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

Emma Sierecki, Serge Turcaud, Thierry Martens,* Jacques Royer

'Synthèse et structure de molécules d'intérêt pharmacologique', UMR 8638 CNRS-Université René Descartes, Faculty of Pharmacy, 4 avenue de l’Observatoire, 75270 Paris Cedex 06, France
Fax +33(1)43291403; E-mail: thierry.martens@univ-paris5.fr

Received 23 March 2006; revised 23 May 2006

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 ions1 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:

(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 deprotonations11); (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 Shono12 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 reported14 with a phosphol 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.
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).

Pyrrolidines 3a–e were synthesized by condensation of pyrrolidine with 2-chloro-2-oxo-2,5,5-dimethyl-2-oxo-2\(\lambda^5\)-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-2\(\lambda^5\)-1,3,2-dioxaphosphinanes 5a–e has been described\(^6\) and could be reproduced.

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

<table>
<thead>
<tr>
<th>Compd</th>
<th>Ar</th>
<th>Yield 5 (%)(^a)</th>
<th>Yield 3 (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Ph</td>
<td>60</td>
<td>92</td>
</tr>
<tr>
<td>b</td>
<td>2,4-Cl(_2)C(_6)H(_4)</td>
<td>55</td>
<td>85</td>
</tr>
<tr>
<td>c</td>
<td>2,6-Cl(_2)C(_6)H(_4)</td>
<td>50</td>
<td>94</td>
</tr>
<tr>
<td>d</td>
<td>2,6-F(_2)C(_6)H(_4)</td>
<td>30</td>
<td>64</td>
</tr>
<tr>
<td>e</td>
<td>2-F-6-F(_3)C(_6)H(_3)</td>
<td>5</td>
<td>77</td>
</tr>
</tbody>
</table>

\(^a\) 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-

---

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

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

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

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 $\pi$-nucleophile with a limited steric effect, and is widely used in

![Scheme 4](image)

Scheme 4  Preparation of $\alpha$-allylated 1-(1,3,2-dioxaphosphinan-2-yl)pyrrolidines from the corresponding $\alpha$-unsubstituted pyrrolidines by $\alpha$-methoxoylation followed by allylation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>Product$^a$</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>6</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>7</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>3a</td>
<td>8a</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>3b</td>
<td>8b</td>
<td>98</td>
</tr>
<tr>
<td>5</td>
<td>3c</td>
<td>8c</td>
<td>96</td>
</tr>
<tr>
<td>6</td>
<td>3d</td>
<td>8d</td>
<td>97</td>
</tr>
<tr>
<td>7</td>
<td>3e</td>
<td>8e</td>
<td>95</td>
</tr>
</tbody>
</table>

$^a$ Compounds 6 and 7 were mixtures of four diastereomers; compounds 8a–e were mixtures of two diastereomers.
studies of the reactivity of iminium ions. It was, more importantly, used in the two studies\textsuperscript{3,14} we refer to for comparison.

Substitution was achieved with the boron trifluoride–diethyl ether complex as the Lewis acid on a temperature gradient (from \(-78^\circ C\) to r.t.) occurring overnight (Scheme 4). The diastereomeric ratio was determined by \textsuperscript{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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Product\textsuperscript{a}</th>
<th>Yield (%)</th>
<th>dr\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>9</td>
<td>83</td>
<td>60:40</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>10</td>
<td>84</td>
<td>65:35</td>
</tr>
<tr>
<td>3</td>
<td>8a</td>
<td>11a</td>
<td>87</td>
<td>59:41</td>
</tr>
<tr>
<td>4</td>
<td>8b</td>
<td>11b</td>
<td>85</td>
<td>60:40</td>
</tr>
<tr>
<td>5</td>
<td>8c</td>
<td>11c</td>
<td>90</td>
<td>80:20</td>
</tr>
<tr>
<td>6</td>
<td>8d</td>
<td>11d</td>
<td>89</td>
<td>65:35</td>
</tr>
<tr>
<td>7</td>
<td>8e</td>
<td>11e</td>
<td>90</td>
<td>60:40</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Compounds 9 and 10 were mixtures of four diastereomers; compounds 11a–e were mixtures of two diastereomers.

\textsuperscript{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 1 hour at \(-78^\circ C\), and gave a diastereomeric ratio of 83:17.

This result must be compared to those obtained with a BINOL-substituted phosphoryl group\textsuperscript{14} or a phenyl menthyl carbamate group\textsuperscript{14} 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\textsuperscript{30} (a phenyl menthyl carbamate). D’Oca et al.\textsuperscript{4} reported a 86:14 ratio for the allylation of this compound. However, simpler chiral carbamates (derived from mandelic acid or \textit{trans}-2-phenylcyclohexanol) gave lower diastereoselectivities (66:33, 50:50 dr). The yields for both the methoxylation and the amidoxycylation steps were also lower than those we obtained. The 4-(2,6-dichlorophenyl)-5,5-dimethyl-2-oxo-2λ\textsuperscript{3}-1,3,2-dioxaphosphinan-2-yl group in pyrrolidine 3e 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 phosphoneiminium 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 phosphoramidate derivatives 8, one can analyze the influence of substitution of the aryl group. Phenylation 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 3e 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, phosphoramidate 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 methoxyla tusation–substitution sequence on a pyrrolidine. We found that 4-aryl-5,5-dimethyl-2-oxo-2λ\textsuperscript{3}-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-
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-2H]-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.

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, BF₃·OEt₂, solvents, and other reagents were purchased from commercial sources unless otherwise noted. Anodic oxidations were carried out under N₂ substitution reactions under argon. MeOH was synthesis grade. CH₂Cl₂ was distilled from CaH₂. Normal processing of organic extracts consisted of drying over MgSO₄, filtering, and concentrating under reduced pressure by use of a rotary evaporator. The compounds were purified by column chromatography on silica gel (60–230 mesh, 230–400 mesh). The electrochemical oxidations were performed with a PFT 120-1 potentiostat/galvanostat equipped with a standard three-electrode system (Pt working electrode, Ag/AgNO₃ reference electrode, and a Pt wire counter electrode). The electrochemical experiments were performed with a Princeton Applied Research Model 273A potentiostat/galvanostat equipped with a standard three-electrode system (Pt working electrode, Ag/AgNO₃ reference electrode, and a Pt wire counter electrode). The electrochemical oxidations were performed with a PFT 120-1 potentiostat/galvanostat equipped with a standard three-electrode system (Pt working electrode, Ag/AgNO₃ reference electrode, and a Pt wire counter electrode). The electrochemical oxidations were performed with a PFT 120-1 potentiostat/galvanostat equipped with a standard three-electrode system (Pt working electrode, Ag/AgNO₃ reference electrode, and a Pt wire counter electrode).

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

Melty Phenyl[pyrrolidin-1-yl]phosphonate (1)

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

Rₜ = 0.45 (heptane–EtOAc, 1:1).

IR (neat): 2951, 2927, 2765, 2586, 2477, 2361, 1594, 1491, 1456, 1223, 1083, 1033, 1023, 999 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 7.65 (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).

13C NMR (75 MHz, CDCl₃): 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.

13P NMR (125 MHz, CDCl₃): δ = 0.1, 1.1.

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


Methyl Phenyl[pyrrolidin-1-yl]phosphonate (2)

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

Rₜ = 0.23 (heptane–EtOAc, 1:1).

Rₜ = 15.8 min (MeCN–H₂O 70:30 to 95:5 in 20 min).

IR (neat): 2954, 2868, 1456, 1437, 1369, 1197, 1133, 1059, 1017, 999 cm⁻¹.

1H NMR (400 MHz, CDCl₃): 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).

13C NMR (125 MHz, CDCl₃): 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.

13P NMR (125 MHz, CDCl₃): δ = 2.91 (minor), 2.69 (major).

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


1,3,2-Dioxaphosphinan-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 solution mixture. 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 solution mixture. 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 solution mixture.

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 solution mixture.

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 solution mixture.

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 solution mixture.

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 solution mixture.
1H NMR (400 MHz, CDCl3): 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).

13C NMR (75 MHz, CDCl3): 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.

1P NMR (125 MHz, CDCl3): δ = 4.22.

MS (Cl): m/z = 386, 388 [M + Na]+.

Anal. Calcld for C15H22NO3P: C, 61.01; H, 7.51; N, 4.74. Found: C, 61.04; H, 7.48, N, 4.36.

1-[4-(2,6-Dichlorophenyl)-5,5-dimethyl-2-oxo-2,1,3,2-dioxa-phosphinan-2-yl]pyrrolidine (3e)

Yield: 685 mg (94%); white solid; mp 135 °C.

Rf = 0.37 (EtO–MeOH, 97:3).

IR (Nujol): 1735, 1668, 1481, 1376, 1272, 1048, 919 cm–1.

1H NMR (400 MHz, CDCl3): δ = 7.28 (d, J = 9.0 Hz, 1 H), 7.28 (d, J = 9.0 Hz, 1 H), 6.25 (d, J = 2.0 Hz, 1 H), 5.84 (d, J = 2.0 Hz, 1 H), 4.47 (dd, J = 11.0, 4.0 Hz, 1 H), 3.82 (dd, J = 11.0, 24.0 Hz, 1 H), 3.37 (3 H), 3.31 (3 H), 1.83 (m, 4 H), 1.26 (s, 3 H), 0.93 (s, 3 H).


1P NMR (125 MHz, CDCl3): δ = 5.60.

MS (Cl): m/z = 386, 388 [M + Na]+.

Anal. Calcld for C15H20Cl2NO3P: C, 49.47; H, 5.54; N, 3.85. Found: C, 49.32; H, 5.55; N, 3.73.

1-[4-(2,6-Difluorophenyl)-5,5-dimethyl-2-oxo-2,1,3,2-dioxa-phosphinan-2-yl]pyrrolidine (3d)

Yield: 432 mg (64%); white solid.

Rf = 0.51 (EtO–MeOH, 97:3).

IR (Nujol): 1624, 1589, 1464, 1377, 1273, 1236, 1203, 1047, 1029, 997 cm–1.

1H NMR (400 MHz, CDCl3): 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).

1C NMR (75 MHz, CDCl3): δ = 130.3, 129.2, 128.8, 81.6, 77.2, 46.7, 39.1, 26.4, 21.7, 21.4.

1P NMR (125 MHz, CDCl3): δ = 5.60.

MS (Cl): m/z = 386, 388 [M + Na]+.

Anal. Calcld for C15H20F2NO3P: C, 49.47; H, 5.54; N, 3.85. Found: C, 49.32; H, 5.55; N, 3.73.
PAPER

Phosphorus-Derived Chiral Auxiliaries for α-Alkylation of Secondary Amines

31P NMR (125 MHz, CDCl3): δ = 3.6.

MS (Cl): m/z = 404, 406 [M + Na]+.

Anal. Calcd for C16H24NO4P (+ H2O): C, 63.39; H, 9.05; N, 3.52. Found: C, 63.18; H, 8.98; N, 3.52.

Compound 7, Isomer A

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

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

1H NMR (400 MHz, CDCl3): δ = 7.66 (t, J = 7.0 Hz, 1 H), 7.33 (m, 3 H, 5.17–4.85 (m, 1 H), 4.42 (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, 1 H), 1.57 (m, 2 H), 1.15 (m, 3 H), 1.01–0.85 (m, 12 H).

13C NMR (75 MHz, CDCl3): δ = 151.5, 134.5, 133.1, 133.0, 129.8, 128.5, 128.2, 127.8, 127.3, 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 (major), 21.3 (minor), 20.5, 17.7.

HRMS: m/z = 416, 418 [M + Na]+.

MS (Cl): m/z = 348, 349 [M + Na]+.

1-(4-(2,6-Dichlorophenyl)-5,5-dimethyl-2-oxo-2-yl)-2-methoxypyrrolidine (8c)

The reaction was stopped once 357 C (3.7 F-mol⁻¹) had been consumed.

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

Rf = 0.70 (Et3O–MeOH, 96.5:3.5). 

1H NMR (400 MHz, CDCl3): 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).

13C NMR (75 MHz, CDCl3): δ = 134.5, 133.1, 133.0, 130.4 (major), 130.3 (minor), 128.9, 126.9, 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 (major), 21.3 (minor), 20.5, 17.7.

PAPERS 125 MHz, CDCl3): δ = 4.64, 4.57 (major).

MS (Cl): m/z = 416, 418 [M + Na]+.

1-[4-(2,4-Dichlorophenyl)-5,5-dimethyl-2-oxo-2,2'-1,3,2-dioxaphosphinan-2-yl]-2-methoxyrylpyrroline (8b)

The reaction was stopped once 357 C (3.7 F-mol⁻¹) had been consumed.

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

Rf = 0.70 (Et3O–MeOH, 96.5:3.5). 

1H NMR (400 MHz, CDCl3): 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).

13C NMR (75 MHz, CDCl3): δ = 134.5, 133.1, 133.0, 130.4 (major), 130.3 (minor), 128.9, 126.9, 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 (major), 21.3 (minor), 20.5, 17.7.

PAPERS 125 MHz, CDCl3): δ = 4.64, 4.57 (major).

MS (Cl): m/z = 416, 418 [M + Na]+.

1-[4-(2,6-Dichlorophenyl)-5,5-dimethyl-2-oxo-2,2'-1,3,2-dioxaphosphinan-2-yl]-2-methoxyrylpyrroline (8c)

The reaction was stopped once 357 C (3.7 F-mol⁻¹) had been consumed.

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

Rf = 0.42 (Et3O–MeOH, 97.3).

IR: 1651, 1557, 1455, 1376, 1261, 1043, 919 cm⁻1.

IR: 1651, 1557, 1455, 1376, 1261, 1043, 919 cm⁻1.

IR: 1651, 1557, 1455, 1376, 1261, 1043, 919 cm⁻1.

IR: 1651, 1557, 1455, 1376, 1261, 1043, 919 cm⁻1.

IR: 1651, 1557, 1455, 1376, 1261, 1043, 919 cm⁻1.
1H NMR (400 MHz, CDCl3): δ = 7.44 (d, 4H), 7.28 (d, 4H), 5.81 (d, 2H), 5.07 (m, 2H), 4.51 (s, 2H), 3.87 (m, 1H), 3.75 (m, 1H), 3.60 (m, 1H), 2.50 (m, 2H), 2.18 (s, 3H), 2.01 (m, 1H), 1.81 (m, 2H), 1.61 (m, 4H), 1.39–0.91 (m, 3H), 0.90–0.66 (m, 9H).

13C NMR (75 MHz, CDCl3): 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.

1P NMR (125 MHz, CDCl3): δ = 3.8 (major), 3.7 (minor), 3.0 (major), 2.6 (minor).

MS (Cl): m/z = 428 [M + Na]+.

Methyl Phenyl-2-allylpyrrolidin-1-ylphosphonate (10)

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

1H NMR (400 MHz, CDCl3): δ = 7.66 (t, 2H), 7.33 (m, 3H), 5.69 (m, 1H), 5.00 (m, 2H), 4.25 (m, 2H), 3.65 (m, 1H), 3.29 (m, 1H), 3.14 (m, 1H), 2.45 (m, 2H), 2.31 (m, 1H), 1.51 (m, 1H), 1.98 (m, 1H), 1.78 (m, 1H), 1.64 (m, 1H), 1.50 (m, 2H), 1.33 (m, 4H), 0.98–0.87 (m, 10H).

13C NMR (75 MHz, CDCl3): 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, 25.6, 22.6, 21.4, 15.9.

MS (Cl): m/z = 412 [M + Na]+.

2-Allyl-1-(5,5-dimethyl-2-oxo-4-phenyl-2,3,2-dioxaphosphinan-2-yl)pyrrolidine (11a)

Yield: 140 mg (95%); white solid. 

1H NMR (400 MHz, CDCl3): δ = 7.40 (m, 3H), 7.37 (d, 2H), 7.16 (d, 2H), 3.92 (dd, 1H), 3.78 (dd, 1H), 3.22 (m, 1H), 2.95 (m, 1H), 1.98 (m, 1H), 1.72 (m, 1H), 1.64 (m, 1H), 1.51 (m, 1H), 1.32 (m, 4H), 1.20 (m, 4H), 1.09 (m, 1H), 0.73 (m, 3H).

13C NMR (75 MHz, CDCl3): 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.

13P NMR (300 MHz, CDCl3): δ = 5.74 (minor), 5.67 (major).

MS (Cl): m/z = 358, 359 [M + Na]+.


2-Allyl-1-[4-(2,4-dichlorophenyl)-5,5-dimethyl-2-oxo-2,3,2-dioxaphosphinan-2-yl]pyrrolidine (11b)

Yield: 165 mg (93%); white solid.

1H NMR (400 MHz, CDCl3): δ = 7.50 (m, 9H), 7.26 (m, 3H), 7.15 (m, 3H), 3.96 (s, 2H), 3.83 (m, 1H), 3.75 (d, 1H), 3.27 (d, 1H), 2.50 (m, 2H), 2.13 (s, 3H), 1.98 (m, 1H), 1.77 (m, 1H), 1.68 (m, 1H), 1.47 (m, 1H), 1.39 (s, 3H).

13C NMR (75 MHz, CDCl3): δ = 133.1, 129.2, 127.3, 127.0, 123.5, 118.1, 114.4, 110.6, 104.4, 920 cm−1.

1H NMR (400 MHz, CDCl3): δ = 6.54 (m, 1H), 5.93 (m, 1H), 5.17 (s, 1H), 4.87 (d, 1H), 2.32 (m, 1H), 2.17 (s, 3H), 2.04 (m, 1H), 1.91 (m, 1H), 1.59 (m, 3H), 0.83–0.63 (m, 11H).

13C NMR (75 MHz, CDCl3): δ = 4.7 (major), 4.5 (minor).

MS (Cl): m/z = 426, 428 [M + Na]+.

Synthesis 2006, No. 19, 3199–3208 © Thieme Stuttgart · New York
2-Allyl-1-(4-(2,6-dichlorophenyl)-5,5-dimethyl-2-oxo-2,5,1,3,2-dioxaphosphinan-2-yl)pyrrolidine (11c)

Yield: 163 mg (92%); white solid; mp 144 °C.

IR (Nujol): 3076, 2975, 2883, 1738, 1641, 1548, 1463, 1312, 1270, 1115, 995 cm⁻¹.

IR (neat): 3076, 2975, 2883, 1738, 1641, 1548, 1463, 1312, 1270, 1115, 995 cm⁻¹.

IR (neat): 3076, 2975, 2883, 1738, 1641, 1548, 1463, 1312, 1270, 1115, 995 cm⁻¹.

Acknowledgment

The authors wish to thank the CNRS and the French Ministry of Education and Research for funding.

References


(20) Similar diastereoselective results were observed through deprotonation of chiral carbamates, see: (a) Madan, S.; Milano, P.; Eddings, D. B.; Gawley, R. E. J. Org. Chem. 2005, 70, 3066. (b) Polniaszek, R. P.; Belmont, S. E. J. Org. Chem. 1990, 55, 4688.