Asymmetric alkylation of dimethoxyphosphoryl-*N*-[1-(*S*)-α-methylbenzyl]acetamide enolates. Synthesis of both stereoisomers from the same source of chirality by changing the equivalents of LDA†

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A new methodology has been developed for the synthesis of both stereoisomers from a single chiral source.

Development of stereoselective reactions is one of the most important topics in modern synthetic chemistry, where the synthesis of both stereoisomers of a chiral compound is a very important topic in asymmetric synthesis. To attain this goal, traditional methods require the use of both chiral auxiliaries to obtain the stereoisomers with opposite configurations. However, due to the lack of its naturally occurring counterpart or equivalent of some chiral auxiliaries, this process is not a general methodology. For this reason, the synthesis of either of the two possible stereoisomers in high optical purity derived from the same source of chirality is an attractive tool.

To the best of our knowledge, only a few synthetic approaches have been used to obtain both individual stereoisomers *via* alkylation of enolates with high optical purity from a single chiral source. The strategies involve the systematic examination of base,[1,2] electrophiles[3] and addition of additives,[2,4] but there is no report for the preparation of the two possible stereoisomers using the same chiral auxiliary by changing the equivalents of base.

On the other hand, the efficient synthesis of optically pure α-aminophosphonic acids is one of the most important topics in organic chemistry.[5] Although various chiral α-aminophosphonic acids have been prepared with high enantiomeric excess by stoichiometric or catalytic asymmetric reaction, only a few examples of stereoselective synthesis of α-aminophosphonic acids, bearing a quaternary chiral α-carbon atom, have been, to the best of our knowledge, reported.[6]

As part of our program to obtain aminophosphonic acids,[7] herein we wish to report the synthesis of both quaternary diastereomers (*R*,*S*)-**4** and (*S*,*S*)-**5** in good diastereoselectivity from β-phosphonoamide **3** bearing (*S*)-α-methylbenzylamine as single inductor of the chirality,[8] where the stereochemistry was strongly influenced by the number of equivalents of LDA used.

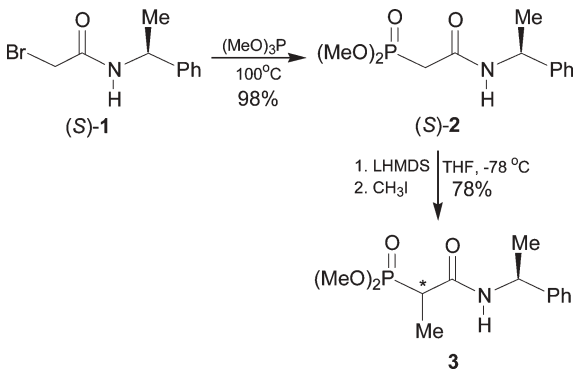
The starting β-phosphonoamide **3** was synthesized in two steps from amide **1**. Thus the Arbuzov reaction[9] of trimethylphosphite with the amide (*S*)-**1** at 100 °C affords the dimethoxyphosphoryl-*N*-[(*S*)-α-methylbenzyl]acetamide [(*S*)-**2**] in quantitative yield. Enolization of (*S*)-**2** with lithium diisopropylamide (2.1 equiv., −78 °C for 1 h) in THF, followed by the addition of methyl iodide (excess, −78 °C for 1 h), led to the α,α-dimethylated compound as principal product; similar results were obtained when LDA (1.5–2.0 equiv.) was used.

In view of the unsatisfactory results for the mono-methylation reaction of (*S*)-**2**, we decided to carried out the deprotonation with another base. Thus, the alkylation of (*S*)-**2** with methyl iodide using lithium bis(trimethylsilyl)amide (2.1 equiv.) as base at −78 °C in THF, affords exclusively the monomethylated product **3** in good yield and with a diastereoselectivity 47 : 53 (Scheme 1).

In order to induce the construction of quaternary carbon centers, we carried out the introduction of the second alkyl group employing the lithium enolate generated by treatment of **3** with different equivalents of LDA.

The results collected in Table 1 show that the enolization of **3** with freshly prepared lithium diisopropylamide (2.0 equiv., −78 °C for 1 h) in THF, followed by the addition of benzyl bromide (1.1 equiv., −78 °C for 1 h), afforded the α,α-disubstituted β-phosphonoamides (*R*,*S*)-**4** and (*S*,*S*)-**5** in good chemical yield and with a diastereoselectivity (90 : 10) with a predominance of diastereomer (*R*,*S*)-**4** as a colorless oil (entry 3). On the other hand, when the enolate of the amide **3** was generated with freshly prepared lithium diisopropylamide (2.5 equiv., −78 °C for 1 h), followed by the addition of benzyl bromide, also led to the α,α-disubstituted β-phosphonoamides (*R*,*S*)-**4** and (*S*,*S*)-**5** in good chemical yield and with a moderate diastereoselectivity (20 : 80), but now with a predominance of diastereomer (*S*,*S*)-**5**, as a crystalline solid (entry 6). Identicals results were obtained with 3 and 4 equiv. of LDA (entries 8, 10). Additionally, the addition of lithium chloride (3 or 6 equiv.) to the reaction did not improve the diastereoselectivity, entries 4 and 7.

The diastereomeric excesses were determined by means of ^{1}H and ^{31}P NMR. In fact, the signals in ^{31}P NMR for diastereomer



Scheme 1

† Electronic supplementary information (ESI) available: Experimental. See http://www.rsc.org/suppdata/cc/b4/b416616g/

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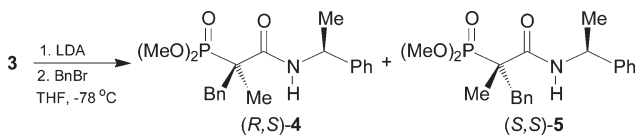
Table 1 Benzylation of **3** with different LDA equivalents



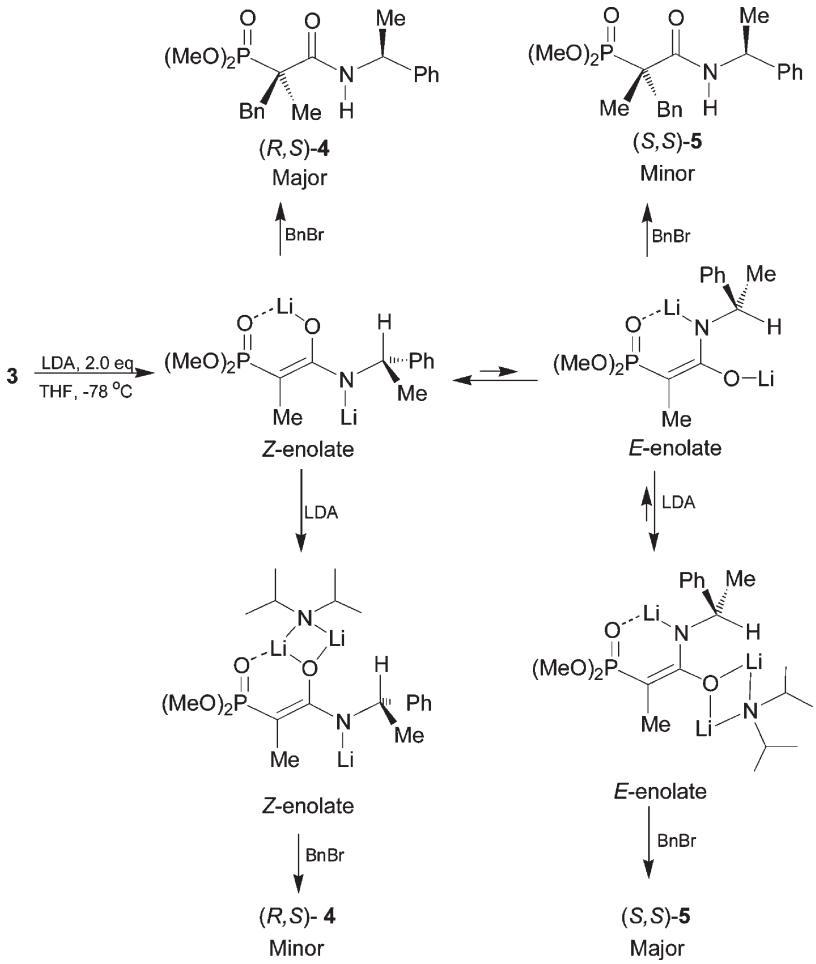
Entry	LDA (equiv.)	Time[a]	LiCl (equiv.)	Yield[b] (%)	(*R*,*S*)-**4** : (*R*,*S*)-**5**[c]
1	1.0	60 min	—	d	88 : 12
2	1.5	60 min	—	d	88 : 12
3	2.0	60 min	—	77	90 : 10
4	2.0	60 min	3 or 6	60	90 : 10
5	2.0	5 min	—	60	86 : 14
6	2.5	60 min	—	83	20 : 80
7	2.5	60 min	3 or 6	80	21 : 79
8	3.0	60 min	—	77	20 : 80
9	3.0	5 min	—	63	83 : 17
10	4.0	60 min	—	78	20 : 80

[a] Time for the enolate generation. [b] Chemical yield after purification by column chromatography. [c] Determined by ^{1}H NMR at 400 MHz and ^{31}P NMR at 200 MHz in the crude reaction. [d] The reaction was not completed.

(*S*,*S*)-**5** were more shielded (33.37 ppm) than those for the diastereomer (*R*,*S*)-**4** (33.59). The absolute configuration of the quaternary carbon center was given by single-crystal X-ray analysis of diastereomerically pure (*S*,*S*)-**5**.‡ Although the absolute configuration of the liquid product was not experimentally confirmed, it is postulated to be (*R*) on the quaternary carbon center.

To explain the strong influence of the number of equivalents of LDA on the inverse diasteroselectivity in the alkylation process of **3**, a model including a chelating intermediated has been proposed (Scheme 2).

When the phosphonoamide **3** is treated with LDA (2.0 equiv.), the enolate geometry may be *Z*, in accordance with the literature precedence and favored by the coordination C–O–Li–O=P.[10] The orientation of the C–H bond of the chiral auxiliary towards the oxygen atom and the relative size of phenyl and methyl groups determines the preferred direction of benzyl bromide addition,[11] in this case for the *re* face, which leads to (*R*,*S*)-**4** diastereomer as principal product. Additionally, the reaction appears to be operating under kinetic control, since no evidence of reversibility was observed and the diastereoselectivity was independent of reaction time (Table 1, entry 5). On the other hand, when **3** was treated with LDA (≥2.5 equiv.) we propose that now the *E* enolate is favored by the coordination with one lithium diisopropylamide molecule,[12] where newly the C–H bond of the chiral auxiliary is oriented towards the oxygen atom, so the relative size of phenyl and methyl groups determines the preferred direction of benzyl bromide addition, in this case for the *si* face,



Scheme 2

yielding the (*S*,*S*)-**5** diastereomer as principal product. In this case the reaction appears to be operating under thermodynamic control, since the diasteroselectivity is dependent of reaction time (Table 1, entry 9).

In practical terms, the chemistry described herein provides useful methodology for the preparation of both diastereomers of α,α-disubstituted β-phosphonoamides using the same source of chirality, changing the equivalents of LDA. In addition, the β-phosphonoamides (*R*,*S*)-**4** and (*S*,*S*)-**5** are of great interest due to the central role of these compounds in the stereoselective synthesis of several classes of valuable compounds, including α- and β-aminophosphonic acids[5] bearing a quaternary chiral α-carbon atom, β-hydroxy-α-aminophosphonic acids[13] and as potential chiral ligands.[14]§

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Notes and references

‡ CCDC 258161. See http://www.rsc.org/suppdata/cc/b4/b416616g/ for crystallographic data in .cif or other electronic format.

§ *Typical experimental procedure for the second alkylation of* **3**. To a solution of the β-phosphonoamide **3** (1 mmol) in dry THF at −78° was added dropwise 2.0 or 2.5 equivalents of freshly preparated LDA from freshly titrated *n*-buthyllithium[15] and freshly distilled diisopropylamine in dry THF. The resulting solution was stirred for 1 h at −78°. The benzyl bromide (1.1 equiv.) was added with continuous stirring, and the mixture reaction was stirred at −78° for 3–4 h and quenched with saturated aqueous NH_4Cl solution. The product was extracted with ethyl acetate, the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The crude product was analyzed by ^1H NMR at 400 MHz and ^{31}P NMR at 200 MHz. The diastereomeric mixture was cleanly separated by column chromathography.

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