# Phosphorus-Derived Chiral Auxiliaries for α-Alkylation of Secondary Amines by Anodic Oxidation

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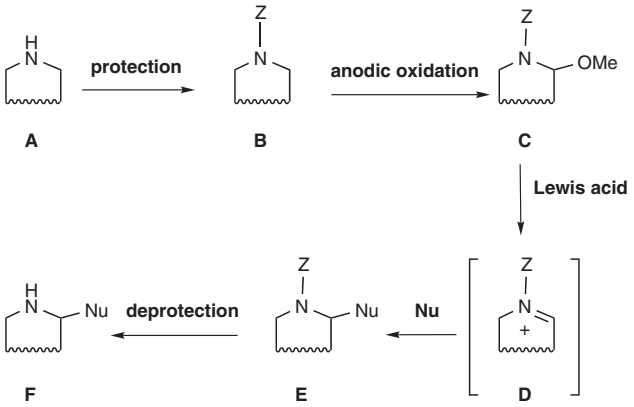
**Abstract:** Chiral phosphorus-based structures were investigated as N-activating groups for anodic oxidation and as chiral inductors. This first study presents the results obtained for pyrrolidine, with allyltrimethylsilane as a standard nucleophile. The methoxylated compounds were obtained in excellent yields (82–98%). The diastereoselectivity of the alkylation step (18–66%) is discussed with regard to the chiral auxiliary.

**Key words:** chiral auxiliaries, phosphorus derivatives, diastereoselective alkylation, secondary amines, pyrrolidines

Functionalization at the α-position of an amine is often a determining step in the synthesis of simple alkaloids and derivatives. The chemistry of iminium and *N*-acyliminium ions[1] is very useful for this purpose and it is well established that asymmetric access to nitrogen-containing natural compounds is possible via such intermediates. Iminiums and acyliminiums can be generated from amines through several oxidative processes, of which we are more interested in anodic oxidation,[2] as it is an elegant and environmentally friendly process.

This method has, indeed, been thoroughly studied for years following the pioneering work of Shono et al. (Scheme 1).[3] In this process, the amine **A** first needs to be protected by an 'activating' group Z (mainly to form a carbamate or an amide). In the second step, the iminium ion **D** is generated and trapped by the solvent (methanol, water, or acetic acid). Iminium ion **D** can be regenerated through the action of a Lewis acid, and reacts with a wide range of nucleophiles. This methodology has been widely used and has proved its efficiency. However, to our knowledge, there have been only a few asymmetric developments of this method starting from an achiral amine and using a chiral auxiliary.[4–5]

Our idea was to investigate new activating groups that can also act as chiral inductors. For this purpose, chiral heteroatom-based structures appeared of interest, since they bring the stereogenic center closer to the reaction center. In this paper, we will focus on the potential of the phosphorus atom. This concept is being developed in parallel with investigations of the sulfur atom.[6] As chiral appendages, phosphorus derivatives present several advantages:




**Scheme 1** The Shono sequence for the α-functionalization of an amine

(i) phosphoryl groups are widely used as chiral moieties in numerous processes (e.g., chiral NMR probes,[7,8] separation of racemic amino alcohols,[9] chiral ligands in organometallic or organic catalytic reactions,[10] deprotonations[11]); (ii) the various valences of phosphorus allow fine-tuning in the substituents; (iii) a large family of phosphorus compounds is accessible, and this allows many electronic distributions to be obtained; (iv) phosphonamides could be oxidized at nitrogen;[12,13] and (v) nucleophilic additions to phosphoryliminium ions occur in moderate to good yields.[12,14]

On the other hand, there are important drawbacks, as shown by two complementary studies. First, electrochemical access to *N*-phosphoryl-*N*,*O*-acetal precursors was described by Shono[12] as difficult, leading to moderate methoxylation yields. However, this study only exploited one achiral phosphoryl group, a phosphonic acid diethyl ester moiety. More recently, the diastereoselectivity of nucleophilic additions has been reported[14] with a phosphoryl group substituted with binaphthol (BINOL) as the chiral moiety. These results proved to be quite disappointing.

Despite these reports, we launched a systematic investigation of various phosphorus derivatives and are pleased to present herein several very encouraging results. We studied and compared different types of phosphorus-based groups, with pyrrolidine as the model amine. We first evaluated the possibility of performing anodic oxidation, and then the diastereoselectivity was investigated by the use of allyltrimethylsilane as a standard nucleophile.

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Three types of structures, reported in the literature for other purposes, were used. We envisaged them as suitable protective groups and chiral inductors for simple amines, and we undertook the synthesis and study of pyrrolidine derivatives **1**–**3** (Figure 1).

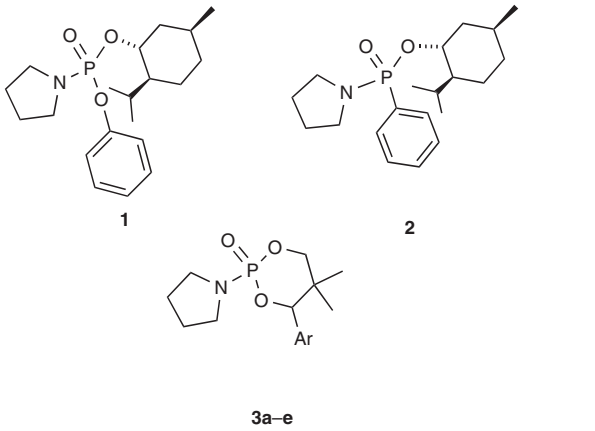
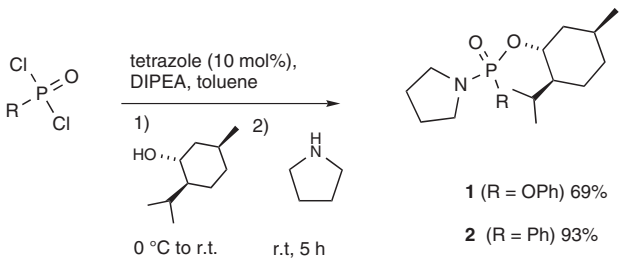



**Figure 1** Phosphorus-based derivatives of pyrrolidine

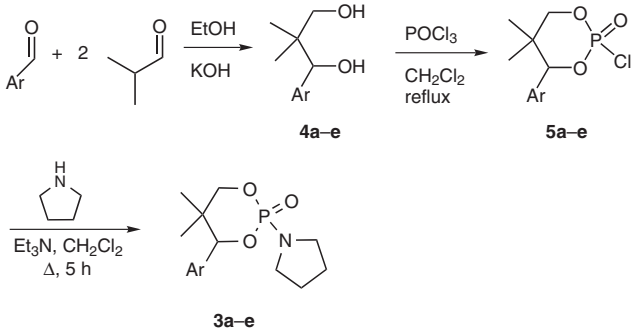
Phosphoramidic ester **1** and phosphonamidic ester **2** are very similar to the corresponding carbamate, but bear one additional substituent owing to the pentavalency of phosphorus. We also exploited the possibility of using cyclic equivalents of phosphoramidic ester **1**. Thus, a family of 1-(4-aryl-5,5-dimethyl-2-oxo-2λ$^5$-1,3,2-dioxaphosphinan-2-yl)pyrrolidines **3** [Ar = Ph (**a**), 2,4-$Cl_2C_6H_3$ (**b**), 2,6-$Cl_2C_6H_3$ (**c**), 2,6-$F_2C_6H_3$ (**d**), 2-F-6-$F_3CC_6H_3$ (**e**)] has been developed. Dioxaphosphinanes have also been used as chiral bases and NMR chiral probes.[7,8]

Phosphoramidic ester **1** and phosphonamidic ester **2** were synthesized by two-step one-pot reactions[15] from commercially available acid chlorides by sequential addition of menthol and pyrrolidine in the presence of a catalytic amount of tetrazole.[16] Both compounds were obtained as a mixture of two diastereomers (**1**, 75:25; **2**, 70:30), difficult to separate by chromatography at this stage (Scheme 2).




**Scheme 2** Preparation of phosphoramidic ester **1** and phosphonamidic ester **2**

Pyrrolidines **3a**–**e** were synthesized by condensation of pyrrolidine with 2-chloro-2-oxo-2λ$^5$-1,3,2-dioxaphosphinanes **5a**–**e** by a literature procedure (Scheme 3).[9] An aldol-Cannizzaro reaction between variously substituted benzaldehydes and two equivalents of isobutyraldehyde allowed for easy access to diols **4a**–**e**, which reacted with phosphorus oxychloride to give the desired dioxaphosphinanes **5a**–**e**, without the necessity for intermediate purification (Scheme 3). In this study, we used racemic starting materials, but access to optically active 4-aryl-2-chloro-5,5-dimethyl-2-oxo-2λ$^5$-1,3,2-dioxaphosphinanes **5a**–**c** has been described[9] and could be reproduced.




**Scheme 3** Synthesis of 1-(4-aryl-5,5-dimethyl-2-oxo-2λ$^5$-1,3,2-dioxaphosphinan-2-yl)pyrrolidines **3a**–**e**

Yields for the formation of chlorodioxaphosphinanes **5a**–**e** and pyrrolidines **3a**–**e** are presented in Table 1. The yields of chlorodioxaphosphinanes **5** decreased as the steric hindrance of the benzaldehyde starting material increased. Condensation of pyrrolidine with chlorodioxaphosphinanes **5a**–**e** in refluxing dichloromethane occurred easily and gave pyrrolidine derivatives **3a**–**e** in good yields (64–94%) (Scheme 3, Table 1).

**Table 1** Yields of Chlorodioxaphosphinanes **5a**–**e** and Pyrrolidines **3a**–**e**

| Compd | Ar | Yield **5** (%)[a] | Yield **3** (%)[b] |
|---|---|---|---|
| **a** | Ph | 60 | 92 |
| **b** | 2,4-$Cl_2C_6H_3$ | 55 | 85 |
| **c** | 2,6-$Cl_2C_6H_3$ | 50 | 94 |
| **d** | 2,6-$F_2C_6H_3$ | 30 | 64 |
| **e** | 2-F-6-$F_3CC_6H_3$ | 5 | 77 |

[a] The yield for **5** is over two steps, from butyraldehyde and the corresponding benzaldehyde.
[b] The yield for **3** is over one step, from the corresponding **5**.

Under these conditions (Scheme 3), only one diastereomer of **5** was obtained. Substitution occurred through an inversion of the configuration at phosphorus, as proved by $^1$H NMR spectra. The coupling constant between the phosphorus atom and the hydrogens in the equatorial positions on the dioxaphosphinane ring depends on the P=O bond position (axial or equatorial).[17] We could use the coupling constant between the phosphorus and the equatorial hydrogen in position 6 for our conformational determinations. For **5**, $J$ = 30 Hz, characteristic of an equatorial position of the P=O bond, whereas $J$ = 24 Hz for com-

pounds **3**, corresponding to an axial situation. The chlorine atom of **5** was therefore in an axial position, and the pyrrolidine ended up in an equatorial position. $^1$H NMR spectra of **5a–e** and **3a–e** also indicate that the aryl group was and remained equatorial, since the coupling constant between the phosphorus and the hydrogen at C-4 is small ($J$ = 2 Hz), corresponding to an axial hydrogen. These stereochemical considerations agree with what was already described for dioxaphosphinanes.[17,18] Therefore, the relative configuration of phosphoramides **3** could be deduced to be that depicted in Figure 2.

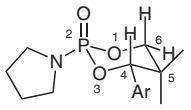



**Figure 2** Configuration of the dioxaphosphinane ring in phosphoramides **3a–e**

Having prepared the different phosphoramides **3a–e**, we investigated their electrochemical behavior. Cyclic voltammetry measurements indicated that these molecules were oxidized at 1.73–2.08 V (vs SCE) on glassy carbon in acetonitrile, with tetraethylammonium tetrafluoroborate as supporting electrolyte; this is nearly at the same potential as a methyl carbamate (1.73 V on platinum, with tetraethylammonium *p*-toluenesulfonate as supporting electrolyte).[2] The α-methoxylated products were obtained through anodic oxidation in methanol (Scheme 4). Reactions were performed in an undivided beaker-type cell with carbon graphite electrodes and at a current density of 2 mA·cm$^{-2}$ at room temperature (Scheme 4). The supporting electrolyte was tetraethylammonium tetrafluoroborate (0.3 equiv). Each protected pyrrolidine **1**, **2**, and **3a–e** could be methoxylated; the results are summarized in Table 2.

We were happy to find that all the starting materials, particularly 1-(1,3,2-dioxaphosphinan-2-yl)pyrrolidines **3a–e** (Table 2, entries 3–7), were excellent electrochemical substrates. Methoxylation occurred in excellent yields, almost quantitatively; there were no traces of over-oxidated products or degradation. Two diastereomers formed, with no selectivity in all cases. Methoxylated derivatives **6**, **7**, and **8a–e** are crystalline, very stable compounds and have been generated on multigram scale. The anodic oxidation behavior of phosphoramides **1**, **2**, and **3a–e** is similar to that of carbamates[2] and is a significant improvement over that of the amidophosphate reported by Shono et al[12] (50% methoxylation yield).

**Table 2** Yields for the Anodic α-Methoxylation of Pyrrolidines **1**, **2**, and **3a–e**

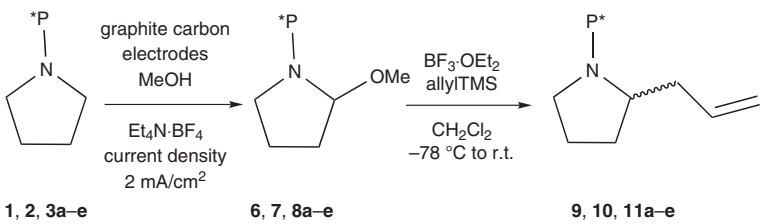
| Entry | Starting material | Product[a] | Yield (%) |
|---|---|---|---|
| 1 | **1** | **6** | 82 |
| 2 | **2** | **7** | 84 |
| 3 | **3a** | **8a** | 95 |
| 4 | **3b** | **8b** | 98 |
| 5 | **3c** | **8c** | 96 |
| 6 | **3d** | **8d** | 97 |
| 7 | **3e** | **8e** | 95 |

[a] Compounds **6** and **7** were mixtures of four diastereomers; compounds **8a–e** were mixtures of two diastereomers.

Since compounds **1** and **2** were used as diastereomeric mixtures, four different products were formed upon methoxylation (each diastereomer gave two methoxylated diastereomers). At this stage, the two pairs of methoxylated products (with only one configuration at the phosphorus center) of compound **7** have been separated by column chromatography.

We want to emphasize the simplicity of this reaction. There is no need for special equipment; the required intensity can be delivered by a simple battery.[19] The cell we used was a beaker-type cell with no separation, and the carbon graphite electrodes are not expensive. The reaction could be performed on large scale (5 g so far), and in concentrated solutions (1 mol·L$^{-1}$). The quantity of supporting electrolyte could be reduced to substoichiometric amounts. We believe that this kind of reaction can be performed easily in any organic chemistry laboratory and is a valuable technique for chemists.

Having demonstrated the advantages of the selected phosphorus-based groups in the anodic oxidation step, we wanted to test the ability of these groups to induce diastereoselective substitution in a model functionalization step (Scheme 4). Allyltrimethylsilane was used as a model nucleophile for amidoalkylation. It is a standard π-nucleophile with a limited steric effect, and is widely used in




**Scheme 4** Preparation of α-allylated 1-(1,3,2-dioxaphosphinan-2-yl)pyrrolidines from the corresponding α-unsubstituted pyrrolidines by α-methoxylation followed by allylation

studies of the reactivity of iminium ions. It was, more importantly, used in the two studies[4,14] we refer to for comparison.

Substitution was achieved with the boron trifluoride–diethyl ether complex as the Lewis acid on a temperature gradient (from –78 °C to r.t.) occurring overnight (Scheme 4). The diastereomeric ratio was determined by $^{31}$P NMR spectroscopy and confirmed in some cases by HPLC on crude mixtures. The yields reported in Table 3 refer to isolated pure products obtained after purification by column chromatography.

**Table 3** Yields and Diastereomeric Ratios Obtained in the Allylation of Methoxy-Substituted Pyrrolidines

| Entry | Reagent | Product[a] | Yield (%) | dr[b] |
|---|---|---|---|---|
| 1 | **6** | **9** | 83 | 60:40 |
| 2 | **7** | **10** | 84 | 65:35 |
| 3 | **8a** | **11a** | 87 | 59:41 |
| 4 | **8b** | **11b** | 85 | 60:40 |
| 5 | **8c** | **11c** | 90 | 80:20 |
| 6 | **8d** | **11d** | 89 | 65:35 |
| 7 | **8e** | **11e** | 90 | 60:40 |

[a] Compounds **9** and **10** were mixtures of four diastereomers; compounds **11a–e** were mixtures of two diastereomers.
[b] For compounds **9** and **10**, the dr was the same for each phosphorus configuration.

It is noteworthy that in all cases, yields of the C–C bond formation are excellent. The diastereoselectivity of allylation was, in most cases, moderate (around 60:40 or 65:35), except for the formation of **11c** (Table 3, entry 5) from **8c**, where the use of 2,6-dichlorophenyl as the aryl substituent gave access to a highly enriched mixture of diastereomers (80:20 dr), which could be completely separated by column chromatography. Furthermore, this diastereoselectivity could be slightly enhanced by use of dibutylboron triflate as Lewis acid. In this case, the reaction occurred in one hour at –78 °C, and gave a diastereomeric ratio of 83:17.

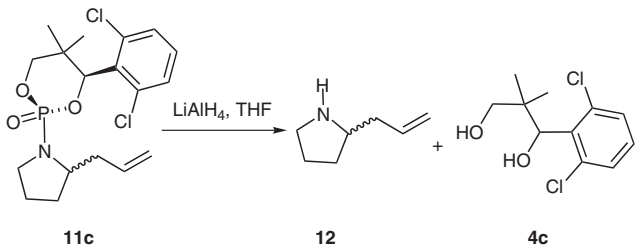
This result must be compared to those obtained with a BINOL-substituted phosphoryl group[14] or a phenyl menthyl carbamate group[4] as chiral inductor. In the case of the BINOL-substituted phosphoryl group, the diastereoselectivity and yield were lower (64:36 dr, 74% yield) than that reported here (80:20 dr, 90% yield). Our best result is comparable to the best result reported with chiral carbamates[20] (a phenyl menthyl carbamate). D'Oca et al.[4] reported a 86:14 ratio for the allylation of this compound. However, simpler chiral carbamates (derived from mandelic acid or *trans*-2-phenylcyclohexanol) gave lower diastereoselectivities (66:33, 50:50 dr). The yields for both the methoxylation and the amidoalkylation steps were also lower than those we obtained. The 4-(2,6-dichlorophenyl)-5,5-dimethyl-2-oxo-2λ$^5$-1,3,2-dioxaphosphinan-2-yl group in pyrrolidine **3c** is therefore a promising chiral inductor.

From the results presented in Table 3, some insights in the diastereoselectivity can be gained. It is, firstly, noticeable that the oxidation state of the phosphorus atom had no significant effect on reactivity or diastereoselectivity (Table 3, entry 1 vs entry 2). This parameter therefore does not seem to be relevant as the origin of the asymmetric induction. Furthermore, the acyclic forms of the phosphoryliminium ions (derived from **6** and **7**) did not give good diastereoselectivities as they both possess two large substituents (a menthyl group and a phenoxy or phenyl group) with significant steric hindrance.

Concerning the cyclic phosphoramide derivatives **8**, one can analyze the influence of substitution of the aryl group. Phenyl substitution does not have significant influence on the diastereoselectivity, except when two chlorine atoms are present at C-2 and C-6 (Table 3, entry 5). The size of the ortho substituent is important, since the replacement of chlorine by fluorine atoms dramatically decreased the diastereoselectivity (**11d**, Table 3, entry 6). To improve the diastereoselectivity in this family of cyclic chiral auxiliaries, a bulky group at each of the ortho positions of the aryl group seemed to be a promising approach. However, this approach was limited by the failure of the corresponding benzaldehydes to undergo aldolization with isobutyraldehyde to form the corresponding diols **4**. For example, 2,6-dimethylbenzaldehyde did not react in the aldol-Cannizzaro reaction for steric reasons. The 2,6-dichlorophenyl derivative **3c** seems then to be the best compromise in this series. Improvement of the inductive effect would necessitate a dramatic change in the structure of the chiral inductor. As mentioned, acyclic forms **6** and **7** did not afford the expected good diastereoselectivity. However, we still felt that these structures were important, as diastereoselective amidoalkylation requires a real facial preference during the addition of the nucleophile. The substituents should then be carefully chosen to give true dissymmetry, as the overall steric hindrance is not the only parameter to be tuned.

Deprotection of the allylated compounds was also addressed. As an example, phosphoramide **11c** was deprotected to give simple allylpyrrolidine **12** (Scheme 5). This was easily achieved by use of lithium aluminum hydride in tetrahydrofuran. After reduction of the dioxaphosphinane, cleavage of the P–N bond was achieved by aqueous workup, yielding the functionalized pyrrolidine **12** in 85% isolated yield. Note that 2,2-dimethyl-1-(2,6-dichlorophenyl)propane-1,3-diol (**4c**) could be recycled.

In conclusion, we studied different phosphoryl groups as N-activating groups and chiral inductors in a methoxylation–substitution sequence on a pyrrolidine. We found that 4-aryl-5,5-dimethyl-2-oxo-2λ$^5$-1,3,2-dioxaphosphinan-2-yl groups are excellent N-activating groups for anodic oxidation, as efficient as carbamates in terms of yields and stability. We then studied the diastereoselectiv-




11c 12 4c

**Scheme 5** Deprotection of an N-substituted 2-allylpyrrolidine

ity of the addition of the standard π-nucleophile allyltrimethylsilane on the methoxylated products. We found interesting diastereoselectivity when 1-[4-(2,6-dichlorophenyl)-5,5-dimethyl-2-oxo-2λ$^5$-1,3,2-dioxaphosphinan-2-yl]pyrrolidine (**3c**) was used. The diastereomeric excess was 60%, yields were excellent, and both diastereomers could be isolated by column chromatography. These results are as good as or better than those found in the literature, making our structure a promising chiral inductor. The results reveal the potential of phosphorus-based structures in electrochemistry as well as in *N*-phosphoryliminium reactivity.

We are currently investigating the reactivity of the most promising phosphoryl group toward different amines and nucleophiles. A second oxidation step, on a functionalized pyrrolidine, is also under investigation.

Allyltrimethylsilane, $BF_3{\cdot}OEt_2$, solvents, and other reagents were purchased from commercial sources unless otherwise noted. Anodic oxidations were carried out under $N_2$, substitution reactions under argon. MeOH was synthesis grade, $CH_2Cl_2$ was distilled from $CaH_2$. Normal processing of organic extracts consisted of drying over $MgSO_4$, filtering, and concentrating under reduced pressure by use of a rotary evaporator. The compounds were purified by column chromatography on silica gel (60 SDS, 35–70 μm). The electrochemical oxidations were performed with a PJT 120-1 potentiostat/galvanostat equipped with a current follower model IG5 N. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker AC-300 or a Bruker Avance-400 spectrometer. $^{31}$P NMR spectra were recorded on a Bruker AC-300 spectrometer. Chemical shifts (δ) are given in ppm relative to the solvent resonance as internal standard or $H_3PO_4$ ($^{31}$P NMR) as external standard. Coupling constants (*J*) were measured in Hz. IR spectra were recorded on an IRFT 1600 Perkin-Elmer spectrometer. Elemental analyses were obtained from the 'Service de microanalyse' of the 'Institut de Chimie des Substances Naturelles' (CNRS, Gif-sur-Yvette, France). Mass spectra were obtained by a chemical ionization technique (reagent gas: $NH_3$) with a Nermag R-10-10C spectrometer. High-resolution mass spectra were obtained on a Q-Tof Micromass spectrometer. Melting points are given uncorrected. For HPLC analyses an LC-10AS Shimadzu apparatus equipped with a Kromasil C18 column (250 × 4.6 mm) was used, with MeCN–$H_2O$ as eluent. Compounds were detected at 210 nm.

**Phosphonate 1 and Phosphinate 2**

$PhP(O)Cl_2$ (1.5 mL, 10 mmol) or $P(O)(OPh)Cl_2$ (90%) (1.5 mL, 10 mmol) was slowly added to a soln of menthol (1.7 g, 11 mmol), tetrazole (140 mg, 2 mmol), and DIPEA (3.5 mL, 20 mmol) in toluene (80 mL) at 0 °C. The cooling bath and the reaction mixture were allowed to warm up to r.t. overnight. Disappearance of menthol was monitored by TLC. The reaction was cooled once again at 0 °C, and pyrrolidine (1.7 mL, 21 mmol) was added. The mixture was allowed to warm up and to react for 5 h. After addition of 1 M aq HCl (40 mL), the layers were separated. The aqueous layer was extracted with $CH_2Cl_2$ (2 × 20 mL) and the organic layers were washed with 1 M aq HCl (2 × 20 mL) and with brine (2 × 20 mL) and worked up by the standard procedure. The product was separated by column chromatography (silica gel, heptane–EtOAc, 1:1) as eluent. The two diastereomers could not be separated at this stage.

**Menthyl Phenyl(pyrrolidin-1-yl)phosphonate (1)**

Yield: 2.537 g (69%); transparent oil.

$R_f$ = 0.45 (heptane–EtOAc, 1:1).

IR (neat): 2951, 2927, 2765, 2586, 2477, 2361, 1594, 1491, 1456, 1223, 1083, 1083, 1023, 999 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 7.30 (m, 4 H), 6.95 (t, *J* = 8.0 Hz, 1 H), 4.15 (m, 1 H), 3.22 (m, 1 H), 3.08 (m, 4 H), 2.10 (m, 2 H), 1.96 (m, 1 H), 1.63 (m, 4 H), 1.51 (m, 2 H), 1.39–0.91 (m, 3 H), 0.90–0.66 (m, 9 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 151.5, 129.7, 124.4, 120.3, 78.7, 48.9, 47.2, 43.0, 34.4, 31.8, 26.5, 25.8 (minor), 25.6 (major), 23.2, 22.7 (major), 22.3 (minor), 21.3, 15.9.

$^{31}$P NMR (125 MHz, $CDCl_3$): δ = 0.1, 1.1.

MS (CI): *m*/*z* = 388, 389 $[M + Na]^+$.

Anal. Calcd for $C_{20}H_{32}NO_3P$: C, 65.73; H, 8.83; N, 3.83. Found: C, 65.13; H, 8.74; N, 3.63.

**Menthyl Phenyl(pyrrolidin-1-yl)phosphinate (2)**

Yield: 3.249 g (93%); yellow oil.

$R_f$ = 0.23 (heptane–EtOAc, 1:1).

$t_R$ = 15.8 min (MeCN–$H_2O$: 70:30 to 95:5 in 20 min).

IR (neat): 2954, 2868, 1456, 1437, 1369, 1197, 1133, 1059, 1017, 999 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.66 (t, 2 H), 7.33 (m, 3 H), 4.22 (m, 1 H), 3.10 (m, 4 H), 2.20 (d, *J* = 12.0 Hz, 1 H, major), 2.10 (d, *J* = 12.0 Hz, 1 H, minor), 1.97 (t, 1 H), 1.69 (m, 4 H), 1.57 (m, 2 H), 1.31 (m, 2 H), 1.20–0.92 (m, 3 H), 0.85 (m, 3 H), 0.77 (m, 6 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 131.7, 128.7, 128.5, 77.1 (minor), 76.4 (major), 49.3, 46.9, 43.6, 34.4, 31.9, 26.5, 26.0, 22.9, 21.5, 21.3, 15.8.

$^{31}$P NMR (125 MHz, $CDCl_3$): δ = 2.91 (minor), 2.69 (major).

MS (CI): *m*/*z* = 372, 373 $[M + Na]^+$.

Anal. Calcd for $C_{20}H_{32}NO_2P$: C, 68.74; H, 9.23; N, 4.01. Found: C, 68.25; H, 9.24; N, 3.84.

**1,3,2-Dioxaphosphinane 2-Oxides 5d and 5e; General Procedure**

The benzaldehyde [2,6-difluoro- or 2-fluoro-6-(trifluoromethyl)benzaldehyde] (33.1 mmol) and isobutyraldehyde (6 mL, 65.7 mmol) were placed in a 100-mL three-neck flask. KOH (2.2 g, 39 mmol) dissolved in absolute EtOH (80 mL) was slowly added to the mixture, which was kept at 10 °C with a cold water bath. The reaction mixture was warmed to 80 °C for 5 h, and then stirred at r.t. overnight. The solvent was evaporated under reduced pressure, the residue was dissolved in $CH_2Cl_2$, and the soln was washed with a sat. aq soln of $NH_4Cl$ (2 × 20 mL) and with brine (2 × 20 mL). The aqueous layer was processed by the standard procedure to give an orange oil. This oil was dissolved in $CH_2Cl_2$ (50 mL). To this soln was slowly added a soln of $POCl_3$ (3.5 mL, 36 mmol) in $CH_2Cl_2$ (20 mL). The mixture was refluxed for 5 h. The soln was washed with a sat. aq soln of $NH_4Cl$ (2 × 20 mL) and with brine (2 × 20 mL). The aqueous layer was processed by the standard procedure and then chromatographed (silica gel; heptane–EtOAc, 1:1).

**2-Chloro-4-(2,6-difluorophenyl)-5,5-dimethyl-1,3,2-dioxaphosphinane 2-Oxide (5d)**
Yield: 3.42 g (35%); white solid.

$R_f$ = 0.36 (heptane–EtOAc, 1:1).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.39 (m, 1 H), 6.98 (dd, *J* = 5.5, 5.5 Hz, 2 H), 5.73 (d, *J* = 2.0 Hz, 1 H), 4.40 (dd, *J* = 3.0, 11.0 Hz, 1 H), 4.12 (dd, *J* = 11.0, 31.0 Hz, 1 H), 1.30 (s, 3 H), 0.86 (s, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 160.7 (dd, $^1J$ = 305 Hz, $^3J$ = 28 Hz), 131.4, 112.0 (m), 82.0, 79.4, 37.5, 20.2, 18.7.

$^{31}$P NMR (125 MHz, $CDCl_3$): δ = –3.00.

MS (CI): *m*/*z* = 319, 321, 323 $[M + Na]^+$.

**2-Chloro-4-[2-fluoro-6-(trifluoromethyl)phenyl]-5,5-dimethyl-1,3,2-dioxaphosphinane 2-Oxide (5e)**
Yield: 615 mg (5.4%); yellow oil.

$R_f$ = 0.39 (heptane–EtOAc, 1:1).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.47 (m, 2 H), 7.28 (t, *J* = 7.5 Hz, 1 H), 5.73 (d, *J* = 3.0 Hz, 1 H), 4.40 (dd, *J* = 3.0, 11.0 Hz, 1 H), 4.12 (dd, *J* = 11.0, 31.0 Hz, 1 H), 1.30 (s, 3 H), 0.86 (s, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 162.0 (d, $^1J$ = 254 Hz), 130.6 (d, $^3J$ = 10 Hz), 130.5 (m), 124.0 (q, $^1J$ = 221 Hz), 122.7 (q, $^3J$ = 10 Hz), 122.2, 121.2 (d, $^2J$ = 25 Hz), 80.0, 77.2, 37.1, 22.3, 20.6.

$^{31}$P NMR (125 MHz, $CDCl_3$): δ = –2.9.

MS (CI): *m*/*z* = 369, 371 $[M + Na]^+$.

**Pyrrolidines 3a–e; General Procedure**
A soln of the appropriate **5** (2 mmol) in $CH_2Cl_2$ (10 mL) was slowly added to a soln of pyrrolidine (345 μL; 4.208 mmol) in $CH_2Cl_2$ (15 mL). The mixture was refluxed for 5 h and then cooled to r.t. After addition of an aq soln of $NH_4Cl$ (10 mL), the layers were separated. The aqueous layer was extracted with $CH_2Cl_2$ and the combined organic layers were washed with brine (2 × 20 mL) and processed by the standard procedure. The product was separated by column chromatography (silica gel, MeOH–$Et_2O$, 3:97).

**1-(5,5-Dimethyl-2-oxo-4-phenyl-2λ$^5$-1,3,2-dioxaphosphinan-2-yl)pyrrolidine (3a)**
Yield: 543 mg (92%); white solid; mp 136 °C.

$R_f$ = 0.41 ($Et_2O$–MeOH, 97:3).

$t_R$ = 5.33 min (MeCN–$H_2O$, 70:30).

IR (Nujol): 1464, 1377, 1269, 1239, 1208, 1042, 1020, 996, 927 $cm^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.34 (m, 3 H), 7.26 (m, 2 H), 5.42 (d, *J* = 1.5 Hz, 1 H), 4.47 (d, *J* = 11.0 Hz, 1 H), 3.81 (dd, *J* = 11.0, 24.0 Hz, 1 H), 3.39 (s, 4 H), 1.90 (s, 4 H), 1.01 (s, 3 H), 0.77 (s, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 136.6, 128.1, 127.7, 127.2, 85.0, 76.6, 46.7, 35.5, 26.4, 21.1, 17.5.

$^{31}$P NMR (125 MHz, $CDCl_3$): δ = 4.55.

MS (CI): *m*/*z* = 318, 319 $[M + Na]^+$.

Anal. Calcd for $C_{15}H_{22}NO_3P$: C, 61.01; H, 7.51; N, 4.74. Found: C, 60.54; H, 7.48; N, 4.36.

**1-[4-(2,4-Dichlorophenyl)-5,5-dimethyl-2-oxo-2λ$^5$-1,3,2-dioxaphosphinan-2-yl]pyrrolidine (3b)**
Yield: 579 mg (78%); white solid; mp 133 °C.

$R_f$ = 0.44 ($Et_2O$–MeOH, 97:3).

IR (Nujol): 2731, 2667, 1585, 1569, 1456, 1376, 1260, 1047, 920 $cm^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.31 (s, 1 H), 7.29 (d, *J* = 6.0 Hz, 1 H), 7.21 (d, *J* = 6.0 Hz, 1 H), 5.83 (d, *J* = 2.0 Hz, 1 H), 4.39 (d, *J* = 11.0 Hz, 1 H), 3.72 (dd, *J* = 11.0, 24.0 Hz, 1 H), 3.27 (s, 4 H), 1.79 (s, 4 H), 0.98 (s, 3 H), 0.73 (s, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 134.6, 133.5, 133.3, 130.5, 129.2, 126.8, 79.8, 76.7, 46.8, 36.9, 26.4, 20.8, 18.1.

$^{31}$P NMR (125 MHz, $CDCl_3$): δ = 4.22.

MS (CI): *m*/*z* = 386, 388 $[M + Na]^+$.

Anal. Calcd for $C_{15}H_{20}Cl_2NO_3P$: C, 49.47; H, 5.54; N, 3.85. Found: C, 49.32; H, 5.55; N, 3.73.

**1-[4-(2,6-Dichlorophenyl)-5,5-dimethyl-2-oxo-2λ$^5$-1,3,2-dioxaphosphinan-2-yl]pyrrolidine (3c)**
Yield: 685 mg (94%); white solid; mp 135 °C.

$R_f$ = 0.37 ($Et_2O$–MeOH, 97:3).

$t_R$ = 7.6 min (MeCN–$H_2O$, 65:35).

IR (Nujol): 1558, 1456, 1378, 1272, 1046, 919 $cm^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 9.0 Hz, 1 H), 7.28 (d, *J* = 9.0 Hz, 1 H), 7.12 (t, *J* = 9.0 Hz, 1 H), 6.25 (d, *J* = 2.0 Hz, 1 H), 4.43 (dd, *J* = 11.0, 4.0 Hz, 1 H), 3.81 (dd, *J* = 11.0, 24.0 Hz, 1 H), 3.37 (m, 2 H), 3.31 (m, 2 H), 1.83 (m, 4 H), 1.26 (s, 3 H), 0.93 (s, 3 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 137.5, 136.5, 136.2, 131.5, 129.5, 128.8, 81.7, 77.2, 46.7, 39.1, 26.4, 21.7, 21.4.

$^{31}$P NMR (125 MHz, $CDCl_3$): δ = 5.60.

MS (CI): *m*/*z* = 386, 388 $[M + Na]^+$.

Anal. Calcd for $C_{15}H_{20}Cl_2NO_3P$: C, 49.47; H, 5.54; N, 3.85. Found: C, 49.60; H, 5.56; N, 3.75.

**1-[4-(2,6-Difluorophenyl)-5,5-dimethyl-2-oxo-2λ$^5$-1,3,2-dioxaphosphinan-2-yl]pyrrolidine (3d)**
Yield: 432 mg (64%); white solid.

$R_f$ = 0.51 ($Et_2O$–MeOH, 97:3).

IR (Nujol): 1624, 1589, 1464, 1377, 1273, 1236, 1203, 1047, 1029, 997, 925 $cm^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.28 (m, 1 H), 6.88 (t, *J* = 9.0 Hz, 2 H), 5.84 (d, *J* = 2.0 Hz, 1 H), 4.47 (dd, *J* = 3.0, 11.0 Hz, 1 H), 3.82 (dd, *J* = 11.0, 24.0 Hz, 1 H), 3.34 (m, 4 H), 1.86 (m, 4 H), 1.18 (s, 3 H), 0.78 (s, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 160.7 (dd, $^1J$ = 305 Hz, $^3J$ = 28 Hz), 130.3, 112.0 (m), 78.5, 76.3, 46.7, 37.5, 26.4, 20.3, 18.8.

$^{31}$P NMR (125 MHz, $CDCl_3$): δ = 4.2.

MS (CI): *m*/*z* = 354, 356 $[M + Na]^+$.

Anal. Calcd for $C_{15}H_{20}F_2NO_3P$: C, 54.38; H, 6.08; N, 4.23. Found: C, 54.66; H, 6.28; N, 4.19.

**1-{4-[2-Fluoro-6-(trifluoromethyl)phenyl]-5,5-dimethyl-2-oxo-2λ$^5$-1,3,2-dioxaphosphinan-2-yl}pyrrolidine (3e)**
Yield: 598 mg (77%); transparent oil.

$R_f$ = 0.45 ($Et_2O$–MeOH, 97:3).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.39 (m, 2 H), 7.24 (m, 1 H), 5.79 (d, *J* = 2.0 Hz, 1 H), 4.28 (dd, *J* = 5.5, 11.0 Hz, 1 H), 3.85 (dd, *J* = 11.0, 21.0 Hz, 1 H), 3.24 (m, 4 H), 1.76 (m, 4 H), 1.07 (s, 3 H), 0.79 (s, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 162.0 (d, $^1J$ = 254 Hz), 131.6 (d, $^3J$ = 10.0 Hz), 131.5 (m), 124.0 (q, $^1J$ = 221 Hz), 122.7 (q, $^2J$ = 10.0 Hz), 122.2, 121.2 (d, $^2J$ = 25.0 Hz), 80.0, 77.2, 46.5, 37.1, 26.2, 22.3, 20.6.

$^{31}$P NMR (125 MHz, $CDCl_3$): δ = 3.6.

MS (CI): *m*/*z* = 404, 406 $[M + Na]^+$.

Anal. Calcd for $C_{16}H_{20}F_4NO_3P$: C, 50.40; H, 5.29; N, 3.67. Found: C, 50.44; H, 5.28; N, 3.64.

**2-Methoxypyrrolidines 6, 7, and 8a–e by Methoxylation of Pyrrolidines 1, 2, and 3a–e; General Procedure**

The protected pyrrolidine **1**, **2**, or **3a–e** (1 mmol), the supporting electrolyte $Et_4NBF_4$ (72 mg; 0.331 mmol), and MeOH (20 mL) as solvent were placed in an undivided beaker-type glass cell. This cell was equipped with a graphite-plate anode and cathode of the same size (3.0 × 1.5 cm). The electrolysis was performed at r.t. under constant current ($I$ = 2 mA·cm$^{-2}$). The reaction was monitored by TLC. The solvent was evaporated in the presence of $Na_2CO_3$ under reduced pressure. The residue was extracted with $Et_2O$, the mixture was filtered, and the soln was evaporated once more.

**Menthyl Phenyl(2-methoxypyrrolidin-1-yl)phosphonate (6)**

$KHCO_3$ (20 mg, 0.200 mmol) was added to the soln described in the general procedure above. The reaction was stopped once 675 C (7 F·mol$^{-1}$) had been consumed.

Yield: 375 mg (95%); transparent oil.

$R_f$ = 0.39 (heptane–EtOAc–MeOH, 48.5:48.5:3).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 7.30 (m, 4 H), 6.95 (t, $J$ = 8.0 Hz, 1 H), 4.97 (m, 1 H), 4.15 (m, 1 H), 3.39–3.12 (m, 6 H), 2.10 (m, 2 H), 1.90 (m, 3 H), 1.51 (m, 3 H), 1.39–0.91 (m, 3 H), 0.90–0.66 (m, 9 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 151.5, 129.7, 124.4, 120.3, 92.3, 91.9, 79.2, 55.4, 49.1, 46.2, 43.0, 34.4, 33.2, 31.8, 25.7, 23.8, 23.6, 23.3, 22.5, 15.9.

$^{31}$P NMR (125 MHz, $CDCl_3$): δ = 0.0 (major), 0.9 (minor), –0.2 (major), 0.6 (minor).

MS (CI): *m*/*z* = 418 $[M + Na]^+$.

**Menthyl Phenyl(2-methoxypyrrolidin-1-yl)phosphinate (7)**

$KHCO_3$ (16 mg, 0.161 mmol) was added to the soln described in the general procedure above. The reaction was stopped once 511 C (5.3 F·mol$^{-1}$) had been consumed. The two sets of methoxylated products were separated by column chromatography (silica gel; heptane–EtOAc–MeOH, 48.5:48.5:3).

**Compound 7, Isomer A**

Yield: 223 mg (59%); transparent oil.

$R_f$ = 0.33 (heptane–EtOAc–MeOH, 48.5:48.5:3).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.66 (t, 2 H), 7.33 (m, 3 H), 5.17–4.85 (m, 1 H), 4.22 (m, 1 H, major), 4.13 (m, 1 H, minor), 3.32–3.10 (m, 4 H), 2.20 (m, 1 H, major), 2.10 (m, 1 H, minor), 1.90 (m, 3 H), 1.60 (m, 2 H), 1.57 (m, 2 H), 1.15 (m, 3 H), 1.01–0.85 (m, 12 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 133.2, 131.9, 131.7, 128.5, 128.3, 91.8, 77.9, 55.1, 49.1, 45.9, 43.7 (major), 43.5 (minor), 34.3 (major), 33.4 (minor), 31.8, 31.4, 25.7, 23.7, 23.0, 22.3, 21.4, 15.6.

MS (CI): *m*/*z* = 402 $[M + Na]^+$.

Anal. Calcd for $C_{21}H_{34}NO_3P$ (+ $H_2O$): C, 63.39; H, 9.05; N, 3.52. Found: C, 62.59; H, 8.89; N, 3.52.

**Compound 7, Isomer B**

Yield: 96 mg (25%); transparent oil.

$R_f$ = 0.21 (heptane–EtOAc–MeOH, 48.5:48.5:3).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.66 (t, 2 H), 7.33 (m, 3 H), 4.76 (m, 1 H, minor), 4.70 (m, 1 H, major), 4.32 (m, 1 H, major), 4.16 (m, 1 H, minor), 3.32–3.10 (m, 2 H), 3.57 (s, 3 H, minor), 3.10 (s, 3 H, major), 2.20 (m, 1 H, major), 2.10 (m, 1 H, minor), 1.90 (m, 3 H), 1.60 (m, 2 H), 1.57 (m, 2 H), 1.15 (m, 3 H), 1.01–0.85 (m, 12 H).

**1-(5,5-Dimethyl-2-oxo-4-phenyl-2λ$^5$-1,3,2-dioxaphosphinan-2-yl)-2-methoxypyrrolidine (8a)**

The reaction was stopped once 396 C (4.1 F·mol$^{-1}$) had been consumed.

Yield: 302 mg (93%); white solid.

$R_f$ = 0.51 ($Et_2O$–MeOH, 97:3).

$t_R$ = 4.95 min (minor), 5.02 min (major) (MeCN–$H_2O$, 70:30).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.32 (m, 3 H), 7.24 (m, 2 H), 5.46 (d, $J$ = 2.0 Hz, 1 H), 5.10 (m, 1 H), 4.49 (dd, $J$ = 11.0, 2.3 Hz, 1 H), 3.86 (dd, $J$ = 11.0, 25 Hz, 1 H), 3.42 (m, 2 H), 3.33 (s, 3 H, major), 3.35 (s, 3 H, minor), 2.10 (m, 1 H), 1.86 (m, 2 H), 1.77 (m, 1 H), 0.99 (s, 3 H), 0.75 (s, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 136.8, 128.3, 127.8, 127.3, 91.4, 85.2, 76.9, 55.1, 46.9, 35.7, 30.0, 26.5, 21.2, 17.6.

$^{31}$P NMR (125 MHz, $CDCl_3$): δ = 5.07, 5.00.

MS (CI): *m*/*z* = 348, 349 $[M + Na]^+$.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{24}NO_4NaP$: 348.1341; found: 348.1325.

**1-[4-(2,4-Dichlorophenyl)-5,5-dimethyl-2-oxo-2λ$^5$-1,3,2-dioxaphosphinan-2-yl]-2-methoxypyrrolidine (8b)**

The reaction was stopped once 357 C (3.7 F·mol$^{-1}$) had been consumed.

Yield: 363 mg (92%); white solid.

$R_f$ = 0.70 ($Et_2O$–MeOH, 96.5:3.5).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.34 (d, $J$ = 5.0 Hz, 1 H), 7.33 (s, 1 H), 7.23 (d, $J$ = 6.0 Hz, 1 H), 5.90 (d, $J$ = 2.0 Hz, 1 H), 5.05 (m, 1 H), 4.49 (d, $J$ = 11.0 Hz, 1 H), 3.80 (d, $J$ = 11.0 Hz, 1 H), 3.39 (m, 2 H), 3.32 (s, 3 H, major), 3.24 (s, 3 H, minor), 2.07 (m, 1 H), 1.93 (m, 2 H), 1.85 (m, 1 H), 1.04 (s, 3 H), 0.78 (s, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 134.5, 133.1, 133.0, 130.4 (major), 130.3 (minor), 128.9, 126.6, 90.8 (major), 90.7 (minor), 79.7, 76.5, 54.4 (major), 54.3 (minor), 45.8 (major), 45.5 (minor), 36.7, 33.1 (major), 32.9 (minor), 23.2 (minor), 23.1 (major), 20.5, 17.7.

$^{31}$P NMR (125 MHz, $CDCl_3$): δ = 4.64 (minor), 4.57 (major).

MS (CI): *m*/*z* = 416, 418 $[M + Na]^+$.

**1-[4-(2,6-Dichlorophenyl)-5,5-dimethyl-2-oxo-2λ$^5$-1,3,2-dioxaphosphinan-2-yl]-2-methoxypyrrolidine (8c)**

The reaction was stopped once 396 C (4.1 F·mol$^{-1}$) had been consumed.

Yield: 374 mg (95%); white solid; mp 127 °C.

$R_f$ = 0.42 ($Et_2O$–MeOH, 97:3).

$t_R$ = 7.1 min (major), 7.3 min (minor) (MeCN–$H_2O$, 65:35).

IR: 1651, 1557, 1455, 1376, 1261, 1043, 919 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.35 (d, $J$ = 7.0 Hz, 1 H), 7.33 (d, $J$ = 7.0 Hz, 1 H), 7.28 (t, $J$ = 7.0 Hz, 1 H), 6.32 (d, $J$ = 2.0 Hz, 1 H, major), 6.22 (d, $J$ = 2.0 Hz, 1 H, minor), 5.03 (m, 1 H), 4.52 (dd, $J$ = 11.0, 4.0 Hz, 1 H), 3.84 (dd, $J$ = 11.0, 23.0 Hz, 1 H), 3.42 (m, 2 H), 3.39 (s, 3 H, major), 3.29 (m, 3 H, minor), 1.85 (m, 4 H), 1.28 (s, 3 H), 0.97 (s, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 137.5, 136.2, 132.2, 130.3, 129.5, 128.8, 91.7, 82.5, 78.1, 55.1, 46.3 (major), 46.1 (minor), 39.1, 34.0, 23.9, 22.6, 22.0.

$^{31}$P NMR (125 MHz, $CDCl_3$): δ = 5.70, 4.56.

MS (CI): *m*/*z* = 416, 418 $[M + Na]^+$.

Anal. Calcd for $C_{16}H_{22}Cl_2NO_4P$: C, 48.75; H, 5.62; N, 3.55. Found: C, 48.46; H, 5.64; N, 3.51.

**1-[4-(2,6-Difluorophenyl)-5,5-dimethyl-2-oxo-2λ$^5$-1,3,2-dioxaphosphinan-2-yl]-2-methoxypyrrolidine (8d)**
The reaction was stopped once 405 C (4.2 F·mol$^{-1}$) had been consumed.

Yield: 350 mg (97%); white solid.

$R_f$ = 0.56 ($Et_2O$–MeOH, 97:3).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.28 (m, 1 H), 6.91 (d, *J* = 9.0 Hz, 1 H), 6.87 (d, *J* = 9.0 Hz, 1 H), 5.91 (d, *J* = 2.0 Hz, 1 H), 5.11 (m, 1 H), 4.47 (dd, *J* = 3.0, 11.0 Hz, 1 H), 3.83 (dd, *J* = 11.0, 24.0 Hz, 1 H), 3.44 (m, 2 H), 3.33 (s, 3 H, 1st dia), 3.30 (s, 3 H, 2nd dia), 2.04 (m, 1 H), 1.92 (m, 2 H), 1.78 (m, 1 H), 1.16 (s, 3 H), 0.78 (s, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 160.7 (dd, $^1J$ = 305 Hz, $^3J$ = 28.0 Hz), 130.3, 130.2, 111.9 (m), 91.5, 78.5, 76.3, 55.4, 46.7, 36.5, 33.5, 26.4, 20.6, 18.8.

$^{31}$P NMR (125 MHz, $CDCl_3$): δ = 4.0, 3.9.

MS (CI): *m*/*z* = 384 [M + Na]$^+$.

**1-{4-[2-Fluoro-6-(trifluoromethyl)phenyl]-5,5-dimethyl-2-oxo-2λ$^5$-1,3,2-dioxaphosphinan-2-yl}-2-methoxypyrrolidine (8e)**
The reaction was stopped once 1351 C (14.0 F·mol$^{-1}$) had been consumed.

Yield: 395 mg (96%); transparent oil.

$R_f$ = 0.60 ($Et_2O$–MeOH, 97:3).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.55–7.40 (m, 2 H), 7.32 (m, 1 H), 5.89 (d, *J* = 2.0 Hz, 1 H), 5.08 (m, 1 H), 4.35 (dd, *J* = 2.0, 11.0 Hz, 1 H), 3.98 (dd, *J* = 11.0, 24.0 Hz, 1 H), 3.42 (m, 1 H), 3.33 (s, 3 H, 1st dia), 3.30 (s, 3 H, 2nd dia), 3.30 (m, 1 H), 2.04 (m, 1 H), 1.86 (m, 2 H), 1.75 (m, 1 H), 1.17 (s, 3 H, 1st dia), 1.11 (s, 3 H, 2nd dia), 0.94 (s, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 162.0 (d, $^1J$ = 254 Hz), 131.6 (d, $^3J$ = 10.0 Hz), 131.5 (m), 124.0 (q, $^1J$ = 221 Hz), 122.7 (q, $^2J$ = 10.0 Hz), 122.2, 121.2 (d, $^2J$ = 25.0 Hz), 91.1/91.0, 80.3, 77.4, 54.8, 45.5, 37.1, 33.2/33.1, 23.4, 22.8/22.4, 20.8.

$^{31}$P NMR (125 MHz, $CDCl_3$): δ = 3.6, 3.2.

MS (CI): *m*/*z* = 434 [M + Na]$^+$.

**2-Allylpyrrolidines 9, 10, and 11a–e by Allylation of 2-Methoxypyrrolidines 6, 7, and 8a–e ; General Procedure**
A soln of 2-methoxypyrrolidine **6**, **7**, or **8a–e** (0.440 mmol) in $CH_2Cl_2$ (15 mL) was placed in a three-neck flask under argon and cooled at –78 °C. $BF_3{\cdot}OEt_2$ (111 μL, 0.875 mmol) was slowly added by syringe. The mixture was allowed to react for 15 min before allyltrimethylsilane (94 μL, 0.594 mmol) was added. The acetone–dry ice bath was allowed to warm to r.t. overnight, and the reaction took place over 15 h. The reaction was quenched with diluted aq $NH_3$. The layers were separated. The aqueous layer was extracted with $CH_2Cl_2$ (2 × 20 mL) and the combined organic layers were washed with brine (2 × 20 mL) and processed by the standard procedure. The products were separated by column chromatography (silica gel; heptane–EtOAc, 1.5:1).

**Menthyl Phenyl(2-allylpyrrolidin-1-yl)phosphonate (9)**
Yield: 155 mg (87%); transparent oil.

$R_f$ = 0.25 (heptane–EtOAc, 1.5:1).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 7.30 (m, 4 H), 6.95 (t, *J* = 8.0 Hz, 1 H), 5.82 (m, 1 H), 5.03 (m, 2 H), 4.27 (m, 1 H), 3.76 (m, 1 H), 3.41 (m, 1 H), 3.28 (m, 1 H), 3.12 (m, 1 H), 2.50 (m, 1 H), 2.18 (m, 3 H), 2.01 (m, 1 H), 1.81 (m, 2 H), 1.61 (m, 4 H), 1.39–0.91 (m, 3 H), 0.90–0.66 (m, 9 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 151.5, 135.2, 129.7, 124.4, 120.3, 115.8, 78.7, 55.6, 47.2, 43.0, 40.6, 34.4, 33.2, 31.8, 26.5, 25.6, 23.2 (major), 22.3 (minor), 21.3, 15.9.

$^{31}$P NMR (125 MHz, $CDCl_3$): δ = 3.8 (major), 3.7 (minor), 3.0 (major), 2.6 (minor).

MS (CI): *m*/*z* = 428 [M + Na]$^+$.

**Menthyl Phenyl(2-allylpyrrolidin-1-yl)phosphinate (10)**
The major methoxy derivative **7** ($R_f$ = 0.33) was used as starting material.

Yield: 143 mg (84%); transparent oil.

$R_f$ = 0.58 (major), 0.21 (minor) (heptane–EtOAc–MeOH: 48.5:48.5:3).

$^1$H NMR (400 MHz, $CDCl_3$, major): δ = 7.66 (t, 2 H), 7.33 (m, 3 H), 5.69 (m, 1 H), 5.00 (m, 2 H), 4.25 (m, 1 H), 3.62 (m, 1 H), 3.29 (m, 1 H), 3.14 (m, 1 H), 2.45 (m, 2 H), 2.31 (m, 1 H), 2.15 (m, 1 H), 1.98 (m, 1 H), 1.78 (m, 1 H), 1.64 (m, 2 H), 1.50 (m, 2 H), 1.33 (m, 4 H), 0.98–0.87 (m, 10 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 131.9, 130.6, 128.3, 127.7, 115.2, 76.7, 55.3, 47.0, 43.4, 40.4, 34.2, 33.2, 31.8, 26.7, 25.8, 25.6, 22.0, 21.4, 15.9.

MS (CI): *m*/*z* = 412 [M + Na]$^+$.

**2-Allyl-1-(5,5-dimethyl-2-oxo-4-phenyl-2λ$^5$-1,3,2-dioxaphosphinan-2-yl)pyrrolidine (11a)**
Yield: 140 mg (95%); white solid.

$R_f$ = 0.42 ($Et_2O$–MeOH, 96:4).

IR (neat): 3068, 2975, 2880, 1640, 1495, 1475, 1454, 1367, 1256, 1125, 1056, 927 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.32 (m, 3 H), 7.24 (m, 2 H), 5.81 (m, 1 H), 5.43 (d, *J* = 2.0 Hz, 1 H, major), 5.41 (d, *J* = 2.0 Hz, 1 H, minor), 5.04 (m, 2 H), 5.01 (m, 1 H), 4.49 (dd, *J* = 11.0, 2.0 Hz, 1 H), 3.92 (dd, *J* = 11.0, 23.0 Hz, 1 H), 3.46 (m, 1 H), 3.37 (m, 1 H), 2.55 (m, 1 H), 2.21 (m, 2 H), 1.90 (m, 2 H), 1.76 (m, 1 H), 1.00 (s, 3 H), 0.75 (s, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 136.6, 135.1, 128.1, 127.7, 127.3, 117.2, 85.0, 76.7, 58.4, 47.2, 40.8 (major), 40.5 (minor), 35.6, 30.5, 24.9, 21.2, 17.6.

$^{31}$P NMR (300 MHz, $CDCl_3$): δ = 5.74 (minor), 5.67 (major).

MS (CI): *m*/*z* = 358, 359 [M + Na]$^+$.

Anal. Calcd for $C_{18}H_{26}NO_3P$: C, 64.46; H, 7.81; N, 4.18. Found: C, 64.32; H, 7.99; N, 4.04.

**2-Allyl-1-[4-(2,4-dichlorophenyl)-5,5-dimethyl-2-oxo-2λ$^5$-1,3,2-dioxaphosphinan-2-yl]pyrrolidine (11b)**
Yield: 165 mg (93%); white solid.

$R_f$ = 0.51 ($Et_2O$–MeOH, 97:3).

IR (neat): 3074, 2972, 2882, 1734, 1640, 1590, 1562, 1471, 1436, 1363, 1259, 1206, 1105, 1044, 920 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.34 (d, *J* = 5.0 Hz, 1 H), 7.33 (s, 1 H), 7.23 (d, *J* = 6.0 Hz, 1 H), 5.93 (d, *J* = 2.0 Hz, 1 H, major), 5.91 (d, *J* = 2.0 Hz, 1 H, minor), 5.74 (m, 1 H), 5.02 (m, 2 H), 4.51 (dd, *J* = 2.0, 11.0 Hz, 1 H), 3.86 (m, 1 H), 3.79 (dd, *J* = 11.0, 25.0 Hz, 1 H), 3.42 (m, 1 H), 3.30 (m, 1 H), 2.46 (m, 1 H), 2.29 (m, 2 H), 1.88 (m, 2 H), 1.72 (m, 1 H), 1.05 (s, 3 H), 0.79 (s, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 135.0, 134.6, 133.7, 130.5, 129.2, 126.8, 79.8, 76.5, 58.5, 47.2, 40.7 (major), 40.5 (minor), 37.0, 30.5, 29.7, 24.8, 20.9, 18.2.

$^{31}$P NMR (125 MHz, $CDCl_3$): δ = 4.7 (minor), 4.5 (major).

MS (CI): *m*/*z* = 426, 428 [M + Na]$^+$.

**2-Allyl-1-[4-(2,6-dichlorophenyl)-5,5-dimethyl-2-oxo-2λ$^5$-1,3,2-dioxaphosphinan-2-yl]pyrrolidine (11c)**
Yield: 163 mg (92%); white solid; mp 144 °C.

$R_f$ = 0.43 (major), 0.49 (minor) ($Et_2O$–MeOH: 97:3).

$t_R$ = 11.7 min (major), 11.9 min (minor) (MeCN–$H_2O$, 70:30).

IR (Nujol): 1638, 1580, 1562, 1455, 1377, 1258, 1202, 1086, 1048, 919 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 8.0 Hz, 1 H), 7.28 (d, *J* = 8.0 Hz, 1 H), 7.13 (t, *J* = 8.0 Hz, 1 H), 6.29 (d, *J* = 2.0 Hz, 1 H, major), 6.33 (d, *J* = 2.0 Hz, 1 H, minor), 5.75 (m, 1 H), 5.00 (m, 2 H, major), 5.05 (m, 2 H, minor), 4.47 (dd, *J* = 11.0, 3.0 Hz, 1 H), 3.95 (m, 1 H, major), 3.91 (m, 1 H, minor) 3.83 (dd, *J* = 11.0, 23.0 Hz, 1 H), 3.42 (m, 1 H, major), 3.57 (m, 1 H, minor), 3.32 (m, 1 H), 2.49 (m, 1 H), 2.14 (m, 1 H), 1.80 (m, 3 H), 1.65 (m, 1 H), 1.28 (s, 3 H), 0.93 (s, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 137.5, 136.2, 135.2, 131.6, 130.3, 129.6, 128.9, 117.2, 81.7, 77.2, 58.3, 47.2, 40.6, 39.1, 30.7, 25.0, 21.9, 21.5.

$^{31}$P NMR (125 MHz, $CDCl_3$): δ = 5.25 (major), 6.00 (minor).

MS (CI): *m*/*z* = 426, 428 [M + Na]$^+$.

Anal. Calcd for $C_{18}H_{24}Cl_2NO_3P$: C, 53.48; H, 5.98; N, 3.46. Found: C, 53.45; H, 5.95; N, 3.38.

**2-Allyl-1-[4-(2,6-difluorophenyl)-5,5-dimethyl-2-oxo-2λ$^5$-1,3,2-dioxaphosphinan-2-yl]pyrrolidine (11d)**
Yield: 145 mg (89%); white solid.

$R_f$ = 0.46 ($Et_2O$–MeOH: 97:3).

IR (Nujol): 3075, 1625, 1560, 1469, 1364, 1271, 1204, 1120, 1048, 994 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.29 (m, 1 H), 6.91 (d, *J* = 9.0 Hz, 1 H), 6.87 (d, *J* = 9.0 Hz, 1 H), 5.91 (d, *J* = 2.0 Hz, 1 H), 5.76 (m, 1 H), 5.04 (m, 2 H), 4.49 (dd, *J* = 2.0, 11.0 Hz, 1 H), 3.93 (m, 1 H), 3.83 (dd, *J* = 11.0, 24.0 Hz, 1 H), 3.41 (m, 1 H, major), 3.48 (m, 1 H, minor), 3.37 (m, 1 H, major), 3.27 (m, 1 H, minor), 2.51 (m, 1 H), 2.18 (m, 1 H), 1.89 (m, 3 H), 1.72 (m, 1 H), 1.18 (s, 3 H), 0.79 (s, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 160.7 (dd, $^1J$ = 305 Hz, $^3J$ = 28.0 Hz), 135.2, 130.3, 112.0 (m), 78.3, 76.3, 58.2, 46.2, 40.5, 36.7, 30.5, 24.8, 21.1, 18.8.

$^{31}$P NMR (125 MHz, $CDCl_3$): δ = 4.9 (minor), 4.7 (major).

MS (CI): *m*/*z* = 394 [M + Na]$^+$.

**2-Allyl-1-{4-[2-fluoro-6-(trifluoromethyl)phenyl]-5,5-dimethyl-2-oxo-2λ$^5$-1,3,2-dioxaphosphinan-2-yl}pyrrolidine (11e)**
Yield: 172 mg (93%); yellow oil.

$R_f$ = 0.46 ($Et_2O$–MeOH, 97:3).

IR (neat): 3076, 2975, 2883, 1738, 1641, 1614, 1587, 1463, 1312, 1270, 1115, 995 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.56–7.46 (m, 2 H), 7.31 (m, 1 H), 5.90 (d, *J* = 2.0 Hz, 1 H, major), 5.89 (d, *J* = 2.0 Hz, 1 H, minor), 5.78 (m, 1 H), 5.05 (m, 2 H), 4.39 (dd, *J* = 2.0, 11.0 Hz, 1 H, major), 4.36 (dd, *J* = 2.0, 11.0 Hz, 1 H, minor), 3.93 (dd, *J* = 11.0, 24.0 Hz, 1 H, major), 3.92 (dd, *J* = 11.0, 24.0 Hz, 1 H, minor), 3.89 (m, 1 H), 3.41 (m, 1 H), 3.30 (m, 1 H), 2.50 (m, 1 H), 2.18 (m, 1 H), 1.86 (m, 3 H), 1.70 (m, 1 H), 1.19 (s, 3 H, major), 1.18 (s, 3 H, minor), 0.89 (s, 3 H, major), 0.87 (s, 3 H, minor).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 162.0 (d, $^1J$ = 254 Hz), 135.2, 131.6 (d, $^3J$ = 10.0 Hz), 131.5 (m), 124.0 (q, $^1J$ = 221 Hz), 122.7 (q, $^2J$ = 10.0 Hz), 122.2, 121.2 (d, $^2J$ = 25.0 Hz), 117.0, 80.0, 77.4, 58.5 (major), 58.2 (minor), 47.1, 40.6, 40.5, 37.3, 30.4, 24.8, 22.5, 20.8.

$^{31}$P NMR (125 MHz, $CDCl_3$): δ = 4.2 (major), 4.4 (minor).

MS (CI): *m*/*z* = 444 [M + Na]$^+$.

Anal. Calcd for $C_{19}H_{24}F_4NO_3P$: C, 54.16; H, 5.74; N, 3.32. Found: C, 54.03; H, 5.61; N, 3.12.

**2-Allylpyrrolidine Hydrochloride (12)**
LAH (18 mg, 0.474 mmol) was suspended in THF (2 mL). A soln of 2-allylpyrrolidine **11c** (85 mg, 0.191 mmol) in THF (2 mL) was slowly added. The mixture was stirred for 24 h at r.t. The excess of LAH was quenched by addition of $H_2O$ (20 μL), 13% aq KOH (20 μL), and $H_2O$ again (20 μL). After the mixture had stirred for 30 min, the white precipitate was removed by filtration. The filtrate was extracted with $Et_2O$ (2 × 20 mL). This organic phase was then extracted with 1 M aq HCl (2 × 4 mL). The combined organic layers were purified by column chromatography (silica gel; heptane–EtOAc, 1:1); this gave 1,3-propanediol **4c**; yield: 40 mg (85%). The acidic aqueous phase was evaporated under reduced pressure; this gave 2-allylpyrrolidine hydrochloride (**12**) as a white solid; yield: 25 mg (89%).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 5.88–5.77 (m, 1 H), 5.24 (d, *J* = 18.0 Hz, 1 H), 5.19 (d, *J* = 9.0 Hz, 1 H), 3.66 (m, 1 H), 3.30 (m, 2 H), 2.52 (m, 2 H), 2.21 (m, 1 H), 2.09 (m, 2 H), 1.65 (m, 1 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 133.3, 119.1, 60.0, 45.3, 35.8, 29.3, 23.1.

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