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Synthesis, reactivity and stereochemistry of new phosphorus heterocycles with 5- or 6-membered rings

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Abstract

Syntheses of novel phosphorus heterocycles containing α-amino or α-hydroxyphosphonic or phosphinic acids motifs are developed. 2,3-dihydro-1,3-oxaphospholes (**1**) and 1,4,2-oxazaphosphinanes (**2**) exhibit a reactive part, respectively the enolether moiety and the P–H bond, which allows various structural modifications: (i) for **1a**, by introduction of amino substituents, (ii) for **2a**, by hydroxy- or aminoalkylation, by Michael addition or by P-arylation. These reactions present generally a good or even an excellent kinetic diastereoselectivity which can often be predicted by molecular models of the transition states.

Keywords: Phosphorus heterocycles; 1,3-oxaphosphole; 1,4,2-oxazaphosphinane; Stereoselective synthesis

1. Introduction

Phosphorus compounds with a nitrogen or oxygen heteroatom on the carbon α to phosphorus very often exhibit interesting biological properties, as exemplified by the following compounds (Scheme 1).

As a part of our search for new biologically active compounds in the fields of human health or plant protection, we are interested in introducing such P–C-heteroatom pattern into heterocyclic structures. Very few such phosphorus heterocycles are investigated in the literature. The results presented in this account concern two different heterocycles (Scheme 2):

- the 2,3-dihydro-1,3-oxaphospholes (**1**), five-membered heterocycles with a P–C–O design,
- the 1,4,2-oxazaphosphinanes (**2**), six-membered heterocycles with a P–C–N design.

2. Results and discussion

2.1. 2,3-Dihydro-1,3-oxaphospholes (*1*) [1]

For the synthesis of compounds **1**, we considered a simple retrosynthesis involving a double disconnection of the P–C and C–O bonds (Scheme 3).

The resulting synthons are:

(i) A dianionic structure, of which the mesomeric enolate form affords a simple synthetic equivalent with the corresponding malonic diester in presence of two equivalents of base,

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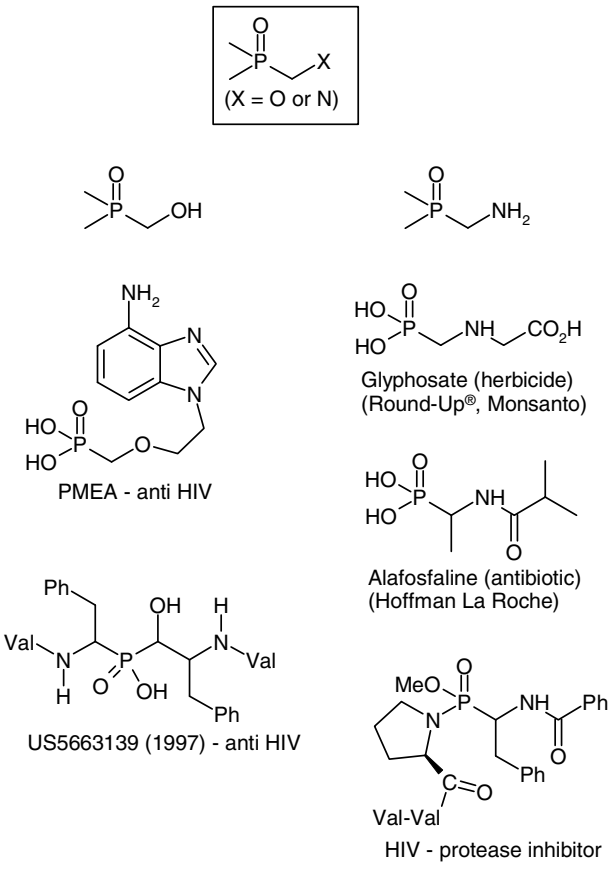


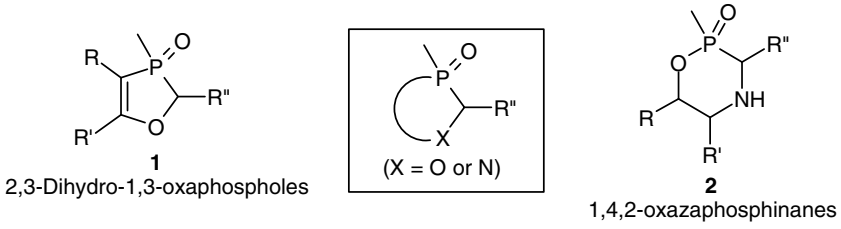
Scheme 1.

(ii) A dicationic phosphorus synthon, corresponding to a simple dielectrophilic synthetic equivalent obtained by introducing a good leaving group, such as chloride, both on the phosphorus and on the α-carbon atoms.

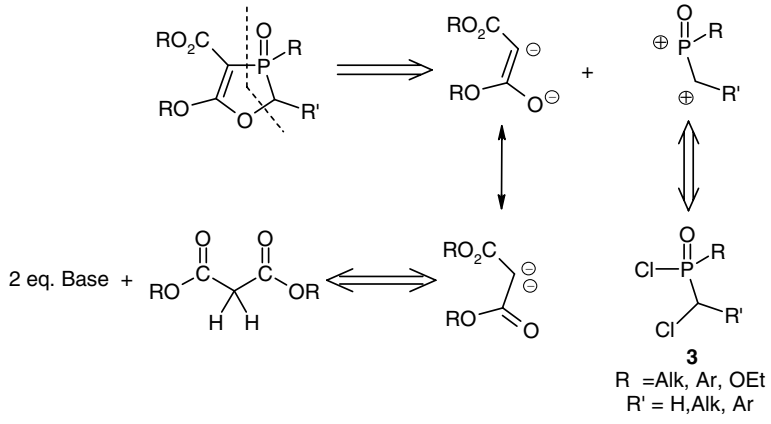
Thus, according to the disconnection approach, the direct synthesis of 2,3-dihydro-1,3-oxaphospholes (**1**) can be achieved by reaction of α-chloroalkylphosphinic or phosphonic chlorides **3** with malonic diester in presence of two equivalents of base.

The phosphorus precursors **3** are easily prepared according to the literature in satisfactory yields about 70% (Scheme 4). For the phosphinic compounds, an Abramov addition of the P–H bond of phosphinous acids on aldehydes in acidic medium affords first the corresponding α-hydroxylalkylphosphinic acids which undergo a double chlorination of both hydroxy groups at phosphorus and at α-carbon atom using an excess of thionyl chloride. For the phosphonic derivatives, the starting material is diethyl phosphite, and after addition on aldehydes in basic medium, the chlorination occurs first with Appel's reagent and then with $P(O)Cl_3$.

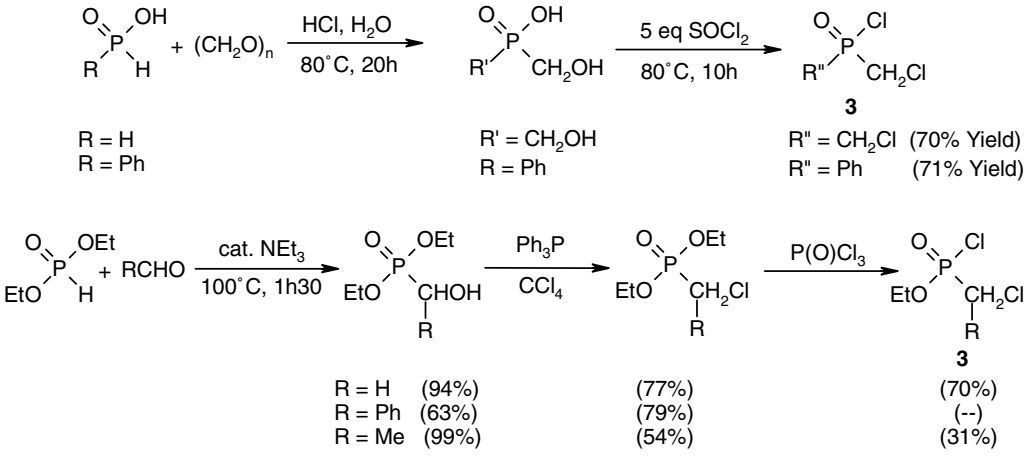
The phosphinic or phosphonic chlorides **3** were then successfully transformed into the corresponding 5-alkoxy-2,3-dihydro-1,3-oxaphospholes **1** by reaction with diethyl malonates in presence of two equivalents of sodium hydride (Scheme 5). The yields of isolated heterocycles are satisfactory, up to 70%.



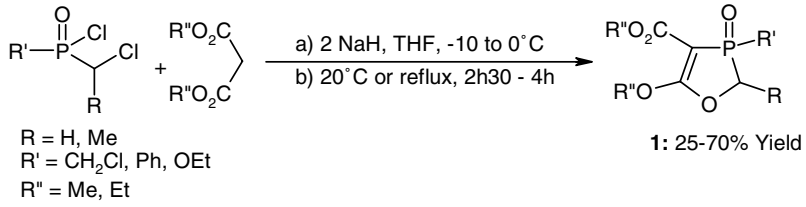
Scheme 2.



Scheme 3.



Scheme 4.



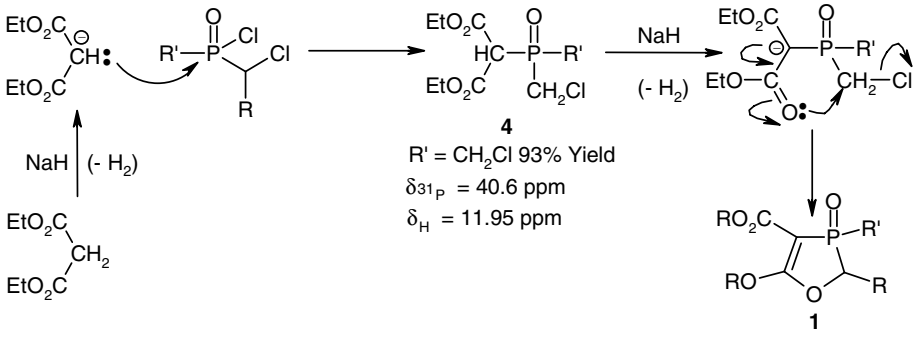
Scheme 5.

It is likely that the mechanism of formation involves first, a monodeprotonation resulting in the formation of malonic enolate which gives a nucleophilic substitution at phosphorus to afford a malono-intermediate **4** with P–C bond formation (Scheme 6). There was no evidence of P–O bond formation in the crude ^{31}P NMR spectra of reaction mixtures. The intermediate **4** could be isolated in a separate experiment (R′ = CH_2Cl) using only one equivalent of sodium hydride and is fully characterized by its NMR data. In the last step of synthesis, a second deprotonation occurs on intermediate **4** and results in the intramolecular O-alkylation of the enolate, affording the heterocycle **1**.

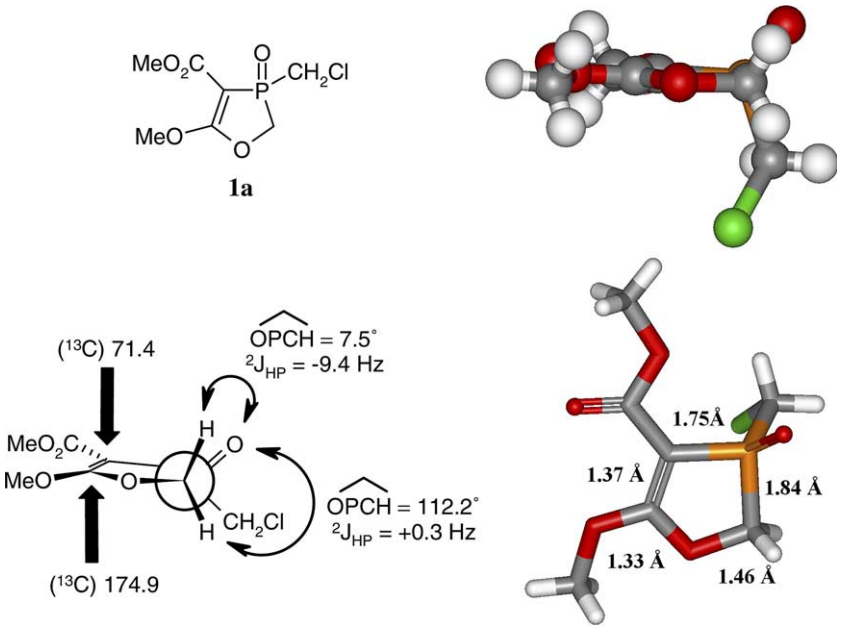
From a structural point of view, a crystal X-ray analysis of compound **1a** (R = CO_2Me, R′ = OMe, R″ = CH_2Cl) shows that the 5-membered ring is almost flat with values of 7° 5 and 112° 2 for the OPCH dihedral angle, which are in good agreement with the corresponding $^2J_{PH}$ coupling constants (respectively −9.4 Hz and +0.3 Hz) (Scheme 7) [2].

Noteworthy are the values of the shifts (174.9 and 71.4 ppm), in the ^{13}C NMR spectra, for the two sp^2 carbon atoms, which indicate a strong polarization of the C=C double bond: indeed, the C=C double bond belongs to the capto-dative class of olefins, with two electron-withdrawing groups on one side, and two donating groups on the other side.

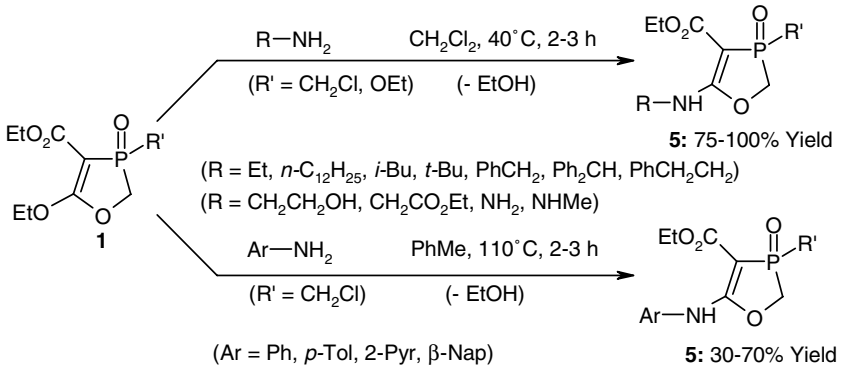
Indeed, the 5-alkoxy substituted heterocycles **1** react easily with primary amines to afford the corresponding 5-amino substituted heterocycles **5** (Scheme 8) [3]. For



Scheme 6.



Scheme 7.



Scheme 8.

aliphatic amines, the reaction occurs easily in refluxing dichloromethane and affords high yields in isolated compounds **5**, between 75% and 100%. In the case of the less reactive aromatic amines, the reaction occurs at higher temperature in refluxing toluene and the yields range from 30% up to 70%.

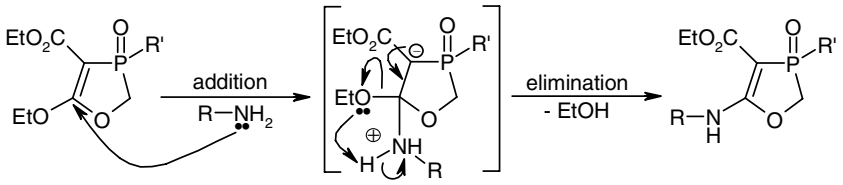
It is likely that the substitution of the alkoxy group by amino group on the dihydro-oxaphosphole **1**, proceeds through an addition–elimination process as illustrated in Scheme 9.

Finally, concerning this family of heterocycles, we succeed in applying the substitution reaction to functional primary amines (1,2-ethanolamine, ethyl glycinate, mono- or di-methylhydrazine). Investigations on the possible building of a second fused cycle by intramolecular reaction between the ester group and the functional R nitrogen substituent are now in progress.

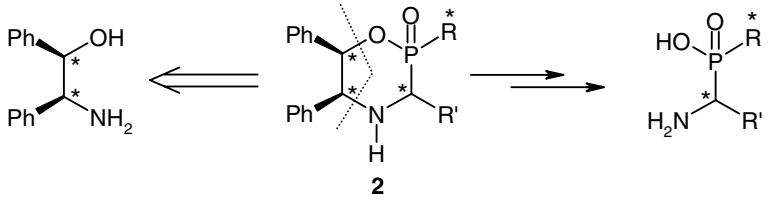
*2.2. 1,4,2-oxazaphosphinanes (**2**) [4]*

From the beginning, to build such 6-membered rings with a PCN design, we chose to use 1,2-diphenylethanolamine (R=R′=Ph), which presents two complementary advantages in the resulting heterocycle **2** (Scheme 10):

- firstly, the presence of benzylic C–O and C–N bonds should allow their cleavage by hydrogenolysis in order to obtain the corresponding free α-amino alkylphosphinic or phosphonic acids.
- secondly, the 1,2-diphenylethanolamine pattern is chiral and the use of one pure enantiomer would introduce asymmetric inductions in the ring building and further in the reactivity at phosphorus.



Scheme 9.



Scheme 10.

2.2.1. Synthesis of (±) 1,4,2-oxazaphosphinanes (2)

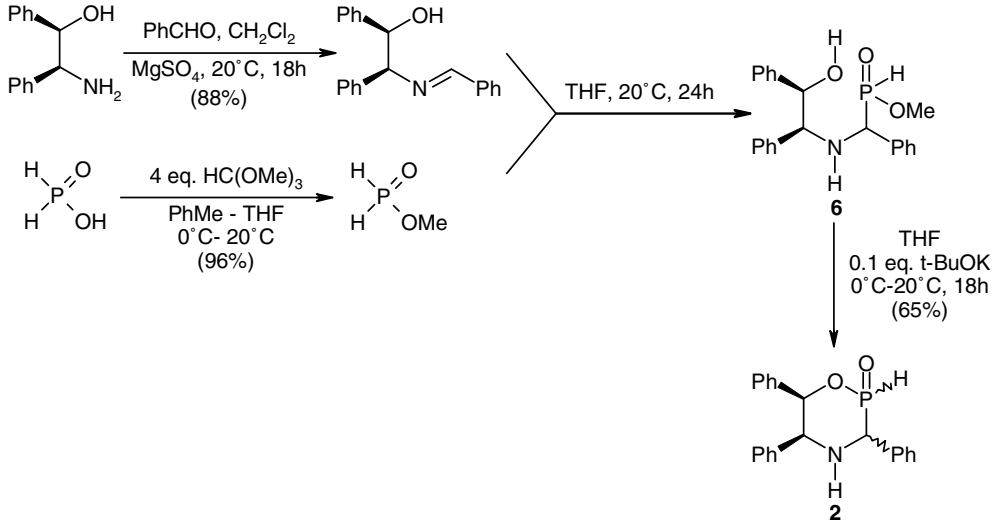
The synthesis of the 5,6-diphenyl-1,4,2-oxazaphosphinanes (**2**) has been achieved by cyclisation at phosphorus of an open chain precursor **6** (Scheme 11), through a base catalysed transesterification, which affords the cycle **2** in 65% yield. The precursors are, on one side, the imine of the racemic 1,2-diphenyl ethanolamine with benzaldehyde, and, on the other side, methyl phosphinate obtained from hypophosphorous acid esterified by trimethyl orthoformate.

From a stereochemical point of view, four diastereoisomers could be formed in the first addition step, because there are two new stereogenic centres created. Actually, four diastereoisomers are detected by ^{31}P NMR for the open chain intermediate, in the ratio shown in Scheme 12. But, only two diastereoisomers (ratio 75/25) are obtained after the second step, probably as the result of a rapid epimerisation at phosphorus in the basic conditions used for the cyclisation by transesterification.

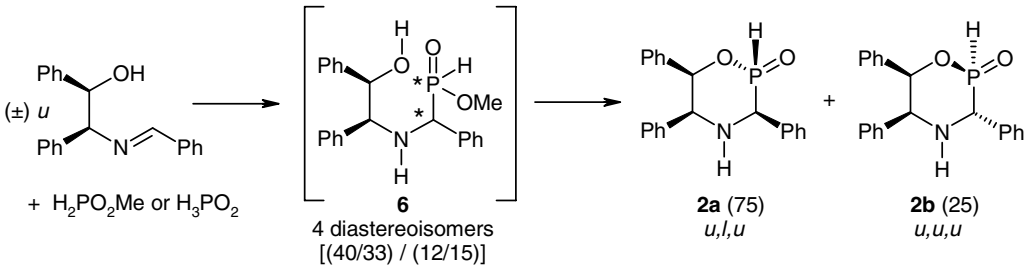
The *u*,*l*,*u* structure [5] of the major isomer **2a** was determined by a monocrystal X-ray analysis which indicated further the twisted boat structure of the heterocycle [4]. Finally, ^{1}H NMR chemical shifts and coupling constants of **2a** are in good agreement with those observed by Juaristi et al. for the 2-ethoxy-2-oxo-1,4,2-oxazaphosphinanes (Scheme 13) [6].

We could not obtain suitable crystals of the second diastereoisomer **2b** for X-ray analysis, but the *u*,*u*,*u* structure could be ascertained indirectly from stereoselective reactivities.

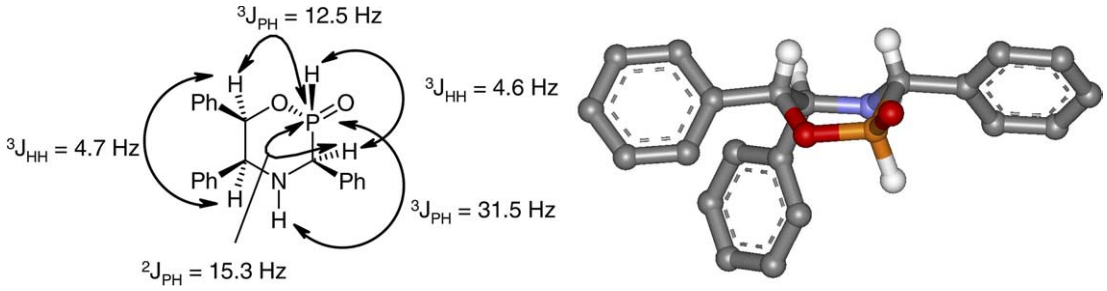
Concerning the diastereoselectivity observed, the diastereoisomeric ratio for compounds **2a** and **2b** is directly related to the ratio of the open intermediates **6** showing



Scheme 11.



Scheme 12.



Scheme 13.

that the carbon chirality α to phosphorus is determined in the first step. Indeed, we could show in competition experiments that the P–C bond formation is irreversible in this step, and, in a separate experiment, that no C–H epimerisation takes place in the reaction conditions. Therefore, the diastereoselectivity is under kinetic control and results from the favoured addition of the methyl phosphinate anion on the *Si* side of the imine, as shown in Scheme 14. The proposed structure of the transition state involving the *anti* configuration of the imine and hydrogen bonding between the free hydroxyl group and the polar phosphorus reagent accounts well for the preferential formation of the *u*,*l*,*u* diastereoisomer.

2.2.2. Reactivity of 2-hydrogeno-1,4,2-oxazaphosphinanes (*2a*)

The reactivity of 2-hydrogeno-1,4,2-oxazaphosphinanes (**2**) was investigated on the pure major isomer **2a**, which can be easily isolated by preferential crystallisation, and concerns mainly the reactivity of the P–H bond.

2.2.2.1. Addition on aldehydes [7].

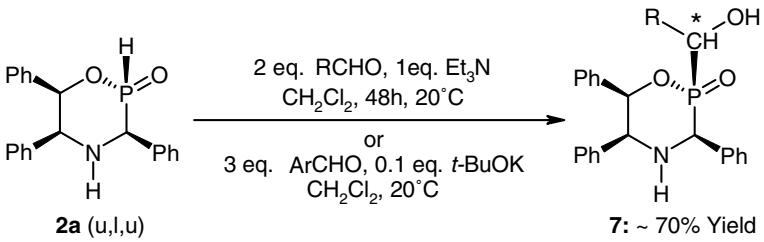
Abramov [8] or Pudovik [9] reactions of compound **2a** with aldehydes afford good yields in α-hydroxyalkyl derivatives phosphoaldol adducts [10], which exhibit an interesting N–C–P–C–O framework (Scheme 15).

The reaction is easier with aliphatic aldehydes in presence of tertiary amines than with aromatic aldehydes which need catalysis by potassium *tert*-butoxide. But concerning the diastereoselectivity obtained in the creation of the new carbon chiral center, the *de* are moderate (lower than 40%) with aliphatic aldehydes while the *de* come up to 84% with aromatic ones.

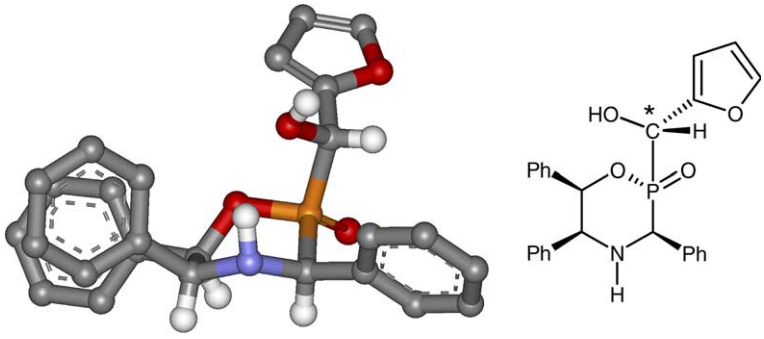
It was possible to obtain suitable single crystal for X-ray analysis of the major isomer of the adduct **7a** from furfuraldehyde, which appears to be the *u*,*u*,*l*,*u* isomer (Scheme 16).

In agreement with the literature for a similar case [11], we could ascertain, through competition reactions, that the phosphoaldol reaction is under kinetic control in our reaction conditions. Actually, two possible transition states result from the attack of the phosphinate

Scheme 14.



Scheme 15.



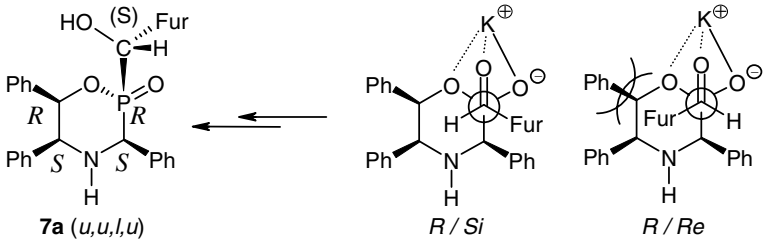
Scheme 16.

anion on the *Si* side or the *Re* side of the aldehyde with retention of configuration at phosphorus. Examinating the molecular models of the transition states in which the carbonyl oxygen is coordinated to the potassium cation together with the two oxygen atoms linked to the phosphorus, it appears that the steric hindrance between the phenyl ring α to oxygen and the incoming furyl groups, accounts well for the observed diastereoselectivity (Scheme 17).

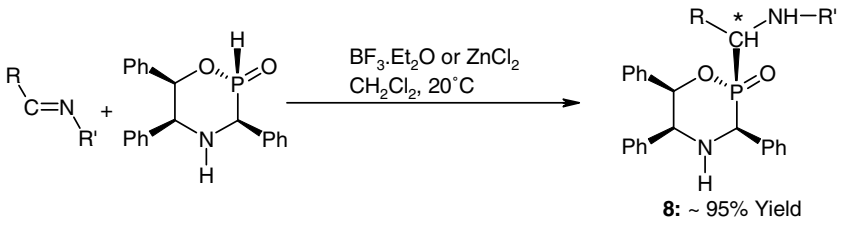
2.2.2.2. Addition on imines [7]. Kabachnik–Fields reactions [12] of compounds **2a** with aliphatic or aromatic imines afford the corresponding α-aminoalkyl derivatives, with a NCPCN pattern.

Activation of the C=N double bond with Lewis Acids affords excellent yields of the corresponding adducts (Scheme 18). In presence of boron trifluoride, the diastereoisomeric excess are moderate (35–50%), but the diastereoselectivity can be increased up to 90% using one equivalent of zinc chloride. This excellent diastereoselectivity is probably the result of a more rigid transition state formed by a double coordination of the zinc cation with the imino and the phosphoryl groups.

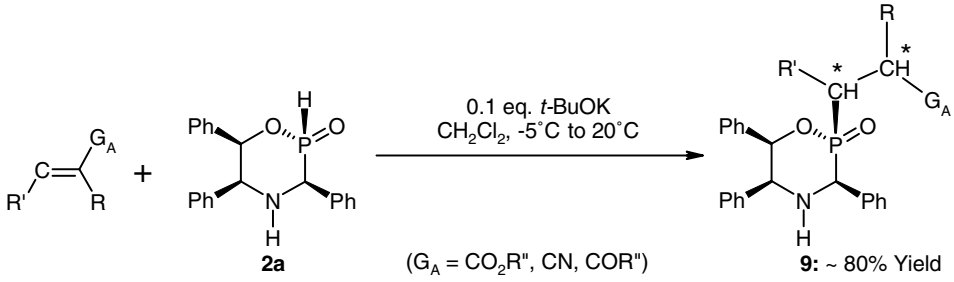
2.2.2.3. Addition to Michael olefins [13,14]. Compounds **2a** reacts also easily with activated C=C double bonds, α,β-unsaturated ester or ketones, in Michael additions catalysed by potassium *tert*-butoxide. The reactions afford excellent yields in the corresponding adducts which can have two new stereogenic centres α and/or β to phosphorus, depending on the nature of R and R′ substituents (Scheme 19). The diastereoisomeric excess is in the range between 30% and 80%.



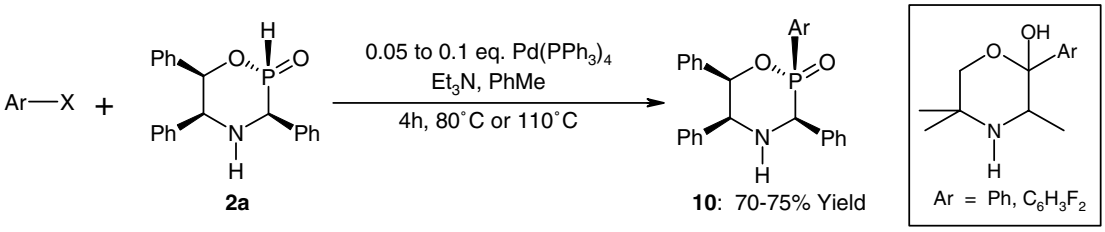
Scheme 17.



Scheme 18.



Scheme 19.

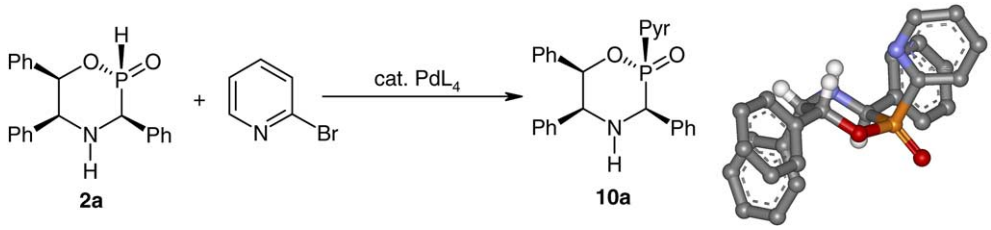


Scheme 20.

*2.2.2.4. P-Arylation of 1,4,2-oxazaphosphinane (**2a**) [15].* The structural analogy between arylmorpholinols [16], which exhibit interesting antidepressant activities, and the P-arylated 1,4,2-oxazaphosphinanes **10** led us to investigate the P-arylation of compounds **2a** (Scheme 20).

The direct arylation of the P–H bond was performed with aryliodides or bromides, catalysed by 5% mol $Pd(PPh_3)_4$, in presence of triethylamine, in refluxing toluene. The yields are good, between 70% and 75%, and the reaction can also be applied to heteroarylation with derivatives of thiophene or pyridine.

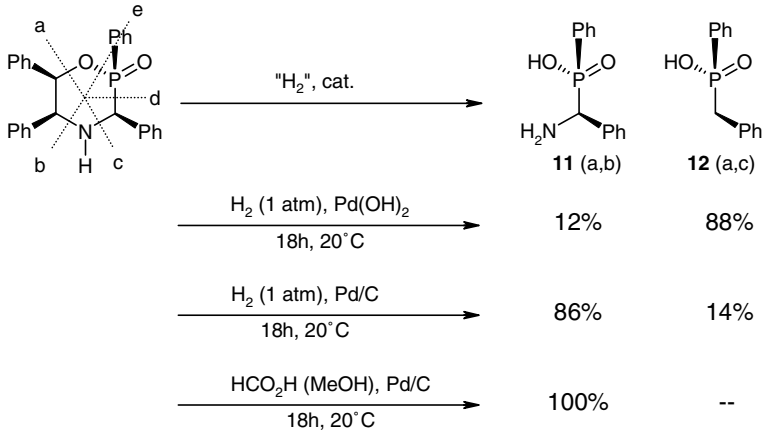
From the stereochemical point of view, the reaction affords only one compound, demonstrating a full diastereoselectivity in the P–Ar bond formation. In good agreement with the literature [17], we could prove the complete retention of configuration at phosphorus, in the arylation compound **2a** with 2-bromopyridine. In this case, both structures of the starting compound **2a** (Scheme 13) and the arylated product **10** (Ar = 2-pyridyl) (Scheme 21) were determined by crystal X-ray analysis showing unambiguously the retention of configuration at phosphorus.



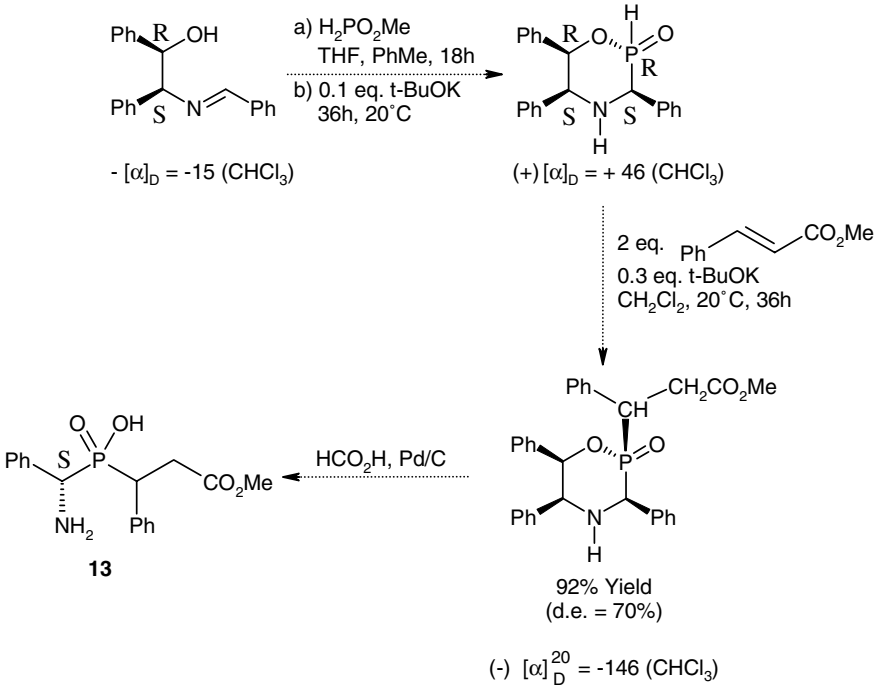
Scheme 21.

2.2.2.5. Hydrogenolysis of 5,6-diphenyl-1,4,2-oxazaphosphinanes. In the various derivatives obtained from 1,4,2-oxazaphosphinane (**2a**) by Abramov–Pudovik hydroxyalkylations, by Kabachnik–Fields aminoalkylations or by Michael additions, the diastereoselectivity in the formation of the new stereogenic centres was induced by the chiral 1,2-diphenylethanolamine auxiliary, chosen for the possibility of subsequent cleavage by hydrogenolysis.

Our model 1,4,2-oxazaphosphinane (**2a**) was built deliberately, from the beginning, with a third phenyl ring α to phosphorus in order to check the likelihood of double deprotection at oxygen and at nitrogen. Moreover, we investigated the hydrogenolysis on compound **10b** (Ar=Ph) which exhibits a fourth phenyl substituent on the phosphorus. Therefore compound **10b** can virtually undergo five different hydrogenolyses of benzylic or pseudo-benzylic heteroatomic bonds, corresponding to cleavages a–e (Scheme 22). As expected, the pseudobenzylic P–O or P–C bonds were not cleaved in our experiments, but the cleavage of benzylic C–O or C–N bonds occurred resulting in two different deprotected products: (i) the target α-amino-benzyl phenylphosphinic acid **11** (cleavage *a*, *b*) and (ii) the unsubstituted benzyl phenylphosphinic acid **12** (cleavages *a* and *c*). The ratio of products depends on the hydrogen source and on the



Scheme 22.



Scheme 23.

nature of the catalyst. As shown in Scheme 22, the pure α-aminobenzyl phenylphosphinic acid **11** is obtained using formic acid in presence of palladium on charcoal.

2.2.3. Synthesis from enantiopure 1(S),2(R)-diphenylethanolamine [14]

Based on the chemistry developed in the preceding part from the racemic starting material, we are now elaborating the synthesis of diastereoisomerically and enantiomerically pure functional α-aminophosphinic acids (Scheme 23).

Starting from the enantiomerically pure 1(*S*),2(*R*)-diphenylethanolamine, the formation of the corresponding imine with benzaldehyde occurs almost quantitatively. Then the base-catalysed addition of methyl phosphinate followed by cyclisation through transesterification affords two diastereoisomers (ratio 75/25), and the major dextrogyre product can be isolated by crystallisation. Its Michael addition on the *trans* methyl cinnamate affords also two diastereoisomers (ratio 85/15), which can be separated chromatographically.

Our next step will be the O- and N-deprotections by hydrogenolysis to obtain the enantiomeric pure *like* and *unlike* compounds **13**.

3. Conclusion

In order to obtain novel phosphorus heterocycles containing a P–C–O or P–C–N motif in their cyclic framework, we developed new syntheses of 2,3-dihydro-1,3-oxaphospholes **1** and of 1,4,2-oxazaphosphinanes **2**. In both cases, the parent compounds **1a** and **2a** contain a reactive part, respectively the enolether moiety and the P–H bond. This allows various structural modifications: (i) for **1a**, by introduction of amino substituents, (ii) for **2a**, by hydroxy- or aminoalkylation, by Michael addition or by P-arylation.

These reactions exhibit generally a good to excellent kinetic diastereoselectivity which can often be predicted by molecular models of the transition states.

Acknowledgements

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