)Me_2-substituted piperidines **44f** and **44g** as compared to **44a**. In this case, the substitution pattern appeared to be the most important factor since other isomers did not demonstrate such pronounced effect.

Virtual library generation. To evaluate potential of the saturated heterocyclic P(O)Me_2-substituted building blocks for exploring lead-like areas of chemical space, we have used LLAMA, an open-access computational tool developed by



Scheme 11. Synthesis of compounds **35** and **36**.

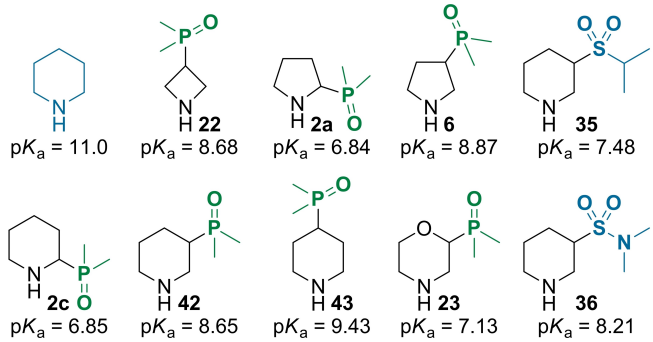
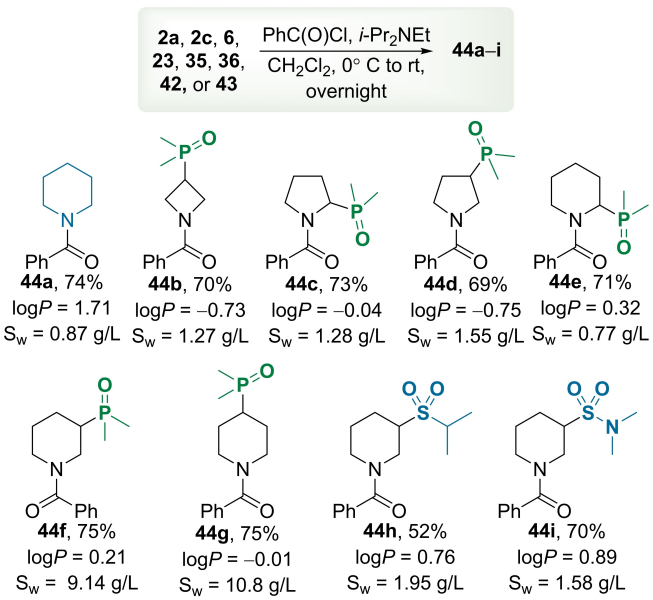


Figure 4. Dissociation constants (pK_a) of cyclic amines bearing the P(O)Me_2, SO_2*i*-Pr, or SO_2NMe_2 groups compared to that of parent piperidine.



Scheme 12. Lipophilicity (Log*P*) and aqueous solubility (S_w) of *N*-benzoyl derivatives **44**.

Nelson and co-authors.[49] Their approach relies on the so-called lead-likeness penalty (LLP), a combined measure of the compound compliance with the lead-likeness criteria chemical space based on its physico-chemical properties (*i.e.* heavy (non-hydrogen) atom count, ALog*P*, number of aromatic rings, and an undesirable functional group filter).[50] The LLP parameter has the lowest value of zero and increases as the compound violates the Churcher's lead-likeness definition.[51]

For the virtual library generation, six piperidines shown in Figure 4 (**2c**, **35**, **36**, **42**, **43**, and the parent compound) were used as the building blocks. It was found that libraries generated from the P(O)Me_2-bearing amines had somewhat higher mean lead-likeness penalty (LLP) as compared to those obtained from either **35** or **36**; nevertheless, it was substantially lower than for the case of parent piperidine derivatives (Table 1). One of the reasons behind that might be a strong penalization of library members with too low heavy (non-hydrogen) atom count by the LLP tool. All the enumerated library members fit perfectly the lead-like chemical space as defined by "rule-of-four" (MW < 400, Log*P* < 4)[52] and even partially – by far more strict Churcher's rules (MW = 200…350, Log*P* = −1…3)[51] (Figure 5, *A*). The three-dimensionality of all the four library members was similar (see Table 1 for the average Fsp^3 and plane of best fit (PBF) values), and all of them occupied similar part of the principal moment of inertia (PMI) plot illustrating the overall molecular shape (Figure 4, *B*). Expectedly, the parent piperidine derivatives lacking the *C*-substituents performed somewhat worse according to the aforementioned criteria.

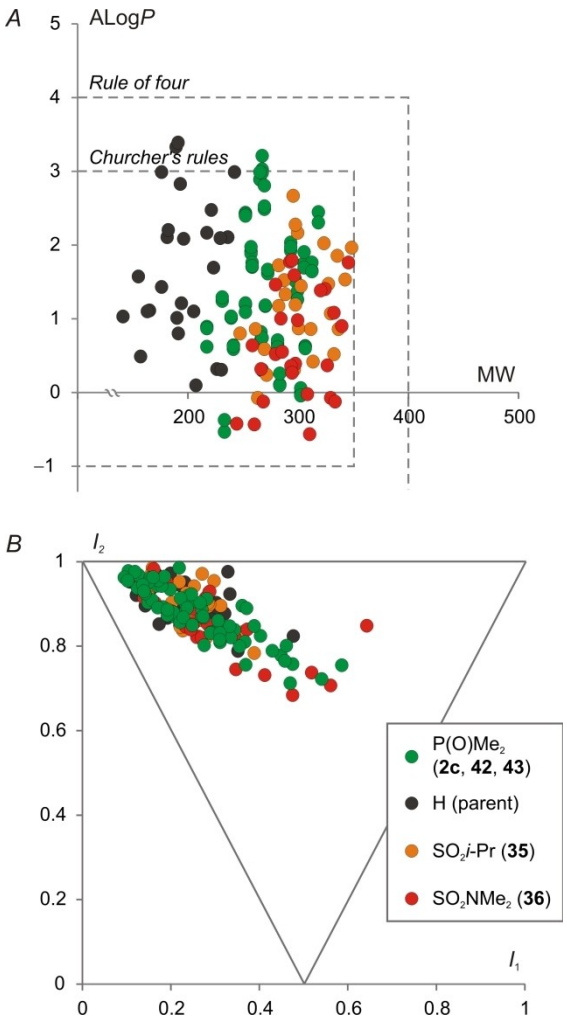


Figure 5. LLAMA-based virtual libraries generated from P(O)Me_2-containing piperidines and their analogues: (*A*) MW-ALog*P* plot; (*B*) principal moment of inertia (PMI) plot.

Conclusions

Despite the known biological activities, well-defined functions and high abundance in living organisms, organophosphorous compounds had been considered exotic for routine drug discovery until recently, which resulted in low accessibility of the simplest building blocks bearing the P(O)Me_2 group. In this work, we have disclosed several scalable synthetic approaches to saturated heterocyclic dimethylphosphine oxides, i.e. azetidine, pyrrolidine, piperidine, and morpholine derivatives.

The key steps of the reaction sequences typically relied on the reactions of HP(O)Me_2 with electrophiles, namely, the *phospha*-Mannich (the Kabachnik-Fields-type) condensation with cyclic imines or monoprotected diamines in the presence of formaldehyde, palladium-catalyzed reactions of alkenyl halides or triflates, base-mediated nucleophilic substitution in alkyl iodides, Michael addition, or oxirane ring-opening reaction as the key steps. Notably, very efficient approaches to the multigram synthesis of valuable low-molecular reagents bearing the P(O)Me_2 groups (i.e. compounds **7** and **24**) were developed as an important side result of this study, which should boost further endeavors in this area.

Table 1. LLAMA analysis of P(O)Me_2-containing saturated heterocyclic building blocks and their analogues.

Building block(s)	Library size	Lead-likeness penalty (LLP)[a]	Fsp^3 [a,b]	Plane of best fit (PBF), [Å] [a,b]
2c, **42**, and **43**	72	0.78	0.728	0.99
Piperidine	26	2.81	0.675	0.85
35	26	0.38	0.743	0.94
36	26	0.38	0.724	0.96

[a] Mean values over the corresponding libraries are given. [b] Fraction of sp^3-hybrid carbon atoms. [c] Plane of best fit, the mean atomic distance from a theoretical plane that passes through the molecule, configured in such a way as to minimize the value.

Physico-chemical properties of the saturated P(O)Me_2-containing heterocycles, as well as some isosteric derivatives thereof, were evaluated by measurement of pK_a, log*P*, and S_w values (Figure 6). It was shown that the inductive effect of dimethylphosphine oxide had a strong impact on the compound's basicity: introducing the P(O)Me_2 group into α, β, and γ positions of the heterocyclic core diminished the pK_a values by ca. 4, 2, and 1.6 units, respectively. Still, this effect was not so pronounced as for the case of SO$_2$*i*-Pr- and SO$_2$NMe_2-containing isosteres that were by 1.1 and 0.4 pK_a units less basic further. In

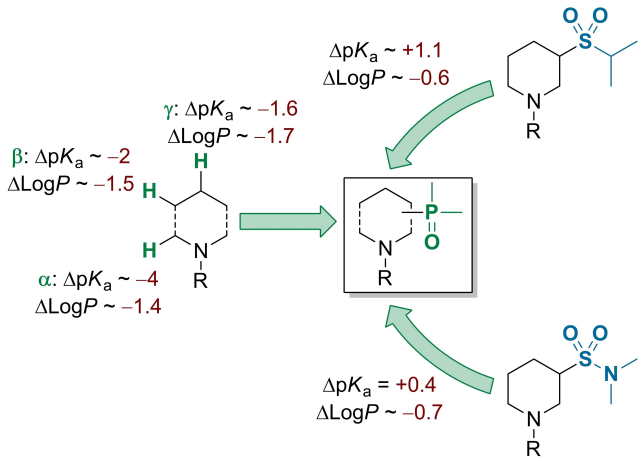


Figure 6. Physico-chemical properties of $P(O)Me_2$-containing saturated heterocycles and their analogues: a brief summary.

all cases, introducing the $P(O)Me_2$ group into the saturated heterocyclic amine scaffolds resulted in significantly increased hydrophilicity (by 1.4–1.7 Log*P* units) that decreased in the isomeric series: $\gamma > \beta > \alpha$. In some cases, significant increase of aqueous solubility was also observed (i.e. for the 3- and 4-substituted piperidine derivatives). Moreover, the $P(O)Me_2$-substituted compounds were by *ca.* 0.7 LogP units more hydrophilic than the corresponding sulfur-containing isosteres.

Generation of virtual libraries based on the $P(O)Me_2$-substituted piperidines using the Nelson's LLAMA tool showed that the title building blocks showed performance more or less similar to their SO_2i-Pr- and SO_2NMe_2-containing isosteres; all three-compound series could easily access the lead-like chemical space even according to the strictest Churcher's criteria.

Taking into account all of the above, we believe that the saturated heterocyclic dimethylphospine oxides described in this work are very promising building blocks adding a significant value to the medicinal chemists' toolbox, and they will find their application in early drug discovery in the nearest future.

Experimental Section

The solvents were purified according to the standard procedures.[53] Compounds **42** and **43** were provided by Mr. Maksym Stambirskyi; their synthesis will be published elsewhere. All other starting materials were available from Enamine Ltd. or purchased from other commercial sources. Melting points were measured on MPA100 OptiMelt automated melting point system. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^1H, $^{13}C\{^1H\}$, $^{19}F\{^1H\}$, $^{31}P\{^1H\}$ NMR spectra were recorded on a Agilent ProPulse 600 spectrometer (at 151 MHz for ^{13}C NMR), a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^1H NMR, 126 MHz for $^{13}C\{^1H\}$ NMR, 470 MHz for $^{19}F\{^1H\}$ NMR, and 202 MHz $^{31}P\{^1H\}$ NMR) and Varian Unity Plus 400 spectrometer (at 400 MHz for ^1H NMR, 101 MHz for $^{13}C\{^1H\}$ NMR, 376 MHz for ^{19}F NMR, and 162 MHz $^{31}P\{^1H\}$ NMR). NMR chemical shifts are reported in ppm (δ scale) downfield from TMS as an internal standard and are referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^1H and $^{13}C\{^1H\}$ in $CDCl_3$, 2.50 and 39.52 ppm for ^1H and $^{13}C\{^1H\}$ in DMSO-d_6. Coupling constants (*J*) are given in Hz. Spectra are reported as follows: chemical shift (δ, ppm), multiplicity, integration, coupling constants (Hz). Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Taras Shevchenko National University of Kyiv. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (CI)) and Agilent 5890 Series II 5972 GCMS instrument (electron impact ionization (EI)). High-resolution mass spectra (HRMS) were recorded on Agilent Infinity 1260 UHPLC system coupled to 6224 Accurate Mass TOF LC/MS system.

Representative procedure for the preparation of phosphine oxides 2a–e (given for 2a). $BF_3 \cdot OEt_2$ (5.43 mL, 6.24 g, 44.0 mmol) was slowly added *via* syringe at rt to a solution of the corresponding cyclic imine (15.2 g, 0.220 mol) and dimethylphosphine oxide (17.2 g, 0.220 mol) in THF (450 mL). The mixture was stirred at rt for 12–24 h. The completion of the reaction was monitored by ^1H NMR and TLC. Then, most of THF was evaporated in *vacuo*, and the residue was diluted with CH_2Cl_2 (250 mL). The resulting mixture was washed with saturated aq $NaHCO_3$ (30 mL), dried over Na_2SO_4, filtered, and evaporated in *vacuo*. For the preparation of hydrochlorides, the crude residue was dissolved in MeOH (200 mL) and 10% HCl-1,4-dioxane (150 mL) was added at rt. The solvents were evaporated, and the crude product was purified by crystallized from *t*-BuOMe (250 mL).

2-(Dimethylphosphoryl)pyrrolidin-1-ium chloride (2a). Yield 21.4 g (53% from imine **1a** (15.2 g, 0.220 mol)). Beige solid; mp 198–201 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 10.69 (s, 1H), 9.33 (s, 1H), 4.11–3.19 (m, 3H), 2.26–2.12 (m, 1H), 2.02–1.84 (m, 3H), 1.65 (d, *J* = 13.5 Hz, 3H), 1.60 (d, *J* = 13.5 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 56.1 (d, *J* = 67.9 Hz), 46.1 (d, *J* = 4.5 Hz), 25.1, 23.9, 15.1 (d, *J* = 67.5 Hz), 14.5 (d, *J* = 68.1 Hz). ^{31}P NMR (202 MHz, DMSO-d_6) δ 40.6. LC/MS (CI): *m/z* = 148 $[M+H–HCl]^+$. HRMS (ESI-TOF) *m/z:* $[M+H–HCl]^+$ calcd. for $C_6H_{15}NOP$ 148.0886, found 148.0884; $[M+Na–HCl]^+$ calcd. for $C_6H_{14}NNaOP$ 170.0705, found 170.0711.

Dimethyl(2-phenylpyrrolidin-2-yl)phosphine oxide (2b). Yield 32.6 g (60% from imine **1b** (35.3 g, 0.243 mol)). Yellowish solid; mp 92–93 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.58–7.47 (m, 2H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.28–7.22 (m, 1H), 3.15 (ddd, *J* = 11.1, 8.0, 5.5 Hz, 1H), 2.99–2.81 (m, 2H), 2.47 (tt, *J* = 12.9, 8.7 Hz, 1H), 2.41–2.29 (m, 1H), 1.97–1.81 (m, 1H), 1.64 (ddt, *J* = 13.5, 10.6, 5.2 Hz, 1H), 1.37 (d, *J* = 12.3 Hz, 3H), 1.29 (d, *J* = 12.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.8 (d, *J* = 3.4 Hz), 128.0 (d, *J* = 2.7 Hz), 126.8 (d, *J* = 3.1 Hz), 126.5 (d, *J* = 3.9 Hz), 68.1 (d, *J* = 77.9 Hz), 46.0 (d, *J* = 9.1 Hz), 33.4 (d, *J* = 3.5 Hz), 25.2 (d, *J* = 6.9 Hz), 12.3 (d, *J* = 65.8 Hz), 12.1 (d, *J* = 68.0 Hz). ^{31}P NMR (202 MHz, $CDCl_3$) δ 50.3. LC/MS (CI): *m/z* = 146 $[M+H–HP(O)Me_2]^+$. HRMS (ESI-TOF) *m/z:* $[M+H]^+$ calcd. for $C_{12}H_{19}NOP$ 224.1199, found 224.1195.

2-(Dimethylphosphoryl)piperidin-1-ium chloride (2c). Yield 18.4 g (44% from imine **1c** (17.6 g, 0.212 mol)). Yellowish solid; mp 171–174 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 9.60 (s, 1H), 9.41 (s, 1H), 3.64–3.49 (m, 2H), 2.97–2.77 (m, 1H), 2.04–1.89 (m, 1H), 1.89–1.70 (m, 3H), 1.65 (d, *J* = 6.5 Hz, 3H), 1.62 (d, *J* = 6.5 Hz, 3H), 1.61–1.30 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 54.2 (d, *J* = 67.3 Hz), 45.5 (d, *J* = 5.6 Hz), 22.6, 21.9 (d, *J* = 10.5 Hz), 21.4, 15.0 (d, *J* = 67.3 Hz), 14.0 (d, *J* = 67.8 Hz). ^{31}P NMR (202 MHz, DMSO-d_6) δ 43.1. LC/MS (CI): *m/z* = 162 $[M+H–HCl]^+$. HRMS (ESI-TOF) *m/z:* $[M+H]^+$ calcd. for $C_7H_{17}NOP$ 162.1042, found 162.1043; $[M+NH_4]^+$ calcd. for $C_7H_{20}N_2OP$ 179.1308, found 179.1308; $[M+Na]^+$ calcd. for $C_7H_{16}NNaOP$ 184.0867, found 184.0861.

2-(Dimethylphosphoryl)-2-methylpiperidin-1-ium chloride (2d). Yield 21.9 g (44% from imine **1d** (0.235 mol)). Beige solid; mp 163–

165 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.83 (s, 1H), 3.11–2.97 (m, 2H), 1.91–1.79 (m, 1H), 1.71 (d, J = 13.0 Hz, 3H), 1.69–1.62 (m, 5H), 1.59 (d, J = 13.0 Hz, 3H), 1.45 (d, J = 14.3 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 55.1 (d, J = 69.8 Hz), 39.5 (d, J = 3.6 Hz), 27.2, 21.2, 16.6 (d, J = 7.3 Hz), 14.7, 13.1 (d, J = 65.5 Hz), 12.5 (d, J = 66.1 Hz). ^{31}P NMR (202 MHz, DMSO-d_6) δ 51.7. LC/MS (CI): m/z = 98 $[M+H–HP(O)Me_2]^+$. HRMS (ESI-TOF) *m/z:* $[M+H–HCl]^+$ calcd. for $C_8H_{19}NOP$ 176.1197, found 176.1199; $[M+Na–HCl]^+$ calcd. for $C_8H_{18}NNaOP$ 198.1018, found 198.1014.

Dimethyl(2-phenylpiperidin-2-yl)phosphine oxide (2e). Yield 52.4 g (58% from imine **1e** (0.380 mol)). Yellowish solid; mp 135–136 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.60–7.45 (m, 2H), 7.39 (t, J = 7.7 Hz, 2H), 7.31–7.19 (m, 1H), 2.86–2.66 (m, 2H), 2.50–2.31 (m, 3H), 1.84 (tdd, J = 13.1, 8.3, 3.6 Hz, 1H), 1.60 (d, J = 13.1 Hz, 1H), 1.38 (p, J = 6.4, 4.9 Hz, 2H), 1.19 (d, J = 12.3 Hz, 3H), 1.14 (d, J = 12.3 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 137.3, 128.6 (d, J = 3.9 Hz), 128.1 (d, J = 2.6 Hz), 126.4 (d, J = 3.1 Hz), 60.4 (d, J = 78.7 Hz), 40.3 (d, J = 11.1 Hz), 27.8, 26.1, 19.9 (d, J = 9.8 Hz), 11.6 (d, J = 12.9 Hz), 11.1 (d, J = 11.8 Hz). ^{31}P NMR (202 MHz, DMSO-d_6) δ 48.5. LC/MS (CI): m/z = 160 $[M+H–HP(O)Me_2]^+$. HRMS (ESI-TOF) *m/z:* $[M+H]^+$ calcd. for $C_{13}H_{21}NOP$ 238.1355, found 238.1332; $[M+Na]^+$ calcd. for $C_{13}H_{20}NNaOP$ 260.1175, found 260.1175.

Benzyl 4-((dimethylphosphoryl)methyl)piperazine-1-carboxylate (4). Paraformaldehyde (6.80 g, 0.227 mol) and *p*TSA (8.06 g, 46.8 mmol) were added to a solution of benzyl piperazine-1-carboxylate (**3**, 49.9 g, 0.227 mol) in THF (500 mL), and the mixture was stirred at 60 °C for 1 h. Then, $HP(O)Me_2$ (17.7 g, 0.227 mol) was added, and the resulting mixture was stirred at 60 °C overnight. The solvent was evaporated in *vacuo*, the residue was dissolved in CH_2Cl_2 (600 mL), washed with H_2O (200 mL) and saturated aq $NaHCO_3$ (200 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and evaporated in *vacuo*. The compound was purified by column chromatography using $CHCl_3$:MeOH (10:1, v/v); R_F = 0.35. Yield 65.2 g (93%). Yellowish oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.44–7.31 (m, 4H), 7.31–7.25 (m, 1H), 5.06 (s, 2H), 3.45–3.33 (m, 4H), 2.65 (d, J = 6.9 Hz, 2H), 2.55–2.47 (m, 4H), 1.37 (d, J = 12.9 Hz, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 154.8, 137.4, 128.8, 128.2, 127.9, 79.7, 66.6, 58.4 (d, J = 83.0 Hz), 55.0 (d, J = 7.8 Hz), 44.0, 15.4 (d, J = 67.7 Hz). ^{31}P NMR (202 MHz, DMSO-d_6) δ 40.2. LC/MS (CI): m/z = 311 $[M+H]^+$. Anal. Calcd. for $C_{15}H_{23}N_2O_3P$: C 58.06; H 7.47; N 9.03. Found: C 57.70; H 7.42; N 9.41.

Mono(1-((dimethylphosphoryl)methyl)piperazine-1,4-diium) dichloride (5). Pd–C (10%, 6.00 g) and HCl-1,4dioxane (200 mL) were added to a solution of Cbz-protected amine **4** (65.15 g, 0.231 mol) in MeOH (400 mL). The resulting mixture was hydrogenated with H_2 (1 atm) at rt overnight. After the completion of absorption of H_2, the reaction mixture was filtered through Celite, and the filtrate was evaporated in *vacuo*. The compound was purified by crystallization from MeCN (150 mL). Yield 47.5 g (91%). Beige solid; mp 219–222 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 9.81 (s, 2H), 3.69–3.46 (m, 6H), 3.46–3.37 (m, 4H), 1.63 (d, J = 13.6 Hz, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 54.1 (d, J = 66.9 Hz), 50.5 (d, J = 4.6 Hz), 40.2, 16.6 (d, J = 69.4 Hz). ^{31}P NMR (202 MHz, DMSO-d_6) δ 39.1. LC/MS (CI): m/z = 177 $[M+H–2HCl]^+$. HRMS (ESI-TOF) *m/z:* $[M+H–2HCl]^+$ calcd. for $C_7H_{18}N_2OP$ 177.1151, found 177.1153; $[M+Na–2HCl]^+$ calcd. for $C_{13}H_{20}NNaOP$ 199.0971, found 199.0976.

Dimethyl(vinyl)phosphine oxide (7).[45,46] A solution of vinyl bromide (110 g, 1.03 mol), dimethylphosphine oxide (80.0 g, 1.03 mol), and $Pd(PPh_3)_4$ (23.1 g, 20.0 mol) in argon-purged MeCN (1500 mL) in an autoclave was treated with Et_3N (215 mL, 152 g, 1.50 mol) and heated at 90 °C for 8 h. Then, the reaction mixture was cooled to rt and the solvent was evaporated in *vacuo* to a half of volume. The residue was triturated with *t*-BuOMe (800 mL), the precipitate was filtered off, and the filtrate was evaporated in *vacuo*. The crude product was purified by distillation in *vacuo* (76–77 °C, 1 mbar). Yield 72.9 g (68%). Greyish solid; mp 50–51 °C. ^{1}H NMR (400 MHz,CD_3CN) δ 6.39 (ddd, J = 25.5, 19.0, 12.3 Hz, 1H), 6.23–5.94 (m, 2H), 1.46 (d, J = 13.3 Hz, 6H). ^{13}C NMR (126 MHz, CD_3CN) δ 134.4 (d, J = 91.1 Hz), 130.3, 15.9 (d, J = 72.4 Hz). ^{31}P NMR (202 MHz, CD_3CN) δ 31.1. GC/MS (EI): m/z = 104 $[M]^+$. HRMS (ESI-TOF) *m/z:* $[M+H]^+$ calcd. for $C_4H_{10}OP$ 105.0464, found 105.0469.

(1-Benzylpyrrolidin-3-yl)dimethylphosphine oxide (8). Azomethine ylide precursor (85.0 g, 0.358 mol) was added to a solution of dimethyl(vinyl)phosphine oxide (31.2 g, 0.299 mol) in CH_2Cl_2 (400 mL), and the resulting mixture was cooled to 0 °C. Then, a solution of TFA (2.30 mL, 3.42 g, 30.0 mmol) in CH_2Cl_2 (100 mL) was added dropwise at 0 °C for 1 h (NOTE: the temperature should not exceed 5 °C). The resulting mixture was stirred at rt overnight, then poured into saturated aq $NaHCO_3$ (150 mL). Organic layer was separated, dried over Na_2SO_4, filtered, and evaporated in *vacuo*. The crude product was purified by column chromatography on silica gel using $CHCl_3$:MeOH (10:1, v/v) as eluent; R_F = 0.35. Yield 51.1 g (72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.25 (m, 4H), 7.26–7.19 (m, 1H), 3.62 (s, 2H), 2.80 (q, J = 9.6 Hz, 1H), 2.74–2.53 (m, 3H), 2.40–2.33 (m, 1H), 2.16–2.04 (m, 1H), 2.02–1.91 (m, 1H), 1.44 (d, J = 8.1 Hz, 3H), 1.42 (d, J = 8.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.6, 128.6, 128.3, 127.1, 59.8, 54.0 (d, J = 4.8 Hz), 53.4, 37.9 (d, J = 73.3 Hz), 24.6 (d, J = 1.9 Hz), 14.8 (d, J = 2.2 Hz), 14.2 (d, J = 2.8 Hz). ^{31}P NMR (202 MHz, $CDCl_3$) δ 45.5. LC/MS (CI): m/z = 238 $[M+H]^+$. Anal. Calcd. for $C_{13}H_{20}NOP$: C 65.80; H 8.50; N 5.90. Found: C 66.15; H 8.35; N 6.10.

3-(Dimethylphosphoryl)pyrrolidin-1-ium chloride (6). A mixture of *N*-benzyl amine **8** (4.90 g, 20.6 mmol) and Pd–C (10%, 400 mg) in MeOH (60 mL) was hydrogenated in an autoclave with H_2 (50 atm) at 50 °C overnight. The completion of the reaction was monitored by ^{1}H NMR. Then, catalyst was filtered off, the filtrate was treated with 10% HCl–1,4-dioxane (60 mL) at rt, and the resulting mixture was evaporated in *vacuo*. The crude product was triturated MeCN (*ca.* 20 mL), and the precipitate formed was filtered and dried in *vacuo*. Yield 2.90 g (76%). Colorless solid; mp 164–167 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.81 (s, 1H), 9.58 (s, 1H), 3.48–3.40 (m, 1H), 3.27–3.18 (m, 1H), 3.16–3.01 (m, 2H), 2.58–2.50 (m, 1H), 2.20–2.09 (m, 1H), 2.01–1.86 (m, 1H), 1.45 (d, J = 13.0 Hz, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 45.0 (d, J = 9.3 Hz), 44.2 (d, J = 2.0 Hz), 37.4 (d, J = 70.9 Hz), 24.8, 15.2 (d, J = 69.1 Hz), 14.9 (d, J = 68.4 Hz). ^{31}P NMR (202 MHz, DMSO-d_6) δ 41.4. LC/MS (CI): m/z = 148 $[M+H–HCl]^+$. HRMS (ESI-TOF) *m/z:* $[M+H–HCl]^+$ calcd. for $C_6H_{15}NOP$ 148.0886, found 148.0887; $[M+NH_4–HCl]^+$ calcd. for $C_6H_{18}N_2OP$ 165.1151, found 165.1115; $[M+Na–HCl]^+$ calcd. for $C_6H_{14}NNaOP$ 170.0705, found 170.0707.

***tert*-Butyl 3-(dimethylphosphoryl)-2,2-dimethyl-2,5-dihydro-1*H*-pyrrole-1-carboxylate (12)**. 2.5 M *n*-BuLi in hexanes (214 mL, 0.535 mol) was added to a stirred solution of TMS_2NH (86.3 g, 0.535 mol) in THF (600 mL) at −30 °C, and the mixture was cooled to −78 °C. A solution of ketone **10** (95.0 g, 0.445 mol) in THF (300 mL) was slowly added at −78 °C, and the resulting mixture was stirred at −78 °C for 1 h. Then, a solution of $PnNTf_2$ (207 g, 0.579 mol) in THF (300 mL) at −78 °C, the mixture was stirred for 15 min and warmed up to rt overnight. Next, saturated aq NH_4Cl (350 mL) was added, organic layer was separated and evaporated in *vacuo*. The residue was diluted with EtOAc (1000 mL), washed with brine (300 mL), dried over Na_2SO_4, filtered, and evaporated in *vacuo*. The residue was subjected to column chromatography on silica gel using hexanes:EtOAc (12:1, v/v) as eluent (R_F = 0.45) to give a ca. 1:1 mixture of alkenyl triflate **11** and PhNHTf, which was dissolved in argon-purged MeCN (900 mL) in a sealed vial. Then, Et_3N (66.9 mL, 48.6 g, 0.480 mol), $HP(O)Me_2$ (27.9 g, 0.357 mol), and $Pd(PPh_3)_4$ (7.40 g, 64.0 mmol) were added. The resulting mixture was heated at 90 °C for 3 h, then cooled to rt, and the solvent was

evaporated in *vacuo*. The crude produce was purified by column chromatography on silica gel using gradient $CHCl_3$:MeOH (19:1 to 14:1, v/v) as eluent; $R_F = 0.20$. The compound existed as a ca. 1:1 mixture of rotamers. Yield 50.2 g (58%). Colorless solid; mp 150–152 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.35 (dd, J = 27.2, 10.9 Hz, 1H), 4.11–4.04 (m, 2H), 1.61–1.55 (m, 9H), 1.54 (d, J = 2.8 Hz, 3H), 1.42 (s, 4.5H) and 1.38 (s, 4.5H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 153.1, 152.1, 144.7 (d, J = 94.7 Hz), 134.3 (d, J = 10.1 Hz), 134.1 (d, J = 10.3 Hz), 79.3 and 78.8, 70.0 (d, J = 14.4 Hz) and 69.4 (d, J = 13.9 Hz), 54.3 (d, J = 12.9 Hz) and 54.1 (d, J = 12.9 Hz), 28.6, 26.3 and 25.3, 19.6 (d, J = 72.4 Hz), 19.5(d, J = 72.5 Hz). ^{31}P NMR (202 MHz, DMSO-d_6) δ 29.3 and 29.1. LC/MS (CI): m/z = 274 $[M+H]^+$. Anal. Calcd. for $C_{13}H_{24}NO_3P$: C 57.13; H 8.85; N 5.12. Found: C 57.49; H 9.15; N 5.06.

***tert*-Butyl 3-(dimethylphosphoryl)-2,2-dimethylpyrrolidine-1-carboxylate (13)**. A stirred solution of alkenyl dimethylphosphine oxide **12** (66.0 g, 0.242 mol) and 10% Pd–C (7.00 g) in MeOH (700 mL) was hydrogenated in an autoclave with H_2 (10 atm) at rt overnight. After the completion of absorption of H_2, the reaction mixture was filtered through Celite, and the filtrate was evaporated in *vacuo*. Yield 53.5 g (81%). Colorless solid; mp 121–122 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.48 (t, J = 9.0 Hz, 1H), 3.15 (q, J = 8.8 Hz, 1H), 2.33–2.18 (m, 1H), 1.93–1.80 (m, 2H), 1.55 (d, J = 8.6 Hz, 3H), 1.46 (d, J = 12.8 Hz, 3H), 1.44–1.27 (m, 15H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 152.8 and 152.0, 78.5 and 77.9, 62.3 and 61.8, 51.1 (d, J = 72.9 Hz) and 50.5 (d, J = 72.9 Hz), 46.5 (d, J = 15.6 Hz) and 46.3 (d, J = 15.6 Hz), 28.2, 27.9 (d, J = 141 Hz), 23.3 (d, J = 43.8 Hz), 23.6–21.4 (m), 17.4 (d, J = 68.3 Hz), 15.9 (d, J = 66.7 Hz). ^{31}P NMR (202 MHz, DMSO-d_6) δ 39.8. LC/MS (CI): m/z = 276 $[M+H]^+$. Anal. Calcd. for $C_{13}H_{26}NO_3P$: C 56.71; H 9.52; N 5.09. Found: C 57.11; H 9.12; N 5.37.

(2,2-Dimethylpyrrolidin-3-yl)dimethylphosphine oxide (9). 10% HCl-1.4-dioxane (200 mL) was added to a solution of *N*-Boc amine **13** (53.5 g, 0.196 mol) in 1.4-dioxane (200 mL), and the mixture was stirred at rt overnight. Then, the solvent was evaporated in *vacuo*, the residue was crystallized from MeCN (100 mL). Yield 33.7 g (81%) as a hydrochloride, which was then diluted with $CHCl_3$ (500 mL). K_2CO_3 (110 g, 0.797 mol) was added, and the resulting mixture was stirred at rt for 1 h. The precipitate was filtered off, washed with $CHCl_3$ (150 mL) and MeCN (100 mL), and the filtrate was evaporated in *vacuo*. Yield 23.3 g (84%). Colorless solid; mp 94–97 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.90–2.77 (m, 2H), 2.05–1.86 (m, 2H), 1.84–1.68 (m, 1H), 1.42 (d, J = 12.5 Hz, 3H), 1.35 (d, J = 12.5 Hz, 3H), 1.25 (s, 3H), 1.13 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 61.7, 49.7 (d, J = 68.3 Hz), 43.4 (d, J = 11.5 Hz), 29.3, 27.8, 24.1, 17.4 (d, J = 66.2 Hz), 16.4 (d, J = 67.2 Hz). ^{31}P NMR (202 MHz, DMSO-d_6) δ 40.6. LC/MS (CI): m/z = 176 $[M+H]^+$. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_8H_{19}NOP$ 176.1199, found 176.1198.

1-*tert*-Butyl 2-methyl 4-(dimethylphosphoryl)-1*H*-pyrrole-1,2(2*H*,5*H*)-dicarboxylate (18). 1 M NaHMDS in THF (158 mL, 0.158 mol) was added dropwise to a solution of ketone **14** (35.0 g, 0.144 mol) in THF (500 mL) at −78 °C. After 20 min, $PnNTf_2$ (53.9 g, 0.151 mol) was added at −78 °C, and the reaction mixture was stirred at −78 °C for 3 h, then quenched with saturated aq $NaHCO_3$ (350 mL) at −78 °C. The reaction mixture was extracted with EtOAc (2*350 mL), the organic layer was washed with brine (350 mL), dried over Na_2SO_4, filtered, and evaporated in *vacuo*. The crude compound was purified by flash column chromatography using hexanes:EtOAc (9:1, v/v) as eluent (R_F = 0.40) to give a ca. 1:1 mixture of alkenyl triflate **17** and PnNHTf, which was dissolved in argon-purged MeCN (500 mL) in a sealed vial. Then, Et_3N (28.5 mL, 20.7 g, 0.205 mol), $HP(O)Me_2$ (12.0 g, 0.153 mol), and $Pd(PPh_3)_4$ (7.88 g, 6.82 mmol) were added. The resulting mixture was heated at 90 °C for 3 h, then cooled to rt and the solvent was evaporated in *vacuo*. The crude product was purified by column chromatography on silica gel using $CHCl_3$:MeOH (14:1, v/v) as eluent; R_F = 0.41. The compound existed as a ca. 3:2 of rotamers. Yield 33.4 g (80%). Yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.48–6.37 (m, 0.6H) and 6.38–6.29 (m, 0.4H), 5.19–5.09 (m, 0.4H) and 5.09–5.01 (m, 0.6H), 4.43–4.28 (m, 2H), 3.70 (s, 3H), 3.42–3.37 (m, 1H), 1.62–1.53 (m, 6H), 1.43 (s, 3.6H) and 1.38 (s, 5.4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8 and 168.6, 152.9 and 152.5, 138.7 (d, J = 27.9 Hz) and 137.9 (d, J = 27.9 Hz), 135.7 (d, J = 7.0 Hz) and 134.7 (d, J = 7.7 Hz), 80.5, 67.3 (d, J = 11.8 Hz), 67.1 (d, J = 11.6 Hz), 53.3 (d, J = 16.6 Hz) and 53.2 (d, J = 17.8 Hz), 52.1 and 52.0, 27.8 and 27.7, 16.8, 16.7 (d, J = 9.7 Hz), 16.5 (d, J = 73.4 Hz) and 16.4 (d, J = 73.4 Hz) and 16.3 (d, J = 73.4 Hz). ^{31}P NMR (202 MHz, $CDCl_3$) δ 27.5 and 27.2. LC/MS (CI): m/z = 204 $[M–CO_2–(H_3C)_2C{=}CH_2 + H]^+$, 304 $[M+H]^+$. Anal. Calcd. for $C_{13}H_{22}NO_5P$: C 51.48; H 7.31; N 4.62. Found: C 51.50; H 7.09; N 4.88.

(2*S,4*S**)-1-*tert*-Butyl 2-methyl 4-(dimethylphosphoryl) pyrrolidine-1,2-dicarboxylate (19)**. A stirred solution of alkenyl dimethylphosphine oxide **18** (33.4 g, 0.110 mol) and 10% Pd–C (3.00 g) in MeOH (300 mL) was hydrogenated with H_2 (1 atm) at rt overnight. After the completion of absorption of H_2, the reaction mixture was filtered through Celite, and the filtrate was evaporated in *vacuo*. The compound was purified by column chromatography using $CHCl_3$:MeOH:Et_3N (10:1:0.1, v/v/v). The compound existed as a ca. 5:4 mixture of rotamers. Yield 30.5 g (91%). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.34 (t, J = 8.5 Hz, 0.45H), 4.28 (t, J = 8.5 Hz, 0.55H), 3.93–3.80 (m, 1H), 3.73 (s, 3H), 3.58–3.46 (m, 1H), 2.59–2.36 (m, 2H), 2.21–2.03 (m, 1H), 1.50 (d, J = 12.7 Hz, 6H), 1.45 (s, 4H), 1.40 (s, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.1, 152.8, 80.3, 58.9 (d, J = 9.0 Hz), 58.6 (d, J = 9.0 Hz), 51.8 and 51.7, 46.2, 38.1 (d, J = 72.6 Hz), 30.4 and 29.7, 27.8 and 27.7, 15.2 (d, J = 69.4 Hz) and 14.1 (d, J = 69.4 Hz). ^{31}P NMR (202 MHz, $CDCl_3$) δ 41.3 and 40.8. LC/MS (CI): m/z = 306 $[M+H]^+$. Anal. Calcd. for $C_{13}H_{24}NO_5P$: C 51.14; H 7.92; N 4.59. Found: C 51.46; H 7.61; N 4.34.

(2*S,4*S**)-4-(dimethylphosphoryl)-2-(methoxycarbonyl)pyrrolidin-1-ium chloride (15)**. 10% HCl-1.4-dioxane (100 mL) was added to a solution of *N*-Boc amine **19** (15.5 g, 50.8 mmol) in 1.4-dioxane (200 mL), and the mixture was stirred at rt overnight. Then, the solvent was evaporated in *vacuo*, the residue was crystallized from MeCN (30 mL). Yield 7.24 g (59%). Beige solid; mp 120–122 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.04 (s, 1H), 9.49 (s, 1H), 4.51–4.33 (m, 1H), 3.74 (s, 3H), 3.59–3.47 (m, 1H), 3.32–3.18 (m, 1H), 2.74–2.59 (m, 1H), 2.59–2.52 (m, 1H), 2.15–2.00 (m, 1H), 1.46 (d, J = 13.2 Hz, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 168.2, 58.8 (d, J = 10.2 Hz), 53.0, 44.8, 37.3 (d, J = 69.8 Hz), 28.7, 15.3 (d, J = 34.2 Hz), 14.7 (d, J = 35.3 Hz). ^{31}P NMR (202 MHz, DMSO-d_6) δ 40.5. LC/MS (CI): m/z = 206 $[M+H–HCl]^+$. Anal. Calcd. for $C_8H_{17}ClNO_3P$: C 39.76; H 7.09; N 5.80; Cl 14.67. Found: C 40.11; H 6.78; N 5.94; Cl 14.38. LC/MS (CI): m/z = 176 $[M+H]^+$. HRMS (ESI-TOF) m/z: $[M+H–HCl]^+$ calcd. for $C_8H_{17}NO_3P$ 206.0941, found 206.0939; $[M+Na–HCl]^+$ calcd. for $C_8H_{16}NNaO_3P$ 228.0760, found 228.0753.

(2*S,4*S**)-1-(*tert*-Butoxycarbonyl)-4-(dimethylphosphoryl) pyrrolidine-2-carboxylic acid (16)**. A solution of NaOH (2.51 g, 62.9 mmol) in H_2O (80 mL) was added to a stirred solution of ester **19** (16.0 g, 52.4 mmol) in THF (150 mL) at rt, and the resulting mixture was stirred at rt overnight. Then, 10% aq $NaHSO_4$ was added until pH = 4 was reached, solvents were evaporated in *vacuo*, the residue was triturated with MeCN (50 mL), and the precipitate was filtered off. The filtrate was evaporated in *vacuo*, the residue was triturated with Et_2O (30 mL) and filtered. The compound existed as a ca. 2:1 mixture of rotamers Yield 10.2 g (67%). Colorless solid; mp 201–202 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.74 (s, 1H), 4.10 (t, J = 8.1 Hz, 1H), 3.68 (t, J = 8.8 Hz, 1H), 3.34–3.19 (m, 1H), 2.49–2.37 (m, 2H), 1.99–1.75 (m, 1H), 1.61–1.35 (m, 9H), 1.34 (s, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 174.3 and 173.7, 153.6 and 153.3, 79.5, 59.7 (d, J = 9.5 Hz) and 59.5 (d, J = 9.1 Hz), 46.9 (d, J = 2.7 Hz) and 46.7 (d, J = 3.4 Hz), 38.6 (d, J = 71.4 Hz) and 37.9 (d, J = 71.9 Hz), 30.8 and 30.1, 28.5 and 28.3, 15.6 (d, J = 67.7 Hz) and 15.4

(d, J=67.7 Hz) and 15.3 (d, J=68.3 Hz) and 15.1 (d, J=68.3 Hz). ^{31}P NMR (202 MHz, DMSO-d_6) δ 39.6. LC/MS (CI): m/z=292 $[M+H]+$. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{12}H_{23}NO_5P$ 292.1308, found 292.1309; $[M+Na]^+$ calcd. for $C_{12}H_{22}NNaO_5P$ 314.1128, found 314.1129.

***tert*-Butyl 3-(dimethylphosphoryl)azetidine-1-carboxylate (21)**. A solution of $HP(O)Me_2$ (54.6 g, 0.700 mol) in THF (600 mL) was cooled to 0 °C, and NaHMDS (2 M in THF, 350 mL, 0.700 mol) was added dropwise under Argon atmosphere. The resulting mixture was stirred at rt for 1 h, then cooled to 0 °C, and *tert*-butyl 3-iodoazetidine-1-carboxylate (**20**, 100 g, 0.353 mol) was added. After stirring at rt for 24 h, the reaction mixture was evaporated in *vacuo*, the residue was triturated with EtOAc (800 mL), the precipitate was filtered off, and the filtrate was evaporated in *vacuo*. The crude produce was purified by column chromatography on silica gel using $CHCl_3$:MeOH (10:1, v/v) as eluent; R_F=0.28. Yield 39.2 g (48%). Colorless solid; mp 131–132 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.08 (dt, J=13.1, 9.0 Hz, 2H), 4.03–3.92 (m, 2H), 2.74 (dddd, J=15.5, 9.7, 6.0, 3.9 Hz, 1H), 1.44 (d, J=12.5 Hz, 6H), 1.36 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.8 (d, J=2.1 Hz), 80.0, 48.7, 28.3 (d, J=73.2 Hz), 28.2, 13.7 (d, J=69.8 Hz). ^{31}P NMR (202 MHz, $CDCl_3$) δ 41.8. LC/MS (CI): m/z=178 $[M–(H_3C)_2C{=}CH_2+H]^+$. Anal. Calcd. for $C_{10}H_{20}NO_3P$: C 51.49; H 8.64; N 6.01. Found: C 51.20; H 8.56; N 5.87.

3-(Dimethylphosphoryl)azetidin-1-ium chloride (22). 10% HCl-1,4-dioxane (180 mL) was added to a solution of *N*-Boc amine **21** (39.2 g, 0.17 mol) in Et_2O (200 mL), and the mixture was stirred at rt overnight. Then, the solvent was evaporated in *vacuo* and the residue was crystallized from MeCN (50 mL). Yield 24.5 g (85%). Colorless solid; mp 139–142 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.00 (s, 1H), 9.31 (s, 1H), 4.15–3.93 (m, 4H), 3.25 (p, J=9.3 Hz, 1H), 1.43 (d, J=13.3 Hz, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 44.4 (d, J=4.1 Hz), 30.8 (d, J=71.1 Hz), 14.3 (d, J=68.4 Hz). ^{31}P NMR (202 MHz, DMSO-d_6) δ 40.2. LC/MS (CI): m/z=134 $[M+H–HCl]^+$. HRMS (ESI-TOF) m/z: $[M+H–HCl]^+$ calcd. for $C_5H_{13}NOP$ 134.0729, found 134.0732; $[M+NH_4–HCl]^+$ calcd. for $C_5H_{16}N_2OP$ 151.0995, found 151.0991; $[M+Na–HCl]^+$ calcd. for $C_5H_{12}NNaOP$ 156.0554, found 156.0555.

(2-Chloro-1-hydroxyethyl)dimethylphosphine oxide (26). Chloroacetaldehyde (45% in H_2O, 225 mL, 1.28 mol) was added to $HP(O)Me_2$ (100 g, 1.28 mol) at 15 °C. The resulting mixture was stirred at rt for 1 h, and Et_3N (8.93 mL, 6.50 g, 64.2 mmol) was added. The reaction mixture was stirred at rt overnight, the completion of the reaction was monitored by ^{1}H and ^{31}P NMR until no starting material was observed. Then, the mixture was re-evaporated three times in *vacuo* with MeCN (500 mL), the residue was dried in *vacuo* and triturated with *t*-BuOMe (600 mL) and MeCN (100 mL), then filtered and dried in *vacuo*. Yield 105 g (52%). Colorless solid; mp 126–127 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.01 (s, 1H), 4.10–3.88 (m, 2H), 3.67 (ddd, J=11.5, 8.9, 5.7 Hz, 1H), 1.53 (d, J=13.0 Hz, 3H), 1.47 (d, J=13.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 70.0 (d, J=83.1 Hz), 44.6 (d, J=10.2 Hz), 13.9 (d, J=67.6 Hz), 11.6 (d, J=66.0 Hz). ^{31}P NMR (202 MHz, $CDCl_3$) δ 50.0. LC/MS (CI): m/z=157/159 $[M+Hl]^+$. Anal. Calcd. for $C_4H_{10}ClO_2P$: C 30.69; H 6.44; Cl 22.64. Found: C 30.63; H 6.23; Cl 22.60.

Dimethyl(oxiran-2-yl)phosphine oxide (24). Na (15.3 g, 0.667 mol) was carefully added in MeOH (600 mL), and the resulting solution was cooled to 0 °C. Then, a solution of hydroxyalcohol (105 g, 0.667 mol) in MeOH (300 mL) was added dropwise. The resulting mixture was warmed up to rt, and stirred overnight. The solvent was evaporated in *vacuo*, the residue was triturated with EtOAc (100 mL). The precipitate was filtered off, washed with EtOAc (200 mL), and the solvent was evaporated in *vacuo*. The crude produce was purified by column chromatography on silica gel using $CHCl_3$:MeOH (10:1, v/v) as eluent; R_F=0.35. Yield 68.1 g (85%). Colorless solid; mp 69–70 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.04–2.82 (m, 3H), 1.50 (d, J=13.2 Hz, 3H), 1.37 (d, J=13.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 48.0 (d, J=98.8 Hz), 44.7 (d, J=2.0 Hz), 15.0 (d, J=70.7 Hz), 12.7 (d, J=72.0 Hz). ^{31}P NMR (202 MHz, $CDCl_3$) δ 39.3. GC/MS (EI): m/z=120 $[M]^+$. Anal. Calcd. for $C_4H_9O_2P$: C 40.01; H 7.55. Found: C 39.99; H 7.25.

4-Benzyl-6-(dimethylphosphoryl)morpholin-3-one (28). Oxirane **24** (60.0 g, 0.500 mol) was dissolved in *i*-PrOH (300 mL), and $BnNH_2$ (53.5 g, 0.500 mol) was added. The resulting mixture was stirred at 80 °C overnight, then cooled to rt, and evaporated in *vacuo*. The residue was dissolved in CH_2Cl_2 (1000 mL), then chloroacetyl chloride (46.0 g, 0.407 mol) and *i*-$PrNEt_2$ (59.1 g, 0.457 mol) were added dropwise at 0 °C. The mixture was stirred at rt overnight, then diluted with H_2O (250 ml). Organic layer was washed with saturated aq $NaHCO_3$ (100 mL), brine (100 ml), dried over Na_2SO_4, and evaporated in *vacuo*. Amide **27** was dissolved in THF (1000 mL), the solution was cooled to 0 °C, and *t*-BuONa (32.1 g, 0.334 mol) was added in portions. The reaction mixture was stirred at rt overnight, the precipitate formed was filtered off and the filtrate was evaporated in *vacuo*. Analytical sample was obtained by crystallization from *t*-BuOMe. Yield 81.2 g (91%). Colorless solid; mp 102–103 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.20 (m, 5H), 4.71 (d, J=14.5 Hz, 1H), 4.48 (d, J=14.6 Hz, 1H), 4.34 (dd, J=16.5, 2.1 Hz, 1H), 4.20 (d, J=16.4 Hz, 1H), 3.96 (ddd, J=11.6, 7.4, 4.3 Hz, 1H), 3.55–3.40 (m, 2H), 1.53 (d, J=13.3 Hz, 3H), 1.44 (d, J=13.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.1, 135.1, 128.4, 127.9, 127.5, 71.1 (d, J=86.4 Hz), 68.2 (d, J=12.1 Hz), 49.3, 44.3 (d, J=5.6 Hz), 14.1 (d, J=70.1 Hz), 11.2 (d, J=68.6 Hz). ^{31}P NMR (202 MHz, $CDCl_3$) δ 44.8. LC/MS (CI): m/z=268 $[M+H]^+$. Anal. Calcd. for $C_{13}H_{18}NO_3P$: C 58.42; H 6.79; N 5.24. Found: C 58.75; H 6.44; N 5.45.

(4-Benzylmorpholin-2-yl)dimethylphosphine oxide (29). A solution of I_2 (92.5 g, 0.364 mol) in THF (150 mL) was added slowly at 0 °C to a solution of $NaBH_4$ (27.8 g, 0.735 mol) in THF (600 mL) The resulting solution was stirred at rt for 1 h, and a solution of morpholinone **28** (81.2 g, 0.304 mol) in THF (200 mL) was added dropwise at 10 °C. The resulting mixture was stirred at rt for 18 h, and MeOH (150 mL) was added dropwise at rt. The solvent was evaporated in *vacuo*, and the residue was diluted with saturated aq $NaHCO_3$ (80 mL) and $CHCl_3$ (500 mL). The organic layer was separated, the aqueous layer was extracted with $CHCl_3$ (4×150 mL). Combined organic extracts were dried over Na_2SO_4, filtered, and evaporated in *vacuo*. Yield 62.7 g (84%). Colorless solid; mp 124–125 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46–7.20 (m, 4H), 7.21–7.12 (m, 1H), 3.91–3.73 (m, 2H), 3.61 (td, J=11.3, 2.4 Hz, 1H), 3.49 (dd, J=13.5, 13.0 Hz, 2H), 3.10 (dt, J=11.5, 2.2 Hz, 1H), 2.64 (dt, J=11.8, 2.0 Hz, 1H), 2.24–2.03 (m, 2H), 1.45 (d, J=13.1 Hz, 3H), 1.42 (d, J=13.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.1, 129.0, 128.3, 127.3, 74.3 (d, J=89.7 Hz), 68.1 (d, J=11.5 Hz), 63.2, 52.8, 51.9 (d, J=3.8 Hz), 14.3 (d, J=68.8 Hz), 12.2 (d, J=67.6 Hz). ^{31}P NMR (202 MHz, $CDCl_3$) δ 44.1. LC/MS (CI): m/z=254 $[M+H]^+$. Anal. Calcd. for $C_{13}H_{20}NO_2P$: C 61.65; H 7.96; N 5.53. Found: C 61.75; H 7.94; N 5.17.

2-(Dimethylphosphoryl)morpholin-4-ium chloride (23). A solution of *N*-benzyl amine **29** (62.7 g, 0.256 mol) in EtOH (400 mL), and Pd–C (10%, 20.0 g) were placed in an autoclave. The mixture was hydrogenated with H_2 (100 atm) at 80 °C for 18 h. Then, the catalyst was filtered off, the filtrate was evaporated in *vacuo*, and HCl-1,4-dioxane (350 mL) was added to the residue. The resulting mixture was evaporated in *vacuo*, the residue was diluted with MeCN (30 mL) and *t*-BuOMe (300 mL). The product crystallized after vigorous stirring for 2 h and filtration. Yield 43.1 g (87%). Colorless solid, mp 165–167 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.96 (s, 1H), 9.89 (s, 1H), 4.14 (ddd, J=12.3, 6.4, 2.4 Hz, 1H), 4.02 (dd, J=12.5, 3.7 Hz, 1H), 3.85 (td, J=12.3, 2.4 Hz, 1H), 3.45–3.33 (m, 1H), 3.25–3.16 (m, 1H), 3.16–2.93 (m, 2H), 1.48 (s, 3H), 1.44 (d, J=11.4 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 71.3 (d, J=84.3 Hz), 64.2 (d, J=

10.2 Hz), 42.1, 41.4 (d, J = 5.6 Hz), 13.9 (d, J = 68.6 Hz), 12.2 (d, J = 68.3 Hz). ^{31}P NMR (202 MHz, DMSO-d_6) δ 41.6. LC/MS (CI): m/z = 164 [M–HCl + H]$^+$. HRMS (ESI-TOF) m/z: [M + H–HCl]$^+$ calcd. for $C_6H_{15}NO_2P$ 164.0835, found 164.0838; [2 M + Na–2HCl]$^+$ calcd. for $C_{12}H_{28}N_2NaO_4P_2$ 349.1422, found 349.1433.

Dimethyl(2-(pyridin-2-yl)ethyl)phosphine oxide (32). Na (10.9 g, 0.476 mol) was carefully added in EtOH (200 mL), and the resulting solution was added dropwise to a mixture of 2-vinylpyridine (**31**, 50.0 g, 0.476 mol) and HP(O)Me$_2$ (37.1 g, 0.476 mol) in EtOH (400 mL). After 15 min, the mixture was warmed up to 70 °C, then was stirred at 60 °C overnight. The solvent was evaporated in *vacuo*, the residue was partitioned between H_2O (100 mL) and EtOAc (400 mL). The organic layer was separated, aqueous phase was extracted with EtOAc (4×200 mL). Combined organic layers were dried over Na_2SO_4, filtered, and evaporated in *vacuo*. Analitical sample was obtained by column chromatography on silica gel using $CHCl_3$:MeOH (10:1, v/v) as eluent; R_F = 0.34. Yield 72.3 g (83 %) ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52–8.43 (m, 1H), 7.71 (td, J = 7.7, 1.7 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.26–7.18 (m, 1H), 3.02–2.85 (m, 2H), 2.17–1.99 (m, 2H), 1.37 (d, J = 12.9 Hz, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.6 (d, J = 13.9 Hz), 149.0, 136.6, 122.7, 121.5, 30.6 (d, J = 67.6 Hz), 29.6 (d, J = 2.9 Hz), 16. 1 (d, J = 67.2 Hz). ^{31}P NMR (202 MHz, DMSO-d_6) δ 40.5. LC/MS (CI): m/z = 184 [M + H]$^+$. Anal. Calcd. for $C_9H_{14}NOP$: C 59.01; H 7.70; N 7.65. Found: C 58.66; H 7.82; N 8.00.

2-(2-(Dimethylphosphoryl)ethyl)piperidin-1-ium chloride (30). A mixture of pyridine **32** (80.0 g, 0.437 mol) and Pd–C (10 %, 8.00 g) in HOAc (600 mL) was placed in an autoclave. The mixture was hydrogenated with H_2 (50 atm) at 65 °C for 18 h. The catalyst was filtered off, and filtrate was evaporated in *vacuo* to dryness. Then, 5 M aq NaOH (200 mL) was carefully added at 0 °C to the residue until pH = 12 was reached, and the product was extracted with CH_2Cl_2 (5×300 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated in *vacuo*. The residue was dissolved in MeCN (200 mL), cooled to 0 °C, and 10 % HCl-1.4-dioxane (180 mL) was added. The resulting mixture was stirred for 30 min, the precipitate formed was filtered and dried in *vacuo*. Yield 57.0 g (58 %). Colorless solid; mp 143–144 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.40–9.00 (m, 2H), 3.20 (d, J = 12.8 Hz, 1H), 3.10–2.95 (m, 1H), 2.85–2.73 (m, 1H), 2.04–1.52 (m, 8H), 1.45 (d, J = 3.8 Hz, 3H), 1.42 (d, J = 3.7 Hz, 3H), 1.41–1.22 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 56.1, 56.0, 43.6, 27.4, 26.2 (d, J = 67.5 Hz), 25.2, 21.7 (d, J = 11.6 Hz), 15.3 (d, J = 68.9 Hz), 15.1 (d, J = 68.9 Hz). ^{31}P NMR (202 MHz, DMSO-d_6) δ 55.1. LC/MS (CI): m/z = 190 [M + H–HCl]$^+$. HRMS (ESI-TOF) m/z: [M + H–HCl]$^+$ calcd. for $C_9H_{21}NOP$ 190.1355, found 190.1355; [M + Na–HCl]$^+$ calcd. for $C_9H_{20}NNaOP$ 212.1175, found 212.1163.

2-(Dimethylphosphoryl)ethanesulfonyl fluoride (33). Ethenesulfonyl fluoride (58.0 g, 0.527 mol), HP(O)Me$_2$ (41.1 g, 0.527 mol) and KOH (7.39 g, 0.132 mol) were dissolved in 1,4-dioxane (500 mL). The mixture was stirred at rt for 2 h, then the solvent was evaporated in *vacuo*, and the residue was crystalized with *t*-BuOMe:MeCN (1:1, v/v, 150 mL). Yield 67.4 g (68 %). Colorless solid; mp 132–133 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80–3.62 (m, 2H), 2.30 (ddt, J = 11.6, 8.9, 4.4 Hz, 2H), 1.60 (d, J = 12.8 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 44.0 (d, J = 19.7 Hz), 25.1 (d, J = 63.6 Hz), 16.2 (d, J = 70.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ 51.7. ^{31}P NMR (202 MHz, $CDCl_3$) δ 39.2. LC/MS (CI): m/z = 189 [M + H–HCl]$^+$. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd. for $C_4H_{11}FO_3PS$ 189.0145, found 189.0145; [M + NH$_4$]$^+$ calcd. for $C_4H_{14}FNO_3PS$ 206.0411, found 206.0411; [M + Na]$^+$ calcd. for $C_4H_{10}FNaO_3PS$ 210.9965, found 210.9964.

2-(Dimethylphosphoryl)ethanesulfonamide (34). Sulfonyl fluoride (26.0 g, 0.138 mol) was dissolved in 1,4-dioxane (300 mL), and 25 % aq $NH_3 \cdot H_2O$ (98.0 mL, 0.691 mol) was added. The reaction mixture was stirred at 60 °C for 4 h, then the solvent was evaporated in *vacuo*, and the residue was crystalized from hot EtOH (20 mL). Yield (19.2 g, 75 %). Yellowish crystals; mp 213–215 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.72 (s, 2H), 3.19–3.10 (m, 2H), 2.09 (ddt, J = 12.5, 8.9, 4.5 Hz, 2H), 1.44 (d, J = 13.2 Hz, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 47.8 (d, J = 1.8 Hz), 25.8 (d, J = 65.0 Hz), 15.9 (d, J = 68.2 Hz). ^{31}P NMR (202 MHz, DMSO-d_6) δ 40.0. LC/MS (CI): m/z = 186 [M + H]$^+$. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd. for $C_4H_{13}NO_3PS$ 186.0348, found 186.0348; [M + Na]$^+$ calcd. for $C_4H_{12}NNaO_3PS$ 208.0168, found 208.0165.

3-(Isopropylthio)pyridine (38). *i*-PrSH (2.05 g, 26.9 mmol) was added to a suspension of NaH (60 %, 1.08 g 26.9 mmol) in DMF (20 mL), and the resulting mixture was stirred at rt for 1 h. Then, 3-bromopyridine (**37**, 2.13 g, 13.5 mmol) was added, the reaction mixture was stirred at 50 °C overnight, then cooled to rt, and poured into saturated aq NH_4Cl (25 mL). The mixture was diluted with EtOAc (30 mL), organic phase was separated, washed with H_2O (3×15 mL), brine (10 mL), dried over Na_2SO_4, filtered, and evaporated in *vacuo*. The crude produce was purified by column chromatography on silica gel using *t*-BuOMe:MeOH (60:1, v/v) as eluent; R_F = 0.40. Yield 1.58 g (76 %); yellowish liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (d, J = 2.3 Hz, 1H), 8.36 (dd, J = 4.8, 1.7 Hz, 1H), 7.60 (dt, J = 8.0, 2.0 Hz, 1H), 7.12 (dd, J = 7.9, 4.8 Hz, 1H), 3.26 (sept, J = 6.7 Hz, 1H), 1.19 (d, J = 6.8 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.1, 147.3, 139.1, 131.9, 123.0, 38.0, 22.6. LC/MS (CI): m/z = 154 [M + H]$^+$. Anal. Calcd. for $C_8H_{11}NS$: C 62.7; H 7.24; N 9.14; S 20.92. Found: C 63.07; H 7.20; N 9.47; S 20.99.

3-(Isopropylsulfonyl)pyridine (39). Sulfide **38** (1.58 g, 10.3 mmol), was dissolved in MeCN:H_2O (1:1, v/v, 20 mL), then $NaIO_4$ (4.62 g, 21.6 mmol) and $RuCl_3$ (104 mg, 0.515 mmol) were added. The reaction mixture was stirred at rt overnight, the precipitate was filtered off and washed with EtOAc (3×15 mL). The filtrate was washed with H_2O (2×10 mL), brine (10 mL), dried over Na_2SO_4, filtered, and evaporated in *vacuo*. The crude produce was purified by column chromatography on silica gel using hexane:EtOAc (1:2, v/v) as eluent; R_F = 0.30. Yield 1.29 g (67 %). Yellowish oil. ^{1}H NMR (500 MHz, CD_3CN) δ 8.99 (d, J = 2.5 Hz, 1H), 8.85 (dd, J = 4.9, 1.9 Hz, 1H), 8.20–8.13 (m, 1H), 7.58 (dd, J = 8.1, 4.8 Hz, 1H), 3.31 (sept, J = 6.9 Hz, 1H), 1.21 (d, J = 6.8 Hz, 6H). ^{13}C NMR (126 MHz, CD_3CN) δ 153.8, 149.0, 136.4, 133.1, 123.6, 116.9. LC/MS (CI): m/z = 186 [M + H]$^+$. Anal. Calcd. for $C_8H_{11}NO_2S$: C 51.87; H 5.99; N 7.56; S 17.31. Found: C 52.23; H 5.88; N 7.43; S 17.08.

3-(Isopropylsulfonyl)piperidine (35). Pyridine **39** (1.00 g, 5.40 mmol) and Pd–C (10 %, 300 mg) were mixed HOAc (40 mL) in an autoclave. The mixture was hydrogenated with H_2 (45 atm) at 80 °C for 48 h. The catalyst was filtered off, and filtrate was evaporated in *vacuo* to dryness. The residue was diluted with saturated aq $NaHCO_3$ (30 mL), and extracted with CH_2Cl_2 (6×10 mL). Combined organic layers were dried over Na_2SO_4, filtered, and evaporated in *vacuo*. The crude produce was purified by column chromatography on silica gel using $CHCl_3$:MeOH:Et_3N (10:1:0.1, v/v/v) as eluent; R_F = 0.35. Yield 537 mg (52 %). Yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.38–3.27 (m, 1H), 3.23–3.00 (m, 2H), 3.00–2.90 (m, 1H), 2.87 (t, J = 11.2 Hz, 1H), 2.56 (t, J = 11.6 Hz, 1H), 2.16–2.04 (m, 1H), 1.93 (s, 1H), 1.86–1.70 (m, 2H), 1.52–1.41 (m, 1H), 1.31 (d, J = 6.8 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 55.5, 50.1, 45.8, 45.1, 25.2, 23.6, 15.0, 14.9. LC/MS (CI): m/z = 192 [M + H]$^+$. Anal. Calcd. for $C_8H_{17}NO_2S$: C 50.23; H 8.96; N 7.32; S 16.76. Found: C 50.42; H 8.81; N 7.02; S 16.76.

3-(*N*,*N*-dimethylsulfamoyl)piperidin-1-ium chloride (36). 40 % aq Me_2NH (1.80 mL) was added at 0 °C to a solution of **40** (1.00 g, 3.15 mmol) in CH_2Cl_2 (15 mL). The reaction mixture was stirred at rt for 18 h, then washed with H_2O (15 mL), dried over Na_2SO_4, filtered, and evaporated in *vacuo*. Cbz-protected amine **41** thus obtained was dissolved in MeOH (10 mL), then Pd–C (10 %, 100 mg), and

HCl-1,4-dioxane (2.0 mL) were added. The resulting mixture was hydrogenated with H_2 (1 atm) at rt overnight, then filtered through Celite, and the filtrate was evaporated in *vacuo*. The residue was crystallized from MeCN (2 mL). Yield 409 mg (57%). Colorless solid; mp 181–183 °C. ^{1}H NMR (400 MHz, D_2O) δ 4.66 (s, 2H), 3.71–3.50 (m, 2H), 3.27 (dt, *J* = 12.7, 3.9 Hz, 1H), 3.19–3.07 (m, 1H), 2.91 (td, *J* = 12.3, 3.3 Hz, 1H), 2.83 (s, 6H), 2.20–2.06 (m, 1H), 2.06–1.92 (m, 1H), 1.88–1.56 (m, 2H). ^{13}C NMR (126 MHz, D_2O) δ 54.2, 43.5, 42.5, 37.0, 22.5, 20.3. LC/MS (CI): *m/z* = 193 $[M+H-HCl]^+$. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_7H_{17}N_2O_2S$ 193.1005, found 193.1007.

General procedure for benzoylation. *i*-$PrNEt_2$ (1.2 mmol or 1.76 mmol for hydrochlorides of amines) and PhCOCl (123 mg, 0.880 mmol) were slowly added at 0 °C to a stirred solution of the corresponding amine (0.800 mmol) in CH_2Cl_2 (8 mL). The mixture was stirred at rt overnight, then the solvent was evaporated in *vacuo*. The crude product was purified by flash column chromatography on silica gel using $CHCl_3$:MeOH (14:1 to 10:1, v/v).

Phenyl(piperidin-1-yl)methanone (44a). The crude product was purified by flash column chromatography on silica gel using $CHCl_3$:MeOH (45:1, v/v). Yield 113 mg (75%). Spectral and physical data were analogous to that of reported.[54,55] ^{1}H NMR (400 MHz, CD_3CN) δ 7.46–7.35 (m, 5H), 3.64 (s, 2H), 3.28 (s, 2H), 1.70–1.52 (m, 4H), 1.52–1.36 (m, 2H). ^{13}C NMR (126 MHz, CD_3CN) δ 170.9, 138.5, 130.6, 129.8, 128.1, 49.7, 44.0, 27.6, 26.9, 25.8.

(3-(Dimethylphosphoryl)azetidin-1-yl)(phenyl)methanone (44b). The compound existed as a ca. 1:1 mixture of rotamers. Yield 132 mg (70%). Colorless solid; mp 121–123 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.5 Hz, 2H), 7.47 (t, *J* = 7.2 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 2H), 4.59–4.37 (m, 3H), 4.36–4.23 (m, 1H), 3.01–2.90 (m, 1H), 1.66–1.40 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 131.9, 130.9, 128.0, 127.3, 51.8, 47.8, 28.6 (d, *J* = 72.4 Hz), 13.9 (d, *J* = 69.9 Hz), 13.2 (d, *J* = 69.9 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 41.2. LC/MS (CI): *m/z* = 238 $[M+H]^+$. Anal. Calcd. for $C_{12}H_{16}NO_2P$: C 60.75; H 6.80; N 5.90. Found: C 60.76; H 6.54; N 6.10.

(2-(Dimethylphosphoryl)pyrrolidin-1-yl)(phenyl)methanone (44c). Yield 146 mg (73%). Yellowish solid; mp 33–34 °C. ^{1}H NMR (400 MHz, CD_3CN) δ 7.56–7.51 (m, 2H), 7.47–7.39 (m, 3H), 4.57 (ddd, *J* = 9.1, 5.6, 3.2 Hz, 1H), 3.54–3.46 (m, 1H), 3.46–3.34 (m, 1H), 2.35–2.20 (m, 1H), 2.19–2.07 (m, 1H), 2.04–1.94 (m, 1H), 1.81–1.68 (m, 1H), 1.49 (d, *J* = 12.6 Hz, 3H), 1.44 (d, *J* = 12.6 Hz, 3H). ^{13}C NMR (126 MHz, CD_3CN) δ 171.8, 138.1, 131.6, 129.6, 128.8, 57.5 (d, *J* = 79.3 Hz), 52.2, 26.6, 25.9, 16.6 (d, *J* = 65.4 Hz) and 15.6 (d, *J* = 66.8 Hz). ^{31}P NMR (202 MHz, CD_3CN) δ 45.9. LC/MS (CI): *m/z* = 252 $[M+H]^+$. Anal. Calcd. for $C_{13}H_{18}NO_2P$: C 62.14; H 7.22; N 5.57. Found: C 62.45; H 7.28; N 5.97.

(3-(Dimethylphosphoryl)pyrrolidin-1-yl)(phenyl)methanone (44d). The compound existed as a ca. 5:4 mixture of rotamers. Yield 139 mg (69%). Colorless solid; mp 104–106 °C. ^{1}H NMR (500 MHz, CD_3CN) δ 7.58–7.45 (m, 2H), 7.45–7.36 (m, 3H), 3.83–3.38 (m, 4H), 2.52–2.28 (m, 1H), 2.18–1.95 (m, 2H), 1.46–1.26 (m, 6H). ^{13}C NMR (126 MHz, CD_3CN) δ 170.2, 138.6, 131.2 and 131.2, 129.7 and 129.6, 128.4, 50.7 (d, *J* = 9.3 Hz) and 47.6 (d, *J* = 9.3 Hz), 49.9 and 47.0, 41.1 (d, *J* = 72.5 Hz) and 39.0 (d, *J* = 73.1 Hz), 27.5 and 25.7, 16.5–15.2 (m). ^{31}P NMR (202 MHz, CD_3CN) δ 41.1 and 40.3. LC/MS (CI): *m/z* = 252 $[M+H]^+$. Anal. Calcd. for $C_{13}H_{18}NO_2P$: C 62.14; H 7.22; N 5.57. Found: C 62.29; H 7.34; N 5.23.

(2-(Dimethylphosphoryl)piperidin-1-yl)(phenyl)methanone (44e). The compound existed as a ca. 1:1 mixture of rotamers. Yield 151 mg (71%). Colorless solid; mp 136–137 °C. ^{1}H NMR (400 MHz, CD_3CN) δ 7.50–7.43 (m, 5H), 4.97–4.83 (m, 1H), 3.71 (td, *J* = 13.0, 2.9 Hz, 1H), 3.61 (dt, *J* = 13.3, 3.2 Hz, 1H), 2.34–2.23 (m, 1H), 2.22–2.10 (m, 1H), 1.96–1.60 (m, 3H), 1.57 (d, *J* = 12.5 Hz, 3H), 1.51 (d, *J* = 12.7 Hz, 3H), 1.46–1.27 (m, 1H). ^{13}C NMR (126 MHz, CD_3CN) δ 171.4 (d, *J* = 2.7 Hz), 137.7, 130.8, 129.9, 127.9, 51.0 (d, *J* = 73.3 Hz), 47.4, 27.0, 25.7, 21.9, 16.5 (d, *J* = 66.7 Hz), 16.3 (d, *J* = 66.7 Hz). ^{31}P NMR (202 MHz, CD_3CN) δ 46.2. LC/MS (CI): *m/z* = 266 $[M+H]^+$. Anal. Calcd. for $C_{14}H_{20}NO_2P$: C 63.38; H 7.60; N 5.28. Found: C 62.99; H 7.27; N 5.67.

(3-(Dimethylphosphoryl)piperidin-1-yl)(phenyl)methanone (44f). The compound existed as a ca. 5:4 mixture of rotamers. Yield 159 mg (75%). Colorless solid; mp 100–102 °C. ^{1}H NMR (500 MHz, CD_3CN) δ 7.47–7.40 (m, 3H), 7.40–7.33 (m, 2H), 4.87–4.62 (m, 1H), 4.56 (s, 0.5H) and 4.06–3.74 (m, 0.4H), 3.73–3.40 (m, 1H), 3.11–2.78 (m, 2H), 2.04–1.97 (m, 1H), 1.90–1.56 (m, 3H), 1.54–1.09 (m, 7H). ^{13}C NMR (126 MHz, CD_3CN) δ 171.0, 137.9, 130.8, 129.8, 128.1, 49.1 and 48.5, 43.5 and 42.7, 39.4 and 38.8, 26.8 and 26.4, 25.1, 15.2 (d, *J* = 67.7 Hz) and 14.9 (d, *J* = 67.7 Hz). ^{31}P NMR (202 MHz, CD_3CN) δ 41.6 and 41.2. LC/MS (CI): *m/z* = 266 $[M+H]^+$. Anal. Calcd. for $C_{14}H_{20}NO_2P$: C 63.38; H 7.60; N 5.28. Found: C 63.28; H 7.25; N 5.38.

(4-(Dimethylphosphoryl)piperidin-1-yl)(phenyl)methanone (44g). The compound existed as a ca. 1:1 mixture of rotamers. Yield 159 mg (75%). Yellowish solid; mp 141–142 °C. The compound existed as a ca 1:1 mixture of rotamers. ^{1}H NMR (500 MHz, CD_3CN) δ 7.44–7.39 (m, 3H), 7.38–7.35 (m, 2H), 4.93–4.31 (m, 1H), 3.97–3.48 (m, 1H), 3.08–2.91 (m, 1H), 2.84–2.62 (m, 1H), 1.91–1.80 (m, 2H), 1.80–1.61 (m, 1H), 1.53–1.41 (m, 2H), 1.33 (d, *J* = 12.5 Hz, 6H). ^{13}C NMR (126 MHz, CD_3CN) δ 170.9, 138.1, 130.7, 129.8, 128.1, 48.9, 43.22, 38.64 (d, *J* = 71.8 Hz), 26.34, 25.91, 14.57 (d, *J* = 67.3 Hz). ^{31}P NMR (202 MHz, CD_3CN) δ 42.8. LC/MS (CI): *m/z* = 266 $[M+H]^+$. Anal. Calcd. for $C_{14}H_{20}NO_2P$: C 63.38; H 7.60; N 5.28. Found: C 63.33; H 7.56; N 5.05.

(3-(Isopropylsulfonyl)piperidin-1-yl)(phenyl)methanone (44h). Yield 132 mg (56%). Colorless solid; mp 130–132 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59–7.20 (m, 5H), 5.10–4.73 (m, 1H), 3.90–3.57 (m, 1H), 3.45–2.88 (m, 4H), 2.28 (d, *J* = 13.2 Hz, 1H), 2.05–1.79 (m, 2H), 1.56–1.09 (m, 7H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 135.1, 130.1, 128.6, 127.0, 53.7, 51.1, 47.8, 42.1, 25.0, 22.3, 16.0, 14.1. LC/MS (CI): *m/z* = 296 $[M+H]^+$. Anal. Calcd. for $C_{15}H_{21}NO_3S$: C 60.99; H 7.17; N 4.74; S 10.85. Found: C 60.78; H 6.78; N 4.59; S 10.95.

1-Benzoyl-*N*,*N*-dimethylpiperidine-3-sulfonamide (44i). The compound existed as a ca. 5:4 mixture of rotamers. Yield 166 mg (70%). Colorless solid; mp 102–103 °C. ^{1}H NMR (500 MHz, CD_3CN) δ 7.46–7.36 (m, 5H), 4.85–4.63 (m, 1H), 4.58–4.27 (m, 0.5H), 4.03–3.69 (m, 0.5H), 3.67–3.38 (m, 1H), 3.33–2.61 (m, 9H), 2.19–2.10 (m, 1H), 1.89–1.66 (m, 2H), 1.64–1.38 (m, 1H). ^{13}C NMR (126 MHz, CD_3CN) δ 171.3, 137.6, 131.0, 129.9, 128.1, 58.2, 57.8, 48.7, 43.2, 42.9, 38.4, 26.5, 25.7, 25.0. LC/MS (CI): *m/z* = 297 $[M+H]^+$. Anal. Calcd. for $C_{14}H_{20}N_2O_3S$: C 56.73; H 6.80; N 9.45; S 10.82. Found: C 56.79; H 7.14; N 9.50; S 11.16.

Acknowledgements

*The work was funded by Enamine Ltd, National Academy of Sciences of Ukraine (Grant No. 0119U102718) and Ministry of Education and Science of Ukraine (Grant No. 21BF037-01M). O.O.G. also received additional funding from Ministry of Education and Science of Ukraine (Grant No. 19BF037-03). The authors thank Mr. Maksym Stambirskyi for providing compounds **42** and **43**, Dr. Pavel Mykhailiuk for his vigilance during the manuscript preparation, Ms. Margarita Bolgova and Ms. Olga Kovalenko for pK_a* determinations, and Mr. Artem Skreminskiy for Log*P* and S_w measurements.

Conflict of Interest

The authors declare no conflict of interest.

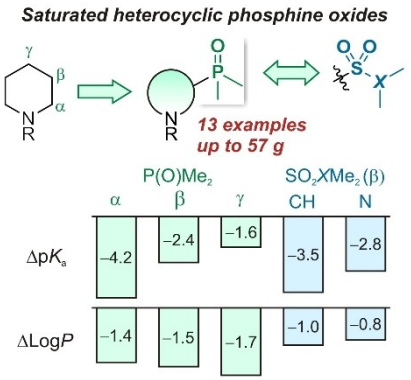
Keywords: Hydrophilicity · Lead-likeness · Organophosphorus compounds · Phosphine oxides · Saturated nitrogen heterocycles

[1] J. Petkowski, W. Bains, S. Seager, *Molecules* **2019**, *24*, 866.
[2] W. C. Weimer, D. E. Armstrong, *Environ. Sci. Technol.* **1979**, *13*, 826–829.
[3] U. Pradere, E. C. Garnier-Amblard, S. J. Coats, F. Amblard, R. F. Schinazi, *Chem. Rev.* **2014**, *114*, 9154–9218.
[4] H. Cao, J. Li, F. Zhang, D. Cahard, J. Ma, *Adv. Synth. Catal.* **2021**, *363*, 688–729.
[5] F. Palacios, C. Alonso, J. M. de los Santos, *Chem. Rev.* **2005**, *105*, 899–932.
[6] J.-A. Ma, *Chem. Soc. Rev.* **2006**, *35*, 630–636.
[7] K. Bera, I. N. N. Namboothiri, *Asian J. Org. Chem.* **2014**, *3*, 1234–1260.
[8] D. C. Batesky, M. J. Goldfogel, D. J. Weix, *J. Org. Chem.* **2017**, *82*, 9931–9936.
[9] W. S. Huang, S. Liu, D. Zou, M. Thomas, Y. Wang, T. Zhou, J. Romero, A. Kohlmann, F. Li, J. Qi, L. Cai, T. A. Dwight, Y. Xu, R. Xu, R. Dodd, A. Toms, L. Parillon, X. Lu, R. Anjum, S. Zhang, F. Wang, J. Keats, S. D. Wardwell, Y. Ning, Q. Xu, L. E. Moran, Q. K. Mohemmad, H. G. Jang, T. Clackson, N. I. Narasimhan, V. M. Rivera, X. Zhu, D. Dalgarno, W. C. Shakespeare, *J. Med. Chem.* **2016**, *59*, 4948–4964.
[10] K. Uchibori, N. Inase, M. Araki, M. Kamada, S. Sato, Y. Okuno, N. Fujita, R. Katayama, *Nat. Commun.* **2017**, *8*, 14768.
[11] G. He, J. P. Krise, R. Oliyai, in *Prodrugs*, Springer New York, New York, NY, **2007**, pp. 923–964.
[12] A. J. Wiemer, D. F. Wiemer, in *Pept. Mater.* **2014**, pp. 115–160.
[13] T. Hunter, *Philos. Trans. R. Soc. London Ser. B* **2012**, 367, 2513–2516.
[14] P. Finkbeiner, J. P. Hehn, C. Gnamm, *J. Med. Chem.* **2020**, *63*, 7081–7107.
[15] E. Łastawiecka, A. Flis, M. Stankevič, M. Greluk, G. Słowik, W. Gac, *Org. Chem. Front.* **2018**, *5*, 2079–2085.
[16] J. Xu, P. Zhang, Y. Gao, Y. Chen, G. Tang, Y. Zhao, *J. Org. Chem.* **2013**, *78*, 8176–8183.
[17] J. Yang, J. Xiao, T. Chen, L.-B. Han, *J. Organomet. Chem.* **2016**, *820*, 120–124.
[18] W. C. Fu, C. M. So, F. Y. Kwong, *Org. Lett.* **2015**, *17*, 5906–5909.
[19] J. Xuan, T. T. Zeng, J. R. Chen, L. Q. Lu, W. J. Xiao, *Chem. A Eur. J.* **2015**, *21*, 4962–4965.
[20] R. Beaud, R. J. Phipps, M. J. Gaunt, *J. Am. Chem. Soc.* **2016**, *138*, 13183–13186.
[21] R. Zhao, X. Huang, M. Wang, S. Hu, Y. Gao, P. Xu, Y. Zhao, *J. Org. Chem.* **2020**, *85*, 8185–8195.
[22] Z. Huang, W. Liu, S. Li, Y. Yang, S. Guo, H. Cai, *Synlett* **2020**, *31*, 1295–1297.
[23] G. Hu, Y. Gao, Y. Zhao, *Org. Lett.* **2014**, *16*, 4464–4467.
[24] T. Chen, C. Q. Zhao, L. B. Han, *J. Am. Chem. Soc.* **2018**, *140*, 3139–3155.
[25] L. Liu, D. Zhou, J. Dong, Y. Zhou, S. F. Yin, L. B. Han, *J. Org. Chem.* **2018**, *83*, 4190–4196.
[26] W. Jiang, G. Allan, X. Chen, J. J. Fiordeliso, O. Linton, P. Tannenbaum, J. Xu, P. Zhu, J. Gunnet, K. Demarest, S. Lundeen, Z. Sui, *Steroids* **2006**, *71*, 949–954.
[27] F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* **2009**, *52*, 6752–6756.
[28] F. Lovering, *MedChemComm* **2013**, *4*, 515–519.
[29] O. O. Grygorenko, D. M. Volochnyuk, S. V. Ryabukhin, D. B. Judd, *Chem. A Eur. J.* **2020**, *26*, 1196–1237.
[30] J. R. Goerlich, I. Neda, M. Well, A. Fischer, P. G. Jones, R. Schmutzler, *Z. Naturforsch. B* **1993**, *48*, 1161–1168.
[31] T. Kaukorat, I. Neda, P. G. Jones, R. Schmutzler, *Phosphorus Sulfur Silicon Relat. Elem.* **1996**, *112*, 247–259.
[32] M. Hatam, J. R. Goerlich, R. Schmutzler, H. Gröger, J. Martens, *Synth. Commun.* **1996**, *26*, 3685–3698.
[33] C. Liek, P. Machnitzki, T. Nickel, S. Schenk, M. Tepper, O. Stelzer, *Z. Naturforsch. B* **1999**, *54*, 1532–1542.
[34] H. Gröger, J. R. Goerlich, R. Schmutzler, J. Martens, *Phosphorus Sulfur Silicon Relat. Elem.* **2000**, *166*, 253–259.
[35] M. Tao, R. Bihovsky, G. J. Wells, J. P. Mallamo, *J. Med. Chem.* **1998**, *41*, 3912–3916.
[36] D. V. Patel, K. Rielly-Gauvin, D. E. Ryono, *Tetrahedron Lett.* **1990**, *31*, 5591–5594.
[37] H.-J. Kleiner, *Justus Liebigs Ann. Chem.* **1974**, *1974*, 751–764.
[38] H.-J. Zeiss, *Tetrahedron* **1992**, *48*, 8263–8270.
[39] B. Lal, A. N. Dohadwalla, N. K. Dadkar, A. D'Sa, N. J. De Souza, *J. Med. Chem.* **1984**, *27*, 1470–1480.
[40] E. J. Glamkowski, J. Strupczewski, E. Wolf, D. L. Woodward, *J. Med. Chem.* **1974**, *17*, 1008–1009.
[41] Y. M. Sokolenko, Y. Y. Yurov, B. V. Vashchenko, O. V. Hryshchuk, Y. Filimonova, E. N. Ostapchuk, A. Artemenko, O. V. Zaremba, O. O. Grygorenko, *J. Org. Chem.* **2019**, *84*, 13908–13921.
[42] V. L. Mykhalchuk, V. S. Yarmolchuk, R. O. Doroschuk, A. A. Tolmachev, O. O. Grygorenko, *Eur. J. Org. Chem.* **2018**, 2870–2876.
[43] V. S. Yarmolchuk, I. L. Mukan, O. O. Grygorenko, A. A. Tolmachev, S. V. Shishkina, O. V. Shishkin, I. V. Komarov, *J. Org. Chem.* **2011**, *76*, 7010–7016.
[44] A. A. Homon, O. V. Hryshchuk, S. Trofymchuk, O. Michurin, Y. Kuchkovska, D. S. Radchenko, O. O. Grygorenko, *Eur. J. Org. Chem.* **2018**, 5596–5604.
[45] R. F. Struck, Y. F. Shealy, *J. Med. Chem.* **1966**, *9*, 414–416.
[46] J. Sander, H.-J. Kleiner, M. Finke, *Angew. Chem.* **2006**, *94*, 561–562.
[47] A. J. Kendall, D. T. Seidenkranz, D. R. Tyler, *Organometallics* **2017**, *36*, 2412–2417.
[48] J. Dong, L. Krasnova, M. G. Finn, K. Barry Sharpless, *Angew. Chem. Int. Ed.* **2014**, *53*, 9430–9448; *Angew. Chem.* **2014**, *126*, 9584–9603.
[49] I. Colomer, C. J. Empson, P. Craven, Z. Owen, R. G. Doveston, I. Churcher, S. P. Marsden, A. Nelson, *Chem. Commun.* **2016**, *52*, 7209–7212.
[50] A. A. Homon, O. V. Hryshchuk, O. V. Mykhailenko, B. V. Vashchenko, K. P. Melnykov, O. Michurin, C. G. Daniliuk, I. I. Gerus, V. O. Kovtunenko, I. Kondratov, O. O. Grygorenko, *Eur. J. Org. Chem.* **2021**, ejoc.202100414.
[51] A. Nadin, C. Hattotuwagama, I. Churcher, *Angew. Chem. Int. Ed.* **2012**, *51*, 1114–1122; *Angew. Chem.* **2012**, *124*, 1140–1149.
[52] M. P. Gleeson, *J. Med. Chem.* **2008**, *51*, 817–834.
[53] W. L. F. Armarego, C. Chai, *Purification of Laboratory Chemicals*, Elsevier: Oxford, **2003**.
[54] M. Sayes, A. B. Charette, *Green Chem.* **2017**, *19*, 5060–5064.
[55] S. K. Verma, R. Ghorpade, A. Pratap, M. P. Kaushik, *Tetrahedron Lett.* **2012**, *53*, 2373–2376.

Manuscript received: May 12, 2021
Revised manuscript received: May 27, 2021
Accepted manuscript online: May 28, 2021

FULL PAPERS

Multigram synthesis of saturated heterocyclic dimethylphosphine oxides (derivatives of azetidine, pyrrolidine, piperidine, and morpholine) – advanced building blocks for medicinal chemistry – as well as their physico-chemical properties (pK_a, log$P$, and S_w) are disclosed.



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