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Diastereoselective α-allylation of secondary amines

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ABSTRACT

We describe the diastereoselective α-allylation of various amines using an anodic oxidation-amidoalkylation sequence. Especially, we found that an acyclic amine, diethylamine, can be allylated with an excellent diastereoselectivity, as high as 94/6. Following our simple protocol, functionalized piperidine, pyrrolidine, morpholine, and tetrahydroisoquinoline were also obtained with moderate to good diastereomeric excesses and in good to excellent yields.

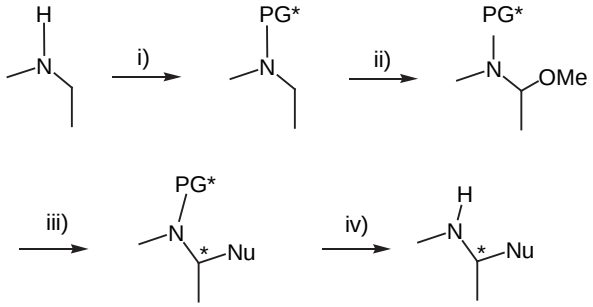
1. Introduction

The development of synthetic methodologies for the preparation of optically active amines constitutes an area of major interest[1] due to their occurrence in many biologically active compounds[2] as well as their utility as chiral auxiliaries,[3a] chiral catalysts[3b,c] or chiral ligands.[3d]

Stereoselective introduction of a substituent at the α-position of nitrogen of an achiral secondary amine is a particularly attractive process, which could be useful in the construction of nitrogen containing compounds.

Among the very few methods, which allow such transformation,[4] we choose to investigate the oxidative pathway and more particularly the anodic oxidation of *N*-protected amines.[5] Thus, to achieve the α-substitution of amines, the overall process would include (as shown in Scheme 1): (i) the protection of the amine nitrogen, (ii) the two-electron oxidation of the latter to an iminium species or *N*,*O*-acetal after trapping by methanol (for mechanism see Ref. 5) (iii) the nucleophilic addition of carbon nucleophiles to this species, (iv) and finally the deprotection of nitrogen atom. This method is a now very well known and largely used. Up to now very few examples of an asymmetric version of this method, using achiral secondary amines as starting materials, have been described.[5]

In order to attain a stereoselective process, it was anticipated that the protective group in the above scheme would be a chiral auxiliary. This protective group is generally an electron withdrawing group (CO_2R, SO_2Ar…), which while making the oxidation more difficult, affords a more electrophilic intermediate and stabilizes the resulting *N*,*O*-acetal.



Scheme 1. General scheme for the α-substitution of secondary amines.

Carbamate groups are classically used in achiral series, their chiral counterparts were checked but did not induce interesting selectivities.[6] We turned our attention to sulfur and phosphorous based electron withdrawing groups, which could bring chirality close to the reactive center.

We have recently studied various heteroatom-based chiral inductors acting as protective groups in an anodic oxidation step.[7,8] In particular, we developed a series of phosphorus based protective groups[8] from which chloro derivative **1** was found to give the best diastereoselectivity in subsequent alkylation reactions. We demonstrated how stereoselective amidoalkylation of pyrrolidine at the α-position of the nitrogen can be achieved.

Herein, we report the application of this sequence to the functionalization of various amines.

We chose to exemplify our methodology with four different amines: piperidine, morpholine, tetrahydroisoquinoline, and diethylamine, and explore the selectivity of allylation step. Along

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with some representative heterocycles we investigated the diastereoselective functionalization of an acyclic amine, such as diethylamine (Fig. 1).

1.1. Synthesis of phosphoramides 2

The first step was the protection of the amine by the phosphoryl chloride **1** (Table 1). This protection step was performed in dichloromethane in the presence of triethylamine as previously described.[7] Yields and diastereoselectivities observed for this reaction are collected in Table 1. Under these conditions (method A), the diastereoselectivity of this reaction step was excellent >95/5 whereas the phosphoryl chloride **1** was a mixture of isomers (67/33). This excellent diastereoselectivity could be the result of an equilibrium between the two isomers of **1** and a much more rapid reaction of the amine with one of these isomers. A cis configuration between the amine and the 2,6-dichlorophenyl group was established for the major diastereomer, the amine occupying an equatorial position. It is noteworthy that the trans isomer could also be obtained as the major isomer as exemplified for isomer trans **3a** and **3e**. When a cooled THF solution of magnesium bromide diethylamine was added to the 67/33 mixture of **1** (method B), a mixture of **3e**/**2e** with the same diastereomeric ratio was obtained in 65% yield. Using an enriched mixture (78/22) of **1**, a 78/22 mixture of **3e**/**2e** was obtained. Under these experimental conditions, the major isomer was the *trans* compound **3e**, which was easily separated from the mixture. Thus, the addition of metalated diethylamine at low temperature gives rise to an apparent retention of configuration. The reaction was also conducted with metalated pyrrolidine to give the phosphonamide **2a**/**3a** in the same diastereomeric ratio as the starting material (entry 2). Thus we can prepare, as will, one diastereoisomer or the other.

1.2. Anodic oxidation of phosphoramides 2

The oxidation potentials of the protected amines **2a**–**e** and **3a**,**e** were determined by cyclic voltammetry using a vitreous carbon anode, a platinum cathode and a saturated calomel reference electrode. The results are collected in Table 2. The resulting type of voltammogram is indicative of a chemically irreversible process with fast follow-up reaction. In all cases, the voltammograms are consistent with an irreversible bielectronic process and the peaks potential are ranging form 1.80 V to 1.91 V versus SCE.

The protected amines **2a**–**e** were subjected to anodic oxidation in an undivided cell, under constant current. The reaction conditions were similar to those described for the oxidation of pyrrolidine.[8] Briefly, the reaction was performed in methanol in the presence of tetraethylammonium tetrafluoroborate as the supporting electrolyte. The cathode and anode were graphite carbon electrodes.[9]

Table 2 presents the oxidation potential, faradaic, and chemical yield, as well as the diastereomeric ratio of the methoxylation reaction for each amine.

In all cases, the chemical yield of the reaction is excellent. We did not notice any correlation between the oxidation potential and the faradaic yield of the reaction. Interestingly but surprisingly the trans derivatives **3a** and **3e** could not be oxidized cleanly though they exhibit very close oxidation potential values as compared to their cis isomers (Table 2). Only by-products were observed, the reaction was slow and not reproducible. A plausible explanation would be an elimination of the intermediary formed cation-radical under the assistance of the lone pairs of the ring oxygens, which are antiperiplanar to the P–N bond in these trans isomers.

The oxidation of tetrahydroisoquinoline and morpholine derivatives **2c** and **2d** was totally regioselective (Fig. 2). As expected, the methoxylation of **2c** occurred only at the benzylic position.[10]

As expected, in the case of morpholine, the methoxy group was introduced at the carbon adjacent to nitrogen and not oxygen. Methoxylation of ethers requires indeed harsher conditions of oxidation.[11]

All the phosphoramides we studied so far proved to be excellent electrochemical substrates; this means that the chiral phosphorus auxiliary increased the nitrogen oxidation potential (relative to the parent amine) to reasonable value (similar to carbamates) and stabilized efficiently the methoxy derivatives.

1.3. Amido allylation of methoxylated compounds 4

With these methoxylated products in hand, we checked the stereoselectivity of the amidoalkylation. We choose to study the addition of allyltrimethylsilane to methoxy compounds **4a**–**e** in a standard protocol using trifluoroboron etherate or dibutylboron triflate as Lewis acid. Two different reaction conditions were used (methods C and D, Table 3).

The yields and diastereomeric ratios of these reactions using either method C or D are collected in Table 3. The yields correspond to isolated products and the diastereomeric ratios were determined using ^{31}P NMR and/or HPLC analysis on the crude reaction mixtures.

In most cases (except entry 7) the allylated product could be isolated with moderate to excellent yields (50–87%).

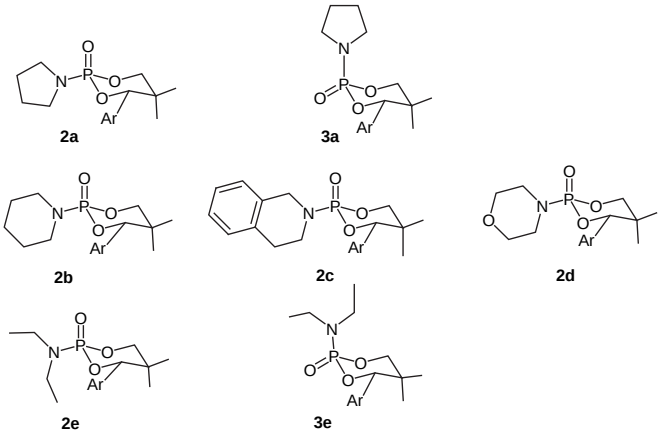
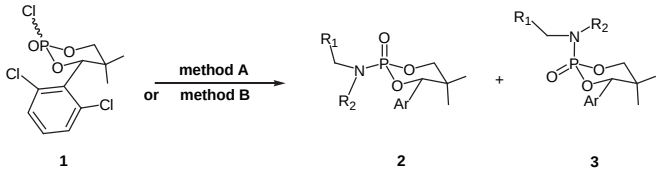


Fig. 1. Protected amines.

Table 1
Protection of the amines

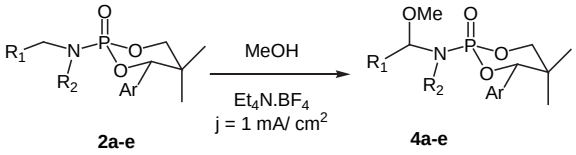


1 2 3

Entry	Amine	**1** (dr)	Method	Product (yield)	d.r.
1	Pyrrolidine	67/33	A	**2a** (86%)	99/1
2	Pyrrolidine	86/14	B	**2a**/**3a** (62%)	14/86
3	Piperidine	67/33	A	**2b** (87%)	99/1
4	Tetrahydro-isoquinoline	67/33	A	**2c** (90%)	99/1
5	Morpholine	67/33	A	**2d** (66%)	99/1
6	Diethylamine	67/33	A	**2e** (68%)	95/5
7	Diethylamine	67/33	B	**2e**/**3e** (80%)	33/67
8	Diethylamine	78/22	B	**2e**/**3e** (88%)	22/78

Method A: CH_2Cl_2, Et_3N, Δ; method B: $(R_1CH_2)R_2NMgBr$, THF, 0 °C.

Table 2
Anodic oxidation of the phosphoramides

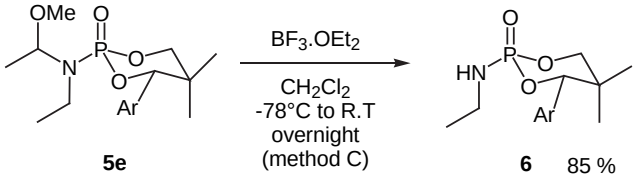


2a-e **4a-e**

Entry	Reactant	E_p	Faradaic yield	Product	Chemical yield	d.r
1	**2a**	1.91	47%	**4a**	95%	51/49
2	**3a**	1.80	—	—	—	—
3	**2b**	2.11	32%	**4b**	95%	70/30
4	**2c**	2.01	26%	**4c**	73%	54/46
5	**2d**	2.25	20%	**4d**	82%	65/35
6	**2d**	"	48%	**4d**	80%	65/35
7	**2e**	2.05	17%	**4e**	90%	65/35
8	**3e**	2.00	—	—	—	—

Ep=oxidation potential (vs sce) at a scan rate of 100 mV s^{-1}, d.r=diastereomeric ratio.

In entry 7, the main isolated product of the reaction was the protected ethylamine **6** resulting from a de-alkylation reaction (Scheme 2).

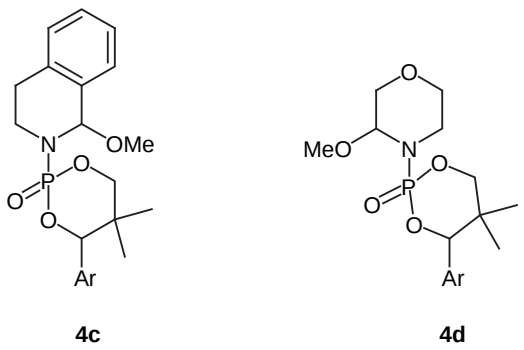


Scheme 2. De-alkylation of the protected diethylamine.

Such a de-alkylation reaction has already been described during an anodic oxidation process.[12] Since compound **6** was the result of the hydrolysis of an intermediary iminium species, it was anticipated that such intermediate must be trapped immediately by a nucleophile to avoid de-alkylation. Indeed, using method C where the nucleophile was introduced before the Lewis acid, the allylation occurred in a 85% yield (entry 8).

Piperidine was allylated with little diastereoselectivity (53/47, entry 13). The loss of diastereoselectivity compared to pyrrolidine had already been noted in other methodological studies.[6,13,14] The presence of the aromatic ring in tetrahydroisoquinoline improves only slightly the diastereomeric ratio to a modest 63/37 (entry 14).

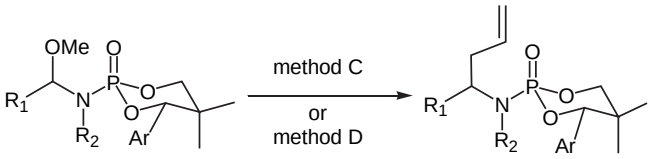
Morpholine turned out to be allylated with a diastereomeric excess comparable with pyrrolidine (80/20). However, the two diastereomers were not separated by chromatographic column as it was the case with pyrrolidine. Examples of functionalization of morpholine are rare[5a] and diastereoselective reactions are rarer. This allylation, obtained with a reasonable diastereoselectivity is therefore very interesting.



4c **4d**

Fig. 2. Regioselectivity of the methoxylation of tetrahydroisoquinoline and morpholine.

Table 3
Amido-allylation



4a-e **5a-e**

Entry	Reactant	Method	Product	Yield	d.r
1	**4a**	C	**5a**	85%	80/20
2	**4a**	D	**5a**	67%	83/17
3	**4b**	C	**5b**	75%	53/47
4	**4c**	C	**5c**	50%	63/37
5	**4d**	C	**5d**	85%	75/25
6	**4d**	D	**5d**	87%	80/20
7	**4e**	C	**5e**	<10%	n.d
8	**4e**	D	**5e**	85%	94/6

Method C: (1) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, 15 min. (2) allylTMS, CH_2Cl_2, −78 °C to rt, overnight.
Method D: allylTMS, then Bu_2BOTf, CH_2Cl_2, −78 °C, 2–4 h.

Unexpectedly, the best results were observed for diethylamine, as the allylated product was formed with an excellent 94/6 diastereoselectivity (entry 18). The two diastereomers could not be separated by column chromatography. To the best of our knowledge, no other diastereoselective amidoalkylation of acyclic amines has been reported to date.

2. Conclusion

In this study, we synthesized stable equivalents of an iminium ion for four different amines with excellent chemical yields. We were then able to allylate different secondary amines with good yields. While the method we developed did not display interesting diastereoselectivity in the allylation of piperidine or tetrahydroisoquinoline, it was found that morpholine and particularly diethylamine could be functionalized with good to excellent diastereoselectivity thanks to the proposed phosphoryl chiral auxiliary.

This oxidation–amidoalkylation sequence, using our phosphorus based chiral inductor seems to be a general method to functionalize secondary amines, in some cases in a diastereoselective manner. This could give access to a variety of molecules with various amine backbones, such as natural products and analogs and bioactive compounds since deprotection of chiral auxiliary could be easily achieved.[8]

The generalisation of our methodology implies to test the behavior of other acyclic amines and to introduce different nucleophiles to attain more diversely substituted scaffolds and eventually to tackle the functionalization of primary amines.

3. Experimental part

3.1. General

Allyltrimethylsilane, trifluoride boron etherate, dibutylboron, solvents, and other reagents were purchased from commercial sources unless otherwise noted. Anodic oxidations were carried out under nitrogen, substitution reaction under argon. MeOH used is of synthesis grade, CH_2Cl_2 was distilled from CaH_2. Normal organic processing of organic extracts consists in drying over $MgSO_4$, filtering, and concentrating under reduced pressure with a rotary

evaporator. The compounds were purified by column chromatography on silica gel (60 SDS, 35–70 μm). The electrochemical oxidations were performed using a PJT 120-1 potentiostat/galvanostat equipped with a current follower model IG5N. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-300 or Avance-400 spectrometer. ^{31}P NMR spectra were recorded on a Bruker Avance-300 spectrometer. Chemical shifts (δ) were recorded in parts per miilion with the solvent resonance as internal standard or using H_3PO_4 as an external standard. Coupling constants (J) are recorded in hertz. Melting points are given uncorrected. HPLC analyses were realized on an LC-10A Shimadzu apparatus equipped with a Kromasyl C18 column (250×4.6 mm) with acetonitrile—water as solvent. Compounds are detected at 210 nm. Mass spectra were obtained by a chemical ionization technique (reagent gas: NH_3) with a Nermag R-10-10C.

3.2. General procedures for the protection of amines

Method A: The amine (1.50 mmol) and triethylamine (210 μL, 1.50 mmol) were introduced in a three-neck flask containing 5 mL of dichloromethane. 2-Chloro-4-(2,6-dichlorophenyl)-5,5-dimethyl-[1,3,2] dioxaphosphinane **1** (492 mg, 1.5 mmol) in 15 mL of dichloromethane was added dropwise (over 15 min) to the amine using a dropping funnel. The reaction mixture was refluxed for 5 h. It was then washed with a saturated aqueous solution of NH_4Cl and with brine. The organic layer was processed as previously described (Ref. 8). The crude product was purified by chromatography on a silica gel column using a diethyl ether/methanol (97/3) mixture as solvent.

Method B: To a cooled (0 °C) solution of amine (7.5 mmol) in 2 mL of anhydrous THF was added dropwise 1.5 mL of a 3 M solution of methylmagnesium bromide in ether. The mixture was stirred for 10 min at 0 °C and for two additional hours at room temperature. The mixture was cooled to 0 °C and a solution of 1.5 mmol of **1** in 3 mL of THF was slowly added. The mixture was stirred for 2 h. at 0 °C and then quenched by the slow addition of 2 mL of a saturated aqueous NH_4Cl solution. The reaction mixture was extracted with AcOEt. The organic phase was washed with a saturated aqueous NH_4Cl solution, then brine and dried over $MgSO_4$. The solvent was distilled off and the residue purified by column chromatography.

*3.2.1. 1-[4-(2,6-Dichloro-phenyl)-5,5-dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl]-pyrrolidine (**3a**).* This compound was obtained following the method B. Yield: 291 mg, 0.802 mmol, 53% as white crystals. Mp: 106 °C, R_f=0.43 (pentane/AcOEt: 50/50), t_R 5.69 min (CH_3CN/H_2O: 50/50, d=1 mL/min), MS (IC): m/z=404/402 (MK^+); 388/386 (MNa^+); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.25 (m, 2H), 7.14 (t, J=8.0 Hz, 1H), 5.94 (d, J=2.3 Hz, 1H), 4.05 (dd, J=4.4, 11.0 Hz, 1H), 3.87 (dd, J=11.0, 21.4 Hz, 1H), 3.15 (m, 4H), 1.83 (m, 4H), 1.75 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=136.2, 135.5, 131.5, 131.2, 129.6, 128.8, 81.7, 77.2, 46.7, 39.0, 26.4, 21.7, 21.4; ^{31}P NMR (121 MHz, $CDCl_3$): δ=3.75 ppm. 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 3.72%.

*3.2.2. [4-(2,6-Dichlorophenyl)-5,5-dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl]-piperidine (**2b**).* This compound was obtained following the method A. Yield: 493 mg (1.29 mmol, 87%) as a yellow oil. R_f=0.46 (Et_2O/MeOH 3%); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.35 (dd, J=2.0, 8.0 Hz, 1H), 7.32 (dd, J=2.0, 8.0 Hz, 1H), 7.22 (t, J=8.0 Hz, 1H), 6.19 (d, J=3.0 Hz, 1H), 4.39 (dd, J=11.0, 3.0 Hz, 1H), 3.79 (dd, J=11.0, 31.0 Hz, 1H), 3.21 (m, 4H), 1.58 (m, 6H), 1.23 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=136.1, 135.8, 131.4, 129.5, 128.7, 81.7, 77.2, 45.1, 39.4, 26.5, 24.8, 21.5, 17.1; ^{31}P NMR (121 MHz, $CDCl_3$): δ=7.2 ppm; IC-MS: m/z [MNa^+] 402/400. Anal. Calcd for $C_{16}H_{22}Cl_2NO_3P$: C 50.81%, H 5.86%, N 3.70%. Found: C 50.73%, H 5.76%, N 3.75%.

*3.2.3. [4-(2,6-Dichlorophenyl)-5,5-dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl]-1,2,3,4-tetrahydroisoquinoline (**2c**).* This compound was obtained following the method A. Yield: 575 mg (1.35 mmol, 90%) as a yellow oil. R_f=0.59 (Et_2O/MeOH 3%), t_R (CH_3CN/H_2O: 60/40): 7.9 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.34 (m, 3H), 7.20–7.05 (m, 5H), 6.34 (d, J=2.5 Hz, 1H), 4.53 (m, 3H), 3.90 (dd, J=11.0, 23.0 Hz, 1H), 3.63 (t, J=6.0 Hz, 1H), 3.60 (t, J=6.0 Hz, 1H), 2.90 (m, 2H), 1.34 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=136.2, 135.8, 135.5, 134.2, 133.3, 131.5, 131.1, 129.9, 129.3, 128.9, 126.4, 82.0, 77.4, 45.9, 42.0, 39.1, 29.0, 21.9, 21.6; ^{31}P NMR (121 MHz, $CDCl_3$): δ=6.4 ppm; IC-MS: m/z [MNa^+] 448/450. Anal. Calcd for $C_{20}H_{22}Cl_2NO_3P$: C 56.35%, H 5.20%, N 3.29%. Found: C 56.27%, H 5.26%, N 3.25%.

*3.2.4. [4-(2,6-Dichlorophenyl)-5,5-dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl]-morpholine (**2d**).* This compound was obtained following the method A. Yield: 376 mg (1.00 mmol, 66%) as a white solid. R_f=0.24 (Et_2O/MeOH 3%), t_R (CH_3CN/H_2O: 60/40): 5.7 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.32 (dd, J=2.0, 8.0 Hz, 1H), 7.31 (dd, J=2.0, 8.0 Hz, 1H), 7.15 (t, J=8.0 Hz, 1H), 6.26 (d, J=3.0 Hz, 1H), 4.45 (dd, J=11.0, 3.0 Hz, 1H), 3.83 (dd, J=11.0, 23.0 Hz, 1H), 3.64 (dd, J=4.0, 5.0 Hz, 2H), 3.28 (ddd, J=4.0, 4.0, 12.0 Hz, 2H), 1.21 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=136.1, 135.5, 131.5, 130.9, 129.8, 128.9, 82.0, 77.4, 67.2, 40.7, 39.1, 21.9, 21.5; ^{31}P NMR (121 MHz, $CDCl_3$): δ=5.8 ppm; IC-MS: m/z [MNa^+] 404/402. Anal. Calcd for $C_{15}H_{20}Cl_2NO_4P$: C 47.39%, H 5.30%, N 3.68%. Found: C 47.30%, H 5.20%, N 3.75%.

*3.2.5. [4-(2,6-Dichlorophenyl)-5,5-dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl]-diethylamine (**2e**).* This compound was obtained following the method A. Yield: 373 mg (1.02 mmol, 68%) as white crystals. Mp 116 °C, R_f=0.45 (Et_2O/MeOH 3%), t_R (CH_3CN/H_2O: 60/40): 7.9 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.35 (dd, J=2.0, 8.0 Hz, 1H), 7.32 (dd, J=2.0, 8.0 Hz, 1H), 7.17 (t, J=8.0 Hz, 1H), 6.30 (d, J=3.0 Hz, 1H), 4.45 (dd, J=11.0, 3.0 Hz, 1H), 3.80 (dd, J=11.0, 22.0 Hz, 1H), 3.21 (m, 4H), 1.27 (s, 3H), 1.15 (t, 6H), 0.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=136.2, 135.8, 135.5, 131.4, 130.9, 129.5, 128.8, 81.7, 77.2, 39.3, 39.0, 21.8, 21.5, 21.4; ^{31}P NMR (121 MHz, $CDCl_3$): δ=8.7 ppm; IC-MS: m/z [MNa^+]: 390/388, [MK^+] 406/404. Anal. Calcd for $C_{15}H_{22}Cl_2NO_3P$: C 49.19%, H 6.06%, N 3.82%. Found: C 49.27%, H 6.15%, N 3.71%.

*3.2.6. [4-(2,6-Dichlorophenyl)-5,5-dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl]-diethylamine (**3e**).* This compound was obtained following the method B and isolated as white crystals (380 mg, 1.04 mmol, 68%). R_f=0.42 (pentane/AcOEt: 50/50); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.28 (dd, J=1.4, 8.0 Hz, 2H), 7.16 (t, J=8.0 Hz, 1H), 5.92 (d, J=2.4 Hz, 1H), 4.04 (dd, J=5.4, 11.1 Hz, 1H), 3.91 (dd, J=11.1, 20.5 Hz, 1H), 3.05 (m, 4H), 1.28 (s, 3H), 1.14 (t, J=7.2 Hz, 6H), 0.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=136.2, 135.5, 131.7, 130.9, 129.9, 128.5, 83.3, 78.3, 39.3, 39.3, 22.1, 21.5, 14.2; ^{31}P NMR (121 MHz, $CDCl_3$) δ (ppm): 3.87 ppm; IC-MS: m/z [MNa^+]: 390/388, [MK^+] 406/404. Anal. Calcd for $C_{15}H_{22}Cl_2NO_3P$: C 49.19%, H 6.06%, N 3.82%. Found: C 49.27%, H 6.15%, N 3.68%.

3.3. General procedure for the anodic oxidation

The protected amine (**2a**–**e**) (0.50 mmol) and tetraethylammonium tetrafluoroborate as the supporting salt (48 mg, 0.22 mmol) were dissolved in 15 mL of methanol. This solution was introduced in an undivided cell equipped with a carbon anode (either graphite or vitreous carbon) and a graphite carbon cathode. The cell was placed in a water bath at room temperature. A constant current of

1 mA/cm^2 was applied to the system. The reaction course was monitored by TLC. When the electrolysis was stopped the solvent was evaporated under reduced pressure in the presence of sodium carbonate. The residue was triturated in diethyl ether and the resulting mixture was filtered and evaporated to give the desired methoxylated product.

*3.3.1. 1-[4-(2,6-Dichlorophenyl)-5,5-dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl]-2-methoxy-piperidine (**4b**).* The electrolysis (using a graphite carbon anode) was stopped once 299 °C (6.2 F) has been consumed. Yield: 194 mg (0.49 mmol, 95%) as a white solid. R_f=0.47 (Et_2O/MeOH 3%); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.36 (d, J=7.0 Hz, 1H), 7.32 (d, J=7.0 Hz, 1H), 7.17 (t, J=7.0 Hz, 1H), 6.29 (d, J=2.0 Hz, 1H, first dia), 6.31 (d, J=2.0 Hz, 1H, second dia), 4.94 (m, 1H, first dia), 4.97(m, 1H, second dia), 4.50 (dd, J=11.0, 3.0 Hz, 1H), 3.88 (dd, J=11.0, 31.0 Hz, 1H), 3.44 (m, 1H), 3.37 (s, 3H, first dia), 3.30 (s, 3H, second dia), 3.07 (m, 1H), 1.92 (m, 1H), 1.62 (m, 4H), 1.06 (s, 3H, first dia), 1.05 (s, 3H, second dia), 0.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=136.1, 135.5, 131.4, 129.5, 128.7, 82.8/82.7, 81.7, 77.2, 65.7, 54.3, 39.0, 30.8, 25.3, 21.8, 21.4, 18.4; ^{31}P NMR (121 MHz, $CDCl_3$): δ=6.0 and 6.5 ppm; IC-MS: m/z [MNa^+] 432/430.

*3.3.2. 2-[4-(2,6-Dichlorophenyl)-5,5-dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl]-1-methoxy-1,2,3,4-tetrahydroisoquinoline (**4c**).* The electrolysis (using a graphite carbon anode) was stopped once 367 C (7.6 F) have been consumed. Yield: 171 mg (0.37 mmol, 74%) as a white solid. R_f=0.60 (Et_2O/MeOH 3%); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.34 (m, 3H), 7.20–7.05 (m, 5H), 6.32 (d, J=2.5 Hz, 1H, first dia), 6.36 (d, J=2.5 Hz, 1H, second dia), 5.73 (d, J=6.5 Hz, 1H, first dia), 5.76 (d, J=6.5 Hz, 1H, second dia), 4.52 (m, 3H), 3.97–3.52 (m, 3H), 3.46 (s, 3H, first dia), 3.50 (m, 3H, second dia), 3.30–2.55 (m, 2H), 1.27 (s, 3H, first dia), 1.30 (s, 3H, second dia), 0.92 (s, 3H, first dia), 0.95 (s, 3H, second dia); ^{13}C NMR (100 MHz, $CDCl_3$): δ=136.2, 135.8, 135.5, 134.2, 133.3, 131.5, 131.1, 129.6, 129.3, 128.9, 126.4, 126.0, 84.1, 82.0, 77.4, 55.6, 39.6, 37.3, 35.3, 28.9, 22.4, 21.9; ^{31}P NMR (121 MHz, $CDCl_3$): δ=6.1 and 7.1 ppm; IC-MS: m/z [MNa^+] 478/480.

*3.3.3. [4-(2,6-Dichlorophenyl)-5,5-dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl]-3-methoxy-morpholine (**4d**).* The electrolysis (using a vitreous carbon anode) was stopped once 205 °C (4.2 F) have been consumed. Yield: 168 mg (0.41 mmol, 82%) as a transparent oil. R_f=0.24 (Et_2O/MeOH 3%), t_R (CH_3CN/H_2O: 60/40): 5.7 and 7.3 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.35 (dd, J=2.0, 8.0 Hz, 1H), 7.32 (dd, J=2.0, 8.0 Hz, 1H), 7.17 (t, J=8.0 Hz, 1H), 6.30 (d, J=2.5 Hz, 1H, first dia), 6.28 (d, J=3.0 Hz, 1H, second dia), 4.87 (m, 1H), 4.73 (dd, J=7.1, 7.2 Hz, 1H), 3.87 (m, 3H), 3.60 (m, 2H), 3.38 (s, 3H, first dia), 3.34 (s, 3H, second dia), 3.45–3.05 (m, 2H), 1.24 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=136.0, 135.5, 131.6, 130.7, 129.8, 128.9, 82.3/82.0, 80.9, 77.4, 70.0, 66.6/66.4, 54.8/54.6, 52.3, 39.1, 21.7, 21.5; ^{31}P NMR (121 MHz, $CDCl_3$): δ=5.0 and 4.4 ppm; IC-MS: m/z [MNa^+] 432/434.

*3.3.4. [4-(2,6-Dichlorophenyl)-5,5-dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl]-ethyl-(1-methoxy-ethyl)-amine (**4e**).* The electrolysis (using a vitreous carbon anode) was stopped once 217 °C (4.5 F) have been consumed. Yield: 178 mg (0.45 mmol, 90%) as a transparent oil. R_f=0.47 (Et_2O/MeOH 3%); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.35 (dd, J=2.0, 8.0 Hz, 1H), 7.32 (dd, J=2.0, 8.0 Hz, 1H), 7.17 (t, J=8.0 Hz, 1H), 6.38 (d, J=3.0 Hz, 1H, first dia), 6.34 (d, J=3.0 Hz, 1H, second dia), 5.11 (m, 1H, first dia), 5.07 (dq, J=6.0, 6.0 Hz, 1H, second dia), 4.51 (m, 1H), 3.87 (dd, J=11.0, 22.0 Hz, 1H, first dia), 3.88 (dd, J=11.0, 22.0 Hz, 1H, second dia), 3.27 (s, 3H, first dia), 3.35 (s, 3H, second dia), 3.21 (m, 2H), 1.40 (t, J=6.0 Hz, 3H, first dia), 1.27 (t, J=6.0 Hz, 3H, second dia), 1.30 (s, 3H), 1.26 (t, 3H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=136.2, 135.3, 131.6, 131.5, 129.5, 128.8, 84.6/84.5, 81.8/81.6, 77.2, 54.8/52.5, 39.3, 39.0, 21.8, 21.5, 21.4; ^{31}P NMR (121 MHz, $CDCl_3$): δ=8.5 and 8.1 ppm.

3.4. General procedure for the allylation

Method C: The methoxylated amine **4a**–**e** (0.17 mmol) in 7 mL of dichloromethane was introduced in a reaction flask. This solution was cooled under argon at −78 °C before trifluoroboron etherate ($BF_3\cdot OEt_2$) (44 μL; 0.35 mmol) was added using a syringe. The reaction was stirred at the same temperature for 15 min, then allyltrimethylsilane (37 μL; 0.23 mmol) was added. The reaction was stirred overnight and the temperature was allowed to reach room temperature.

A saturated aqueous solution of NH_4Cl (4 mL) was added and the product was extracted with dichloromethane. The organic phase was then washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was chromatographed on a silica column using the described eluent.

Method D: The methoxylated amine **4a**–**e** (0.17 mmol) in 7 mL of dichloromethane was introduced in a reaction flask. This solution was cooled under argon at −78 °C before allyltrimethylsilane (37 μL; 0.23 mmol) and dibutylboron triflate (Bu_2BOTf) (1.0 M in CH_2Cl_2, 340 μL; 0.34 mmol) were added via a syringe. The reaction occurred at the same temperature for 2–4 h.

The reaction was quenched by the addition of saturated aqueous solution of NH_4Cl (4 mL) and the product was extracted with dichloromethane. Purification occurred as previously described.

*3.4.1. 2-Allyl-1-[4-(2,6-dichlorophenyl)-5,5-dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl]-pyrrolidine (**5a**).* This compound was obtained using either of the two methods. Using method C, **5a** was obtained as a white solid (28 mg, 0.07 mmol, 87%). Two diastereomers were present in an 80/20 ratio. Using method D, 22 mg of **5a** (0.054 mmol, 87%) were obtained. The diastereomeric ratio was in this case 83/17. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.33 (d, J=8.0 Hz, 1H), 7.31 (d, J=8.0 Hz, 1H), 7.15 (t, J=8.0 Hz, 1H), 6.28 (d, J=2.0 Hz, 1H, first dia), 6.27 (d, J=2.0 Hz, 1H, second dia), 5.75 (m, 1H), 5.05 (m, 2H), 4.47 (dd, J=11.0, 3.0 Hz, 1H), 3.93 (m, 1H), 3.82 (dd, J=11.0, 23.0 Hz, 1H), 3.40 (m, 1H), 3.32 (m, 1H), 2.49 (m, 1H), 2.16 (m, 2H), 1.70 (m, 2H), 1.23 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=136.2, 135.2, 131.6, 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.

All the data were in accordance with those previously described.[8]

*3.4.2. 2-Allyl-1-[4-(2,6-dichlorophenyl)-5,5-dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl]-piperidine (**5b**).* Using method C, two diastereomers were present in a 64/36 ratio. Yield: 46 mg (0.11 mmol, 65%) as a transparent oil. R_f=0.49 (Et_2O/MeOH 3%); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.33 (m, 2H), 7.15 (t, J=8.0 Hz, 1H), 6.27 (d, J=2.0 Hz, 1H, first dia), 6.30 (d, J=2.0 Hz, 1H, second dia), 5.75 (m, 1H), 5.05 (m, 2H), 4.49 (dd, J=11.0, 3.0 Hz, 1H), 3.92 (m, 1H), 3.82 (dd, J=11.0, 23.0 Hz, 1H), 3.57 (m, 1H), 2.95 (m, 1H), 2.46 (m, 2H), 2.08 (m, 2H), 1.62 (m, 4H), 1.06 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=136.1, 135.8, 135.7, 135.5, 131.4, 129.5, 128.7, 116.8, 81.7, 77.2, 51.2, 39.5, 36.4, 35.6, 27.7, 26.0, 21.6, 21.5, 18.4; ^{31}P NMR (121 MHz, $CDCl_3$): δ=7.4 and 7.8 ppm; IC-MS: m/z [MNa^+] 440/442. Anal. Calcd for $C_{19}H_{26}Cl_2NO_3P$: C 54.56%, H 6.27%, N 3.35%. Found: C 54.32%, H 6.12%, N 3.18%.

*3.4.3. 1-Allyl-2-[4-(2,6-dichlorophenyl)-5,5-dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl]-1,2,3,4-tetrahydroisoquinoline (**5c**).* Using method C, two diastereomers were present in a 63/37 ratio. Yield: 55 mg (0.12 mmol, 69%) as a white solid. R_f=0.66 (Et_2O/MeOH 3%); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.39–7.19 (m, 3H), 7.20–7.05 (m, 5H), 6.27 (d, J=2.5 Hz, 1H, first dia), 6.35 (d, J=2.5 Hz,

1H, second dia), 6.08–5.89 (m, 1H), 5.16–4.98 (m, 2H), 4.86 (m, 1H, first dia), 4.95 (m, 1H, second dia), 4.53 (dd, *J*=11.0, 2.0 Hz, 1H), 3.95–2.95 (m, 5H), 2.61 (m, 2H), 1.30 (s, 3H, first dia), 1.32 (s, 3H, second dia), 0.94 (s, 3H, first dia), 0.97 (s, 3H, second dia); ^{13}C NMR (100 MHz, $CDCl_3$): δ=136.2, 135.8, 135.7, 135.5, 134.7, 134.2, 133.3, 131.5, 131.1, 129.6, 129.3, 128.9, 126.4, 126.0, 117.7, 82.0, 77.4, 45.9, 42.0, 39.1, 33.6, 27.5, 21.9, 21.6; ^{31}P NMR (121 MHz, $CDCl_3$): δ=7.1 and 7.9 ppm; IC-MS: *m*/*z* [MNa^+] 487/489. Anal. Calcd for $C_{23}H_{26}Cl_2NO_3P$: C 59.24%, H 5.62%, N 3.00%. Found: C 59.15%, H 5.56%, N 3.05%.

*3.4.4. 3-Allyl-4-[4-(2,6-dichlorophenyl)-5,5-dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl]-morpholine (**5d**).* Using method B, two diastereomers were present in a 80/20 ratio. Yield: 62 mg (0.15 mmol, 87%) as a transparent oil. R_f=0.39 (Et_2O/MeOH 3%), t_R (CH_3CN/H_2O: 60/40): 5.7 and 7.3 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.38 (dd, *J*=2.0, 8.0 Hz, 1H), 7.36 (dd, *J*=2.0, 8.0 Hz, 1H), 7.22 (t, *J*=8.0 Hz, 1H), 6.34 (d, *J*=3.0 Hz, 1H, first dia), 6.30 (d, *J*=3.0 Hz, 1H, second dia), 5.80 (m, 1H), 5.10 (m, 2H), 4.47 (dd, *J*=3.0 Hz, *J*=11, 1H), 3.83 (m, 2H), 3.68–3.12 (m, 6H), 2.67 (m, 1H), 2.52 (m, 1H), 1.26 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=136.2, 135.5, 134.7, 131.5, 131.0, 129.6, 128.9, 117.7, 82.0, 77.4, 68.3, 67.3, 51.2/51.0, 39.4/39.3, 39.1, 33.6, 21.9, 21.5; ^{31}P NMR (121 MHz, $CDCl_3$): δ=6.3 and 5.8 ppm; IC-MS: *m*/*z* [MNa^+] 442/444. Anal. Calcd for $C_{18}H_{24}Cl_2NO_4P$: C 51.44%, H 5.76%, N 3.33%. Found: C 51.27%, H 5.63%, N 3.28%.

*3.4.5. [4-(2,6-Dichlorophenyl)-5,5-dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl]-ethyl-(1-methyl-but-3-enyl)-amine (**5e**).* Using method D, two diastereomers were obtained in a 94/6 ratio. Yield: 36 mg (0.09 mmol, 52%) as a transparent oil. R_f=0.49 (Et_2O/MeOH 3%); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.37 (dd, *J*=2.0, 8.0 Hz, 1H), 7.34 (dd, *J*=2.0, 8.0 Hz, 1H), 7.19 (t, *J*=8.0 Hz, 1H), 6.34 (d, *J*=3.0 Hz, 1H), 5.82 (m, 1H), 5.05 (dd, *J*=15.0, 12.0 Hz, 2H), 4.45 (dd, *J*=3.0, 11.0 Hz, 1H), 3.85 (dd, *J*=11.0, 22.0 Hz, 1H), 3.77 (m, 1H), 3.19 (m, 2H), 2.45 (ddd, *J*=6.5, 7.0, 14.0 Hz, 1H), 2.25 (ddd, *J*=7.5, 8.0, 14.0 Hz, 1H), 1.29 (s, 3H), 1.24 (t, *J*=9.0 Hz, 3H), 1.23 (t, *J*=6.0 Hz, 3H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=136.2, 135.8, 135.5, 131.5, 131.4, 129.5, 128.8, 116.7, 81.5, 77.2, 52.6, 40.5, 39.0, 37.3, 21.9, 21.8, 20.5, 17.5; ^{31}P NMR (121 MHz, $CDCl_3$): δ=8.8 and 9.0 ppm; IC-MS: *m*/*z* [MNa^+] 428/430. Anal. Calcd for $C_{18}H_{26}Cl_2NO_3P$: C 53.21%, H 6.45%, N 3.45%. Found: C 53.07%, H 6.36%, N 3.28%.

*3.4.6. [4-(2,6-Dichlorophenyl)-5,5-dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl]-ethyl amine (**6**).* Compound **6** was obtained using method C. Yield: 55 mg (0.16 mmol, 95%) as a transparent oil. R_f=0.31 (Et_2O/MeOH 3%); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.37 (dd, *J*=2.0, 8.0 Hz, 1H), 7.35 (dd, *J*=2.0, 8.0 Hz, 1H), 7.19 (t, *J*=8.0 Hz, 1H), 6.30 (d, *J*=3.0 Hz, 1H), 4.49 (dd, *J*=3.0, 11.0 Hz, 1H), 3.88 (dd, *J*=11.0, 22.0 Hz, 1H), 3.15 (m, 2H), 3.00 (m, 1H), 1.27 (s, 3H), 1.20 (t, *J*=9.0 Hz, 3H), 0.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=136.1, 135.5, 131.5, 131.4, 129.6, 128.8, 81.8, 77.1, 38.9, 36.4, 21.9, 21.3, 17.5; ^{31}P NMR (121 MHz, $CDCl_3$): δ=6.5 ppm; IC-MS: *m*/*z* [MNa^+] 360/362. Anal. Calcd for $C_{13}H_{18}Cl_2NO_3P$: C 46.17%, H 5.37%, N 4.14%. Found: C 46.07%, H 5.36%, N 4.21%.

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