Base-Dependent Regio- and Diastereoselective Alkylation of Chiral Perhydro 1,3,2-Oxazabenzophosphorinane-2-oxides Derived from (–)-8-Benzylamino Menthol

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Abstract: The regioselectivity in the alkylation of chiral perhydro 1,3,2-benzoxazaphosphorinane-2-oxides is dependent on the base used for deprotonation. The ethyl oxazaphosphorinanes are benzylated at the nitrogen substituent after deprotonation with *n*-BuLi, but α to the phosphorous atom by deprotonation with LDA. On the contrary, the benzyl oxazaphosphorinane is alkylated α to the phosphorous atom after deprotonation with both, *n*-BuLi or LDA.

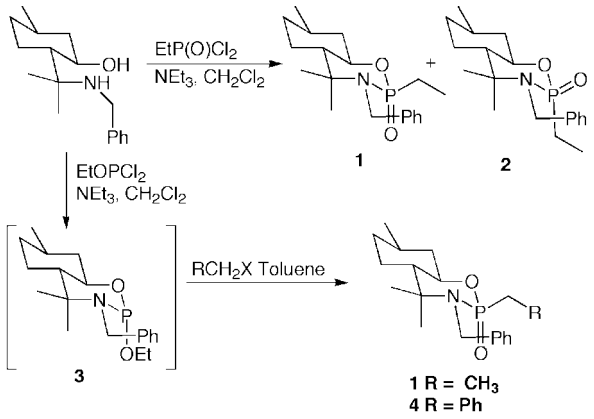
Key words: alkylation, alkyl phosphonates, asymmetric synthesis, diastereoselective reactions, 2-oxo-1,3,2-oxazaphosphorinanes

Phosphorous stabilized chiral carbanions have been widely used in the diastereoselective formation of carbon-carbon bonds. Among them, compounds with stereogenic phosphorous atom and phosphorous derivatives modified by chiral auxiliaries have been successfully employed.[1] Chiral diamines and amino alcohols constitute specially interesting auxiliaries in the formation of cyclic phosphonamides[2] and oxaphosphonamides,[3] which undergo diastereoselective transformations with excellent diastereomeric excess.

It is well known that the diastereoselection of these reactions is dependent on the structure of the electrophile,[4] the stereochemistry of the phosphorous atom,[5] the nature of the substituents at the nitrogen atom,[3b] the size[6] and the configurational and conformational characteristics of the heterocycle.[7] Thus the search for new stereocontrolling elements constitutes an active area of interest.

In this way, (–)-8-aminomenthol derivatives have been shown as excellent auxiliaries in various diastereoselective cyclizations,[8] and now we report on the diastereoselective alkylation of chiral perhydro 1,3,2-oxazabenzophosphorinane-2-oxides derived from this 1,3-amino alcohol.

To this end, perhydro ethyl- (**1**, **2**) and benzyl-1,3,2-oxazabenzophosphorinane-2-oxide (**4**) were prepared as outlined in Scheme 1. Diastereomers **1** (31%) and **2** (61%) were obtained by direct cyclization[9] of (–)-benzylamino menthol with ethyl phosphonic dichloride and triethylamine in methylene chloride. Alternatively, compounds **4** (as a single diastereomer) and **1** (accompanied in ca. 3% by **2**) were prepared by Arbuzov reaction, in refluxing toluene, between benzyl bromide or ethyl iodide and 2-ethoxy-1,3,2-oxazaphosphorinane **3**, itself obtained from (–)-8-benzylamino menthol and ethyl dichlorophosphite.[10]



Scheme 1 Synthesis of perhydro 2-oxo-1,3,2-oxazabenzophosphorinanes **1**–**4**

The stereochemistry of **1** and **2** was tentatively assigned on the basis of the ^{31}P NMR signals (δ = 34 ppm for compound **1** and δ = 30 ppm for **2**),[11] and confirmed by X-ray diffraction studies[12] (Figures 1– 3).

The geometry around the nitrogen atom of this kind of compounds varies from planar[13] to pyramidal,[12] and the conformations[13a] of the six-membered ring are dependent

Figure 1 Chem 3D representation of X-ray for compound **1**. For clarity, only H atoms of CH_2 of the benzyl group attached to the N atom are shown

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Figure 2 Chem 3D representation of X-ray for compound **2**

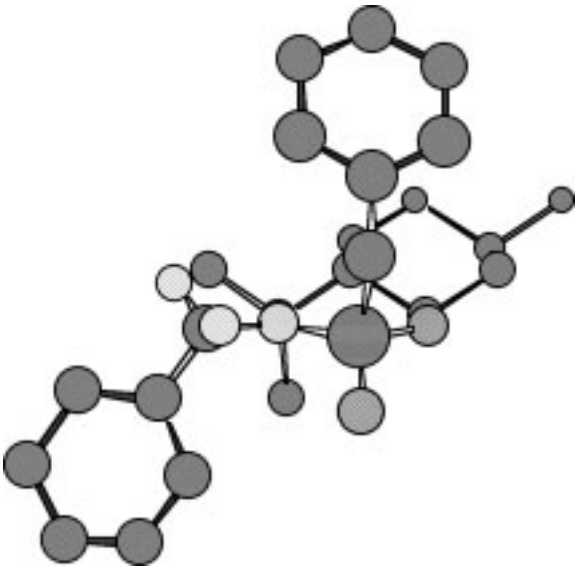
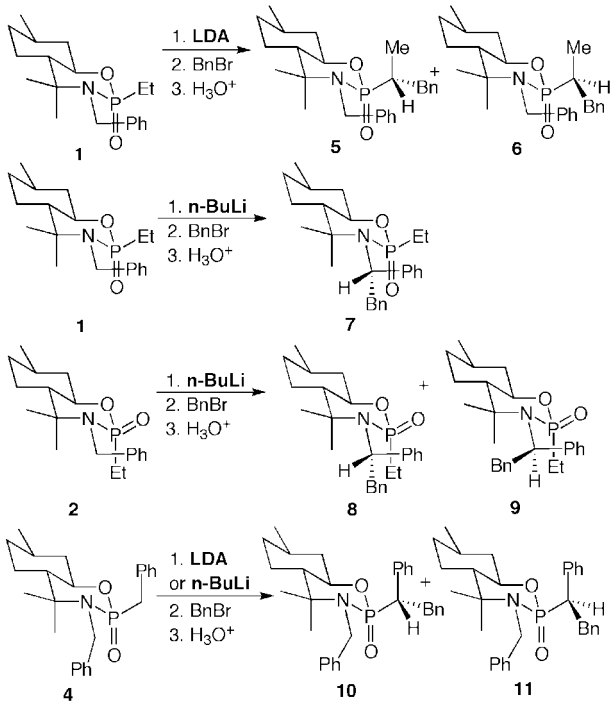


Figure 3 Chem 3D representation of X-ray for compound **4**

on the nature of the substituents. In our case, the nitrogen atom is trigonal in compounds **4** and **2** but pyramidal for compound **1**, and the ring adopts a slightly distorted chair conformation in compounds **1** and **2**. However, in compound **4** the conformation for the ring is half chair, with C(6)-O(1)-P(2)-N(3)-C(4) near planar.

Alkylation[14] of compound **1**, in THF at –78 °C, with LDA as base and benzyl bromide as electrophile led to a mixture of diastereomers **5** and **6** in 45% yield in a ratio 62:38 (determined by ^{31}P NMR; Scheme 2 and entry 1 in Table 1).

Compound **4** also reacts under the same experimental conditions giving a mixture of diastereomers **10** and **11** (71:29) in 71% yield (entry 4 in Table 1). The stereochemistry of the major compounds **5** and **10** was identified, after chromatographic purification, by hydrolysis to the known phosphonic acids.[15] Under the described experimental conditions, but using *n*-BuLi (2 equiv) as base, **4**



Scheme 2 Alkylation of compounds **1**, **2** and **4** with benzyl bromide.

led to a mixture of **10** and **11** (72:28, entry 5 in Table 1), whereas **1** yielded the alkylation product at the benzylic position of the nitrogen **7** in 64%, as a single diastereomer (entry 2 in Table 1).

Compound **2** also led to alkylated products at the nitrogen side **8** and **9** (83:17) after deprotonation with *n*-BuLi and reaction with benzyl bromide (entry 3 in Table 1). The stereochemistry of compound **8** was determined by X-ray crystallography (Figure 4), whereas the configuration of the benzylic carbon attached to the nitrogen atom in **7** was determined by conversion of both to (*S*)-1,2-diphenylethyl amine by heating with 6 N HCl (Scheme 3).

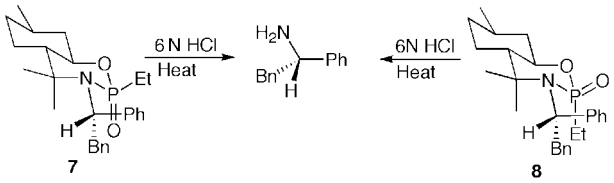
This constitutes the first observation of alkylation at the nitrogen substituent in N-benzyl derivatives, although recently similar reaction products have been obtained in moderate yield, but only for benzhydryl substituted 1,3,2-oxazaphosphorinane-2-oxides.[16] The formation of these

Table 1 Alkylation of **1**, **2** and **4** with Benzyl Bromide

Entry	Substrate	Base	Yield[a]	Products (dr)[b]
1	**1**	LDA	45	**5**:**6** (62:38)
2	**1**	*n*-BuLi	64	**7** (>99:1)
3	**2**	*n*-BuLi	77	**8**:**9** (83:17)
4	**4**	LDA	71	**10**:**11** (71:29)
5	**4**	*n*-BuLi	56	**10**:**11** (72:28)

[a] Yields are given after purification by flash chromatography.
[b] Determined in the reaction mixture by integration of the ^{31}P NMR signals.

Figure 4 Chem 3D representation of X-ray for compound **8**



Scheme 3

compounds has been explained by alkylation of the anion formed by direct deprotonation at the nitrogen side chain or by proton transfer from that position to the anion α to the phosphorous atom, but these and our results can also be explained as a consequence of the formation of dianionic species that are first alkylated α to the nitrogen atom. The stereochemistry of the single (**7**) or major (**8**) diastereomer formed in these reactions is consistent with the model proposed for alkylation of amides with retention at the anionic center.[17]

Taking into account the stereochemistry of the starting compounds and the structure of the anionic intermediates[18] the formation of **5** and **10** as major diastereomers can be explained by accepting that the alkylation occurs from the less hindered oxygen face of the heterocycle.[12]

In summary, both the nature of the substituent at phosphorous atom and the base used in the deprotonation step have a significant influence on alkylation of perhydro 1,3,2-benzoxaphosphorinane 2-oxides. When the deprotonation is carried out with *n*-BuLi both diastereomers (**1** and **2**) of the ethyl oxazaphosphorinanes are alkylated at the nitrogen atom substituent, whereas deprotonation with LDA leads to the alkylation product at the phosphorous substituent. On the contrary, deprotonation with LDA or *n*-BuLi of the benzylphosphorinane **4**, followed by reaction with benzyl bromide yields the alkylation product at the phosphorous substituent.

Further studies on the generality of the described reactions are under investigation in our laboratory.

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(12) CCDC contain supplementary crystallographic data for compounds **1** (CCDC 233645), **2** (CCDC 233647), **4** (CCDC 233644), and **8** (CCDC 233646), respectively. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retreiving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB12 1EZ, UK; fax: (internat.) +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk.
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(14) **Typical Experimental Procedure:** To a cooled (–78 °C) solution of the corresponding 1,3,2-oxazaphosphorinane (0.9 mmol) in dry THF (20 mL) under argon atmosphere was added the base (1.8 mmol), and the mixture was stirred for 30 min. Then, benzyl bromide (1.8 mmol) was added and the stirring was continued until the reaction was finished (TLC). The reaction was quenched with H_2O (9 mL) and stirred until the mixture was reached r.t. THF was removed under reduced pressure and the aqueous mixture extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography on silica gel and hexane–EtOAc (1:2) as eluent.
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