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A new synthetic route to chiral 3-aryl-5-ethyl-1,4,2-oxazaphosphorines

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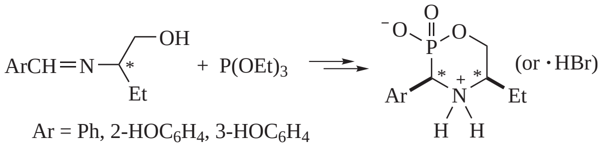
Diastereoselective synthesis of racemic and enantiopure 3-aryl-5-ethyl-1,4,2-oxazaphosphorines, including those bearing phenolic hydroxyl groups in the exocyclic aromatic fragment, was implemented by the reaction of imines derived from (±)- and (*R*)-(–)-2-aminobutan-1-ol and (hydroxy)benzaldehydes with triethyl phosphite and trifluoroacetic acid, followed by the one-pot dealkylation of the intermediate esters.

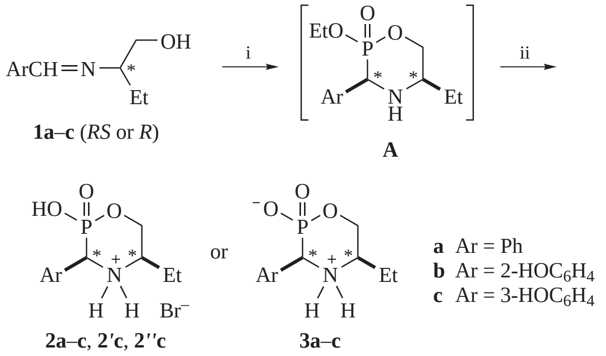


1,4,2-Oxazaphosphorines are interesting phosphorus-containing heterocycles with the O–P–C–N endocyclic fragment, which can be considered as cyclic six-membered α-amino phosphonic acid derivatives. The insertion of the stereogenic carbon and phosphorus atoms into the cycle creates prerequisits for their stereo- and enantioselective synthesis with the formation of various stereoisomers. Since α-amino phosphonic acids are widely used as building blocks for the design of new bioactive molecules,[1] search for the methods of synthesis of 1,4,2-oxazaphosphorines in racemic and enantiomerically pure form, and the study of their structural features is of special interest. Moreover, their structure implies their potential use as organocatalysts as well as ligands for chiral metal complex catalysts.

Previously, 1,4,2-oxazaphosphorines were obtained by the interaction of 1,3,2-oxazaphospholanes with aromatic[2] and aliphatic[3] aldehydes. Their structure was proved by NMR spectroscopy.[4] Later, enantiopure oxazolidines were used in reaction with trimethyl phosphite in the presence of tin tetrachloride to isolate 1,4,2-oxazaphosphorines both in diastereomerically and, for the first time, in an enantiomerically pure form.[5] The reaction of enantiopure amino diols with triethyl phosphite was also used for the synthesis of such heterocycles.[6] Our studies showed[7] that the interaction of imino alcohols with chlorophosphites afforded 1,4,2-oxazaphosphorines, including enantiopure samples. Later, the synthesis of 1,4,2-oxazaphosphorines was carried out by cyclization of both amino phosphonates[8] and amino phosphinates,[9] bearing a hydroxyl group. Note that compounds exhibiting antidepressant activity were found among such amino phosphinates.[10] In view of the aforesaid, a rather limited set of methods for the synthesis of 1,4,2-oxazaphosphorines has been described so far. Most of them involve either hard-to-obtain initial compounds or reagents incompatible with some functional groups.

We have previously reported that the reactions between imines of Betti base [1-(α-aminobenzyl)-2-naphthol] and P^{III} derivatives in the presence of co-electrophiles allowed one to obtain the corresponding α-amino phosphonates under mild conditions with good diastereomeric excess.[11] Assuming that the usage of the imine derivatives of chiral β-amino alcohols in the reaction with trialkyl phosphites and trifluoroacetic acid leads to simultaneous or sequential addition of the corresponding phosphite at the imino alcohol and cyclization, the formation of 1,4,2-oxazaphosphorines can be expected.

To verify this assumption, we first studied the three-component reaction of imine (±)-**1a** derived from benzaldehyde and racemic 2-aminobutan-1-ol with triethyl phosphite and trifluoroacetic acid in the 1 : 1.2 : 2.2 ratio (Scheme 1). To obtain final cyclic amino phosphonic acid, the intermediate esters **A** were treated with the excess of bromotrimethylsilane and further on with methanol. As a result cyclic amino phosphonic acid as hydrobromide salt was isolated, which crystallized from methanol as a single diastereomer (*R*,*R*/*S*,*S*)-**2a** in good yield. The relative configuration of the chiral centers of the product was the same as in 1,4,2-oxazaphosphorine synthesized by us earlier by the reaction of 2-aminobutanol imine derivative with diethyl chlorophosphite.[7(*e*)] Similarly, enantiomerically pure (*R*,*R*)-**3a** was obtained in a good yield from imine (*R*)-**1a** (see Scheme 1).



	stereoisomer
2a	*R*,*R*/*S*,*S*
2b	*R*,*R*/*S*,*S*
2c	*R*,*R*/*S*,*S*
2′c	*R*,*R*
2′′c	*S*,*S*

	stereoisomer
3a	*R*,*R*
3b	*R*,*R*
3c	*R*,*R*/*S*,*S*

Scheme 1 *Reagents and conditions*: i, P(OEt)$_3$, CF$_3$CO$_2$H, CH$_2$Cl$_2$, 5 → 20 °C; ii, Me$_3$SiBr, 5 → 20 °C, then MeOH, EtOH or Pr^{i}OH. Monocrystal of **2′′c** as solvate with Pr^{i}OH was picked up from conglomerate after crystallization of racemate **2c** from Pr^{i}OH. Crystals of **3c** were obtained by recrystallization of **2c** from aqueous Pr^{i}OH causing loss of HBr.

The insertion of an additional binding site into the molecule of oxazaphosphorine, for example, phenolic hydroxyl group, can be very useful for designing ligands or organocatalysts. However, most of the described methods[5–9] for the 1,4,2-oxazaphosphorines synthesis are unacceptable for the preparation of type **2** cyclic acids from reactants bearing reactive functional groups.

Since our procedure comprises mild reaction conditions, it could be expected that the presence of an additional hydroxyl group in the starting imino alcohol would tolerate the process. To this end, compounds **1b**,**c** in racemic and enantiopure forms were prepared from 2-aminobutan-1-ol and 2- or 3-hydroxybenzaldehydes, respectively. Note that compounds (±)-**1c**, (*R*)-**1c**, like the previously described (±)-**1b** and (*R*)-**1b**,[12] exist exclusively in the open-chain (imine) form in solution, unlike imines (±)-**1a**, (*R*)-**1a**, which, due to the ring-chain tautomerism in solution, are in equilibrium with the *cis*- and *trans*-oxazolidine forms.[13]

Reactions of racemic or enantiopure **1b**,**c** with triethyl phosphite and trifluoroacetic acid were carried out similarly to those for imine **1a**. Subsequent dealkylation of intermediate esters **A** and recrystallization from alkanols allowed us to isolate major diastereomers of oxazaphosphorines (*R*,*R*/*S*,*S*)-**2b**, (*R*,*R*)-**3b**, (*R*,*R*/*S*,*S*)-**3c**[†] and (*R*,*R*)-**2′c** (relative configuration of chiral centers were determined by the single crystal X-ray diffraction,[‡] Figure 1 and Figures S5–S8 in Online Supplementary Materials) in 55–70% yields as solvates with one molecule of the corresponding alcohol [excluding (*R*,*R*/*S*,*S*)-**3c**]. It is interesting to note that in four out of six cases, the final products were isolated as hydrobromides and only enantiopure (*R*,*R*)-**3a** and (*R*,*R*)-**3b** were precipitated as internal salts (see Scheme 1).

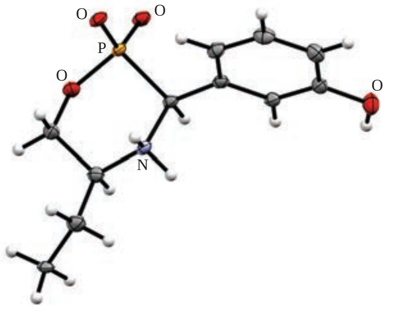


Figure 1 Molecular structure of compound (*R*,*R*/*S*,*S*)-**3c** (ORTEP drawing).

It is known that α-cyclodextrin is a highly efficient shift reagent for the determination of enantiomeric purity of acyclic α-amino phosphonic acids.[19] To date, this reagent was not used for cyclic α-amino phosphonic derivatives. In this work we found that for efficient signal separation of racemic (*R*,*R*/*S*,*S*)-**2a** and (*R*,*R*/*S*,*S*)-**2b** ($\Delta\delta$ = 0.09 and 0.28 ppm, respectively, Figures S1 and S3 in Online Supplementary Materials) in their ^{31}P NMR spectra (D_2O/K_2CO_3), it was sufficient to use 2 equiv. of α-cyclodextrin. However, the signal of (*R*,*R*/*S*,*S*)-**2c** was not splitted even upon addition of 10 equiv. of α-cyclodextrin. It is likely that the hydroxyl group at the 3-position of the exocyclic aryl substituent prevents the effective formation of the molecular diastereomeric complex with cyclodextrin.

In conclusion, we have proposed a new access to 1,4,2-oxazaphosphorines starting from 2-aminobutan-1-ol imines, triethyl phosphite and trifluoroacetic acid. This approach makes it possible to use hydroxybenzaldehyde imines, which results in compounds bearing extra hydroxyl groups. The thus obtained 1,4,2-oxazaphosphorines containing additional active centers seem promising for further modification.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.11.004.

[†] Hydrobromide (*R*,*R*/*S*,*S*)-**2c** after crystallization from a mixture of water and propan-2-ol loses HBr to afford racemic crystal (*R*,*R*/*S*,*S*)-**3c** containing no solvate molecules, with a complicated hydrogen-bonding 3D network. Crystallization of **2c** from dry propan-2-ol gave conglomerate crystals in the form of bromide salt with solvate propan-2-ol molecule with multiple hydrogen bonds involving compound **2c**, as well as bromine ion and solvent molecule. From this conglomerate, (*S*,*S*)-**2″c** enantiomer was incidentally picked up and studied by X-ray analysis. It is known that the formation of solvate can be used to transform racemates into conglomerates and thereby facilitate resolution.[14]

[‡] Data sets for single crystals were collected on a Bruker AXS Kappa APEX Duo diffractometer with graphite-monochromated MoKα radiation (λ = 0.71073 Å). The structures were solved by direct methods using APEX3[15] for data collection, SAINT[16] for data reduction, SHELXS[17] for structure solution, SHELXL[17] for structure refinement by full-matrix least-squares against F^2, and SADABS[18] for multi-scan absorption correction. Hydrogen atoms at carbon atoms were placed into calculated positions and refined as riding atoms. Hydrogen atoms of the hydroxyl groups were revealed from difference Fourier map and refined isotropically with geometry constraints.

Crystal data for (*R*,*R*/*S*,*S*)-**2b**: crystals of $C_{12}H_{21}BrNO_5P$ (M = 370.18) are monoclinic, $P2_1/n$, at 198 K: a = 12.0242(7), b = 9.9598(6) and c = = 13.6024(9) Å, β = 106.171(2)°, V = 1564.55(17) Å^3, Z = 4, d_{calc} = = 1.572 g cm^{-3}, μ(MoKα) = 2.747 mm^{-1}. R_{int} = 0.0151, R_1 = 0.0192, wR_2 = 0.0832.

Crystal data for (*R*,*R*)-**3b**: crystals of $C_{12}H_{20}NO_5P$ (M = 289.26) are orthorhombic, $P2_12_12_1$, at 150 K: a = 7.8945(5), b = 10.5491(6) and c = = 16.9841(10) Å, V = 1414.43(15) Å^3, Z = 4, d_{calc} = 1.358 g cm^{-3}, μ(MoKα) = 0.210 mm^{-1}. R_{int} = 0.0212, R_1 = 0.0252, wR_2 = 0.0764.

Crystal data for (*S*,*S*)-**2″c**: crystals of $C_{14}H_{25}BrNO_5P$ (M = 398.23) are orthorhombic, $P2_12_12_1$, at 198 K: a = 10.6341(2), b = 10.7346(2) and c = 15.4343(3) Å, V = 1761.87(6) Å^3, Z = 4, d_{calc} = 1.501 g cm^{-3}, μ(MoKα) = 2.445 mm^{-1}. R_{int} = 0.0236, R_1 = 0.0252, wR_2 = 0.0685.

Crystal data for (*R*,*R*/*S*,*S*)-**3c**: crystals of $C_{11}H_{16}NO_4P$ (M = 257.22) are monoclinic, $P2_1/c$, at 100 K: a = 9.6572(6), b = 10.8384(6) and c = = 11.2655(7) Å, β = 97.302(3)°, V = 1169.58(12) Å^3, Z = 4, d_{calc} = = 1.461 g cm^{-3}, μ(MoKα) = 0.238 mm^{-1}. R_{int} = 0.0446, R_1 = 0.0393, wR_2 = 0.0934.

The data collection and refinement parameters are given in Table S1 in Online Supplementary Materials.

CCDC 1843105–1843107 and 1843768 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

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