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Phosphonate−Phosphinate Rearrangement

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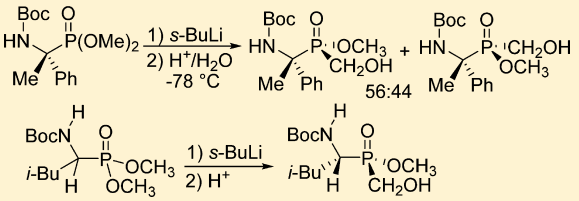
Supporting Information

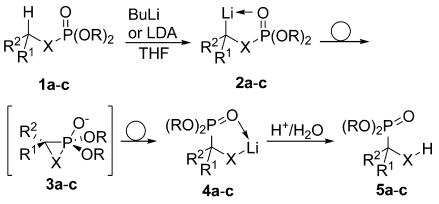
ABSTRACT: LiTMP metalated dimethyl *N*-Boc-phosphoramidates derived from 1-phenylethylamine and 1,2,3,4-tetrahydronaphthalen-1-ylamine highly selectively at the CH_3O group to generate short-lived oxymethyllithiums. These isomerized to diastereomeric hydroxymethylphosphonamidates (phosphate−phosphonate rearrangement). However, *s*-BuLi converted the dimethyl *N*-Boc-phosphoramidate derived from 1-phenylethylamine to the *N*-Boc α-aminophosphonate preferentially. Only *s*-BuLi deprotonated dimethyl hydroxymethylphosphonamidates at the benzylic position and dimethyl *N*-Boc α-aminophosphonates at the CH_3O group to induce phosphonate−phosphinate rearrangements. In the former case, the migration of the phosphorus substituent from the nitrogen to the carbon atom followed a retentive course with some racemization because of the involvement of a benzyllithium as an intermediate.



INTRODUCTION

Phosphonates playing a very minor role in biological systems than phosphates are accessible by a variety of methods. In previous papers, we have shown that phosphoric acid derivates, phosphates, *S*-alkyl thiophosphates, and phosphoramidates can be base-induced isomerized at low temperatures to α-hydroxy-,[1,2] α-mercapto-,[3] and α-aminophosphonates,[4] respectively (Scheme 1). The phosphoric acid derivatives **1a−c** are metalated by strong lithium bases to form presumably short-lived, dipole-stabilized α-heteroatom substituted alkyllthiums **2a−c**, which undergo a migration of the dialkoxyphosphinyl substituent from the heteroatom X (= O, S, NR) to the carbon atom. The three-membered spezies **3a−c** are very likely intermediates, which give lithiated phosphonates **4a−c** and phosphonates **5a−c** after workup. The driving force for these isomerizations, for simplicity called phosphate−phosphonate rearrangements, is the higher stability of the heteroatom−lithium bond compared to the carbon−lithium bond. The substituents R^1 and R^2 are critical. The phosphate−phosphonate rearrangements follow a retentive course[2−4] at the carbon atom, even if it is a benzylic position except for X = S. In that latter case, metalation at the benzylic position of the lithiated α-mercaptobenzylphosphonate of unknown configuration followed by protonation on work up gives a racemic product.[3] The stereochemistry at the phosphorus atom remains to be unraveled. So far, there were always two RO groups in the substrates, but never only one, and a substituted alkyl group instead of the second RO. The reverse reaction, the phosphonate−phosphate rearrangement is also known.[5−8] We reasoned that such a phosphonic acid derivative could undergo the analogous phosphonate−phosphinate rearrangement yielding products containing two P−C bonds. Here we present our first results.

Scheme 1. Various Phosphate−Phosphonate Rearrangements



1a-5a X = O phosphate-α-hydroxyphosphonate rearrangement, R^1 = alkyl, R^2= H or aryl

1b-5b X = S thiophosphate-α-mercaptophosphonate rearrangement, R^1 = alkyl or aryl, R^2= H

1c-5c X = NR phosphoramidate-α-aminophosphonate rearrangement R^1 = aryl, R^2= H or alkyl

R = Et, *i*-Pr

Phosphinates are a class of phosphorus-containing compounds of general structure $R^1R^2P(O)OR^3$ and are of chemical[9] and biological[10,11] importance. Chiral, nonracemic hydroxyalkylphosphinates[12] and α-aminophosphinates[13] have been obtained by lipase-catalyzed kinetic resolution and asymmetric synthesis, respectively. Phosphinothricin, a component of the tripeptide bialaphos (L-phosphinothricyl-L-alanyl-L-alanine), is a naturally occurring phosphinic acid biosynthesized by *Streptomyces hygroscopicus* and *S. viridochromogenes*.[14] It is produced chemically and marketed as herbicide blocking glutamine synthetase.[15]

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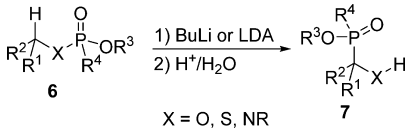
RESULTS AND DISCUSSION

Presumably, the phosphonate−phosphinate rearrangement will be very similar to the phosphate−phosphonate rearrangement mechanistically (Scheme 2). The substituent R^4 of phosphonate

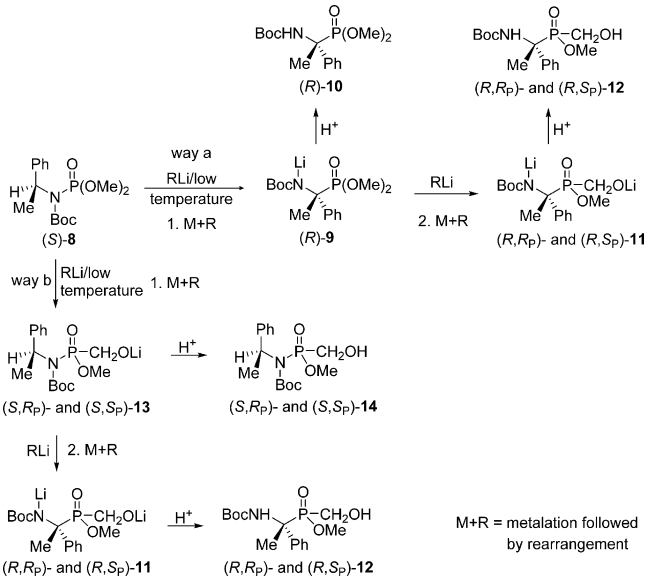
Scheme 2. Phosphonate−Phosphinate Rearrangement of 6



6 will be very critical for the success of the isomerization because it should not contain a proton more acidic than the one which has to be removed to induce the rearrangement. Simple alkyl groups are therefore not tolerated. The best would be a *t*-butyl group, which is not very interesting from a chemical point of view, as the scope of the rearrangement would be very limited. We opted for a phosphoramidate derivative as substrate that could undergo a phosphate−phosphonate and phosphonate−phosphinate rearrangement, with or without isolation of the intermediate phosphonate. Furthermore, use of EtO groups will introduce another stereogenic center on rearrangement so that four diastereomers would result compared to just two with methoxy groups at phosphorus.

We chose dimethyl phosphoramidate (*S*)-**8** to outline possible reaction pathways and perform preliminary experiments (Scheme 3). A hydrogen atom of the MeO group is

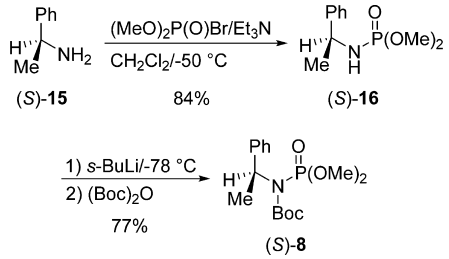
Scheme 3. Possible Reaction Pathways for Phosphoramidate (*S*)-8



somewhat more acidic than the α-hydrogen of the EtO or *i*-PrO group generally used as protecting groups at phosphorus. It is known from previous experiments with the corresponding diethyl ester of (*S*)-**8** that it could undergo the well-known phosphoramidate−α-aminophosphonate rearrangement first (way a), giving (*R*)-**9** when treated with 1.2 equiv of *s*-BuLi at −78 °C (1. M + R = first metalation followed by rearrangement). With excess *s*-BuLi (2.5−3 equiv), a MeO group could be metalated as well, and the intermediate oxymethyllithium formed could undergo the phosphonate−phosphinate rearrangement (2. M + R) and give a mixture of lithiated diastereomeric phosphinates (R,R_P)- and (R,S_P)-**11**. Acidic workup will furnish phosphonate (*R*)-**10** and a diastereomeric mixture of phosphinates (R,R_P)- and (R,S_P)-**12**, respectively. If a hydrogen atom of the MeO group is more acidic than the benzylic hydrogen atom, phosphoramidate (*S*)-**8** could be converted to a mixture of diastereomeric lithiated phosphonamidates (S,R_P)- and (S,S_P)-**13** first (way b) with 1.2 equiv of *s*-BuLi, followed by formation of lithiated phosphinates (R,R_P)- and (R,S_P)-**11** with 2.5−3 equiv, assuming that the configuration at the benzylic carbon and phosphorus atoms will be retained. Acidic workup will yield mixtures of phosphonamidates (S,R_P)- and (S,S_P)-**14** and phosphinates (R,R_P)- and (R,S_P)-**12**, respectively. Taking into account that side reactions could interfere and that both ways could be followed simultaneously, complex reaction mixtures will result. To avoid those, the phosphonate−phosphinate rearrangement will be studied with (*R*)-**10** and the individual diastereomers of **14**.

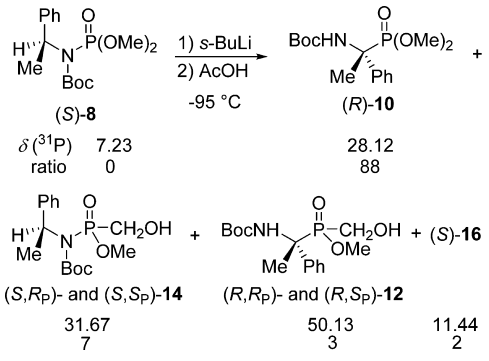
The phosphoramidate (*S*)-**8** used to study the reactions outlined in Scheme 3 was prepared in two steps from (*S*)-1-phenylethylamine (98% ee) in analogy to the synthesis of the diethyl ester (Scheme 4).[4] Dimethyl phosphoryl bromide

Scheme 4. Preparation of Phosphoramidate (*S*)-8



generated from trimethyl phosphite and bromine at −50 °C in dry CH_2Cl_2 was reacted with the amine in the presence of triethylamine. The crystalline phosphoramidate (*S*)-**16** was obtained in 84% yield after purification by flash chromatography. It was metalated at nitrogen in THF using *s*-BuLi and then reacted with $(Boc)_2O$ to give *N*-Boc-protected phosphoramidate (*S*)-**8** in 77% yield as an oil. Phosphoramidate (*S*)-**8** was metalated with 1.4 equiv of *s*-BuLi in dry THF at −95 °C, hoping to have a higher selectivity for the formation of (*R*)-**10** that at −78 °C (Scheme 5). Under these optimized conditions, the crude product was a mixture based on ^{31}P NMR

Scheme 5. *s*-BuLi-Induced Rearrangements of Phosphoramidate (*S*)-8



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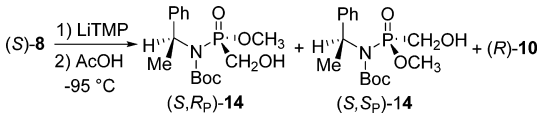
spectroscopy. The main product was undoubtedly the α-aminophosphonate (*R*)-**10** isolated by flash chromatography in 74% yield, indicating that the benzylic hydrogen atom is more acidic than a hydrogen atom of the MeO group. As the phosphoramidate−α-aminophosphonate rearrangement follows a retentive course,[4] (*R*) configuration was assigned to α-aminophosphonate **10**. However, the diastereomeric phosphonamidates **14** and phosphinates **12** were formed as well but in small quantities and unknown ratios. Anticipating later results, each pair of diastereomers displayed just one broad signal in the ^{31}P NMR spectra but very different ones in the ^{1}H NMR spectra.

Lithium 2,2,6,6-tetramethylpiperidide (LiTMP), a sterically hindered amide (pK_a 37),[16] was tested as base as well at the reaction temperature of −95 °C for 1 h (Scheme 6). The crude

Scheme 6. LiTMP-Induced Rearrangements of Phosphoramidate (*S*)-8



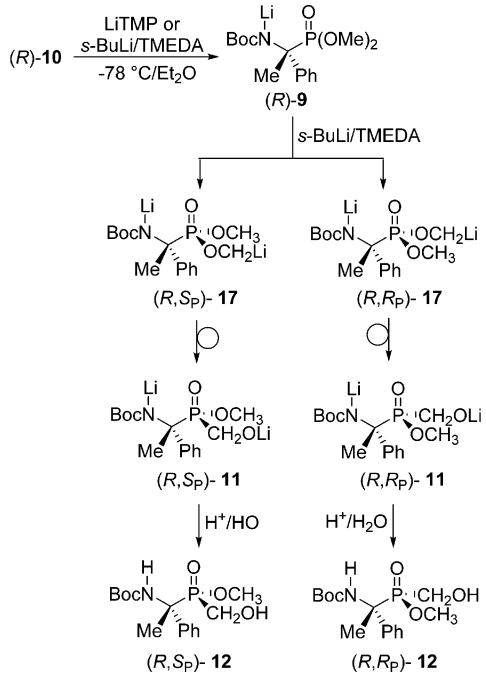
product contained starting material (*S*)-**8**/phosphonate (*R*)-**10**/phosphonamidates **14** [^{31}P NMR: (*S*,*R*)/(*S*,*S*) 60:40] in a ratio of 20:6:74 but no phosphinates **12**. The mixture of phosphonamidates **14** was isolated in 55% yield as a viscous oil. This result shows that LiTMP metalated the methoxy group more easily accessible than the benzyl group selectively. Furthermore, the pK_a of a OCH_3 group of (*S*)-**8** is estimated to be ≤37, similar to that of the benzyl group. Surprisingly, a further metalation at the benzylic position to induce a phosphonate−phosphinate rearranmgement did not take place (see Scheme 3).

The two diastereomers **14** were separated by semipreparative HPLC (t_R 6.01 and 7.25 min) and crystallized from CH_2Cl_2/hexanes. Only the crystals of the less polar diastereomer were suitable for single-crystal X-ray structure analysis. This allowed to assign (*R*) configuration at phosphorus. Therefore, the less polar diastereomer of **14** has (*S*,R_P) configuration, the more polar one (*S*,S_P).

When LiTMP was replaced by LDA (2.5 equiv) to induce the rearrangement under otherwise identical conditions, a crude product with a ratio of starting material (*S*)-**8**/phosphonate (*R*)-**10**/phosphonamidates **14**/phosphinates **12** of 30:35:35:1 (by ^{31}P NMR) resulted. Flash chromatography gave recovered starting material (*S*)-**8** (20%), phosphonate (*R*)-**10** (20%) and diastereomers **14** (27%). Clearly, the yield of the desired diastereomers **14** decreased and that of phosphonate (*R*)-**10** increased compared to LiTMP, which is evidently the best base for selective metalation at the OCH_3 group of a dimethyl phosphoramidate.

We had now the three phosphonates (*R*)-**10**, (*S*,R_P)- and (*S*,S_P)-**14** in our hands to study the phosphonate−phosphinate rearrangement in detail. Phosphonate (*R*)-**10** was investigated first using 2.5 equiv of LiTMP in dry THF at −78 °C for 18 h (Scheme 7). One equiv of base will be consumed rapidly for converting phosphonate (*R*)-**10** to the lithiated spezies (*R*)-**9**. Surprisingly, the ratio of phosphonate (*R*)-**10** and phosphinates (*R*,S_P)- and (*R*,R_P)-**12** was only 88:12 [by ^{31}P NMR; (*R*,S_P)-**12**/(*R*,R_P)-**12** 22:78 by ^{1}H NMR] despite a reaction time of 18 h. The starting material was recovered in 64% yield. Evidently,

Scheme 7. LiTMP- or *s*-BuLi-Induced Phosphonate−Phosphinate Rearrangement of Phosphonate (*R*)-10



metalation at a methoxy group and the ensuing phosphonate−phosphinate rearrangement had occurred only to a small extent. The high electron density at nitrogen of (*R*)-**9** will undoubtedly inductively lower the acidity of the hydrogen atoms of the methoxy group, so that LiTMP is no longer sufficiently basic to deprotonate (*R*)-**9** at a reasonable rate. However, when this phosphonate was reacted with 2.5 equiv of *s*-BuLi/TMEDA in Et_2O for 2 h at −78 °C, the crude product contained starting phosphonate and phosphinates (*R*,S_P)- and (*R*,R_P)-**12** in a ratio of 63:37 based on ^{31}P NMR spectroscopy. The ratio of (*R*,S_P)- and (*R*,R_P)-**12** (56:44) having the same chemical shift in the mixture in the ^{31}P NMR spectrum, had to be determined by ^{1}H NMR spectroscopy. The inseparable mixture of phosphinates was isolated by flash column chromatography in 37% yield. Increasing the amount of base to 3.3 equiv of *s*-BuLi/TMEDA (Et_2O, 1 h, −78 °C) increased the yield of the mixture to just 45%. Homogenous diastereomers of **12** were obtained by semipreparative HPLC using EtOAc as eluent. Both compounds were crystallized from CH_2Cl_2/hexanes. A crystal of the more polar diastereomer subjected to a single- crystal X-ray structure analysis allowed to assign (*R*) configuration to the stereogenic phosphorus atom. The (*R*) configuration at the stereogenic carbon atom was not changed. Consequently, the less polar diastereomer of **12** must have (*R*,S_P) configuration.

The alternative approach to obtain (*R*,S_P)- and (*R*,R_P)-**12** was to start from individual phosphonamidates (*S*,R_P)- and (*S*,S_P)-**14** using 3.3 equiv of *s*-BuLi in dry THF at −95 °C (Scheme 8). The reaction of (*S*,R_P)-**14** was quenched after 1 h with AcOH and worked up. The crude product was a mixture of starting phosphonamidate (*S*,R_P)-**14** and a mixture of diastereomeric phosphinates **12** (**14**/**12** 29:71, by ^{31}P NMR). Flash chromatography furnished recovered starting material in 22% yield and a mixture of phosphinates of unknown relative configuration in 51% yield (ratio 89:11 by ^{1}H NMR; 92:8 by HPLC). As we were expecting just one phosphinate, assuming that the phosphonate−phosphinate rearrangement would

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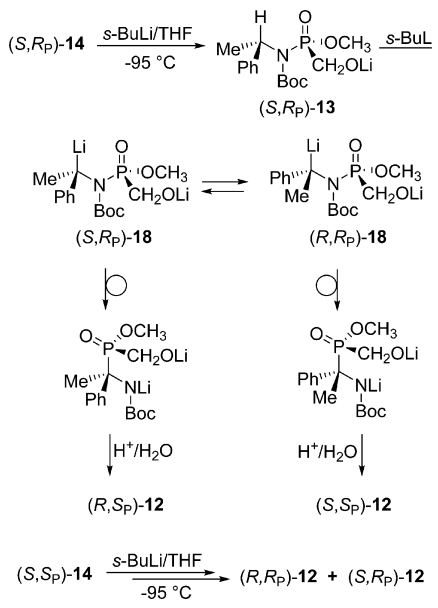
Scheme 8. *s*-BuLi-Induced Phosphonate−Phosphinate Rearrangement of Phosphonates (S,R_P)- and (S,S_P)-14

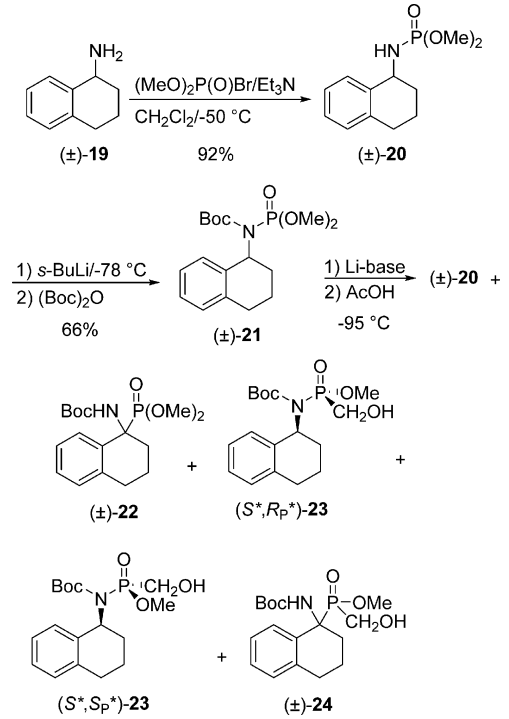


follow a retentive course as the phosphate−phosphonate rearrangement, a change of configuration at one of the two stereogenic centers must have occurred. To determine the relative and absolute configurations at the two centers, the mixture of phosphinates was separated by semipreparative HPLC and compared to the two phosphinates of known relative and absolute configuration obtained according to Scheme 7. The major diastereomer was identical by ^{1}H NMR spectroscopy to (R,S_P)-**12**, so that it could either have (R,S_P) or (S,R_P) configuration. As the specific optical rotation of (R,S_P)-**12** formed from (*R*)-**10** was $[\alpha]_D^{23}$ +25.1 (*c* 1.0, acetone) and that of the major diastereomer formed from (S,R_P)-**14** was $[\alpha]_D^{16}$ +24.6 (*c* 1.0, acetone), the latter has indeed (R,S_P) configuration. Similarly, the minor diastereomer formed from (S,R_P)-**14** was found to have (S,S_P) configuration, also based on its specific optical rotation {(R,R_P)-**12** formed from (*R*)-**10**: $[\alpha]_D^{23}$ +15.6 (*c* 1.0, acetone); minor diastereomer formed from (S,R_P)-**14**: $[\alpha]_D^{16}$ −17.4 (*c* 0.35, acetone)}. Clearly, part of the molecules changed their configuration at the stereogenic benzylic center despite a reaction temperature of −95 °C. The benzylic carbanion (S,R_P)-**18** formed from phosphonate (S,R_P)-**13** by metalation is configurationally unstable and epimerizes in part to (R,R_P)-**18**. Both carbanions undergo a phosphonate−phosphinate rearrangement with retention of configuration and yield phosphinates (R,S_P)- and (S,S_P)-**12**, respectively. This result is not quite surprising compared to the phosphoramidate−phosphonate rearrangement of (*R*)-diethyl *N*-(1-phenylethyl)phosphoramidate at temperatures of −78, −30, and 0 °C.[4] The rearrangement followed a retentive course (ee 98%) at all temperatures. We think that the major factor influencing the half-life of benzyllithiums as intermediates of the phosphoramidate−phosphonate and phosphonate−phosphinate rearrangement is the electrophilicity of the phosphorus substituent. The phosphorus of the $(EtO)_2P(O)O$ group is more electrophilic than that of the $(MeO)P(O)(CH_2OLi)$-(NBoc) group. This leads to a longer half-life for the intermediate benzyllithium (S,R_P)-**18** in the latter case, as the reaction rate for the rearrangement is smaller and consequently has a higher chance for inversion of configuration at the benzylic center.

Diastereomer (S,S_P)-**14** was isomerized in the same way as (S,R_P)-**12** (see Scheme 8). Here more starting phosphonate was recovered (52%), and the yield of the mixture of phosphinates was lower [25%; (S,R_P)-**12**/(R,R_P)-**12** 11:89 by ^{1}H NMR]. Again, a small portion of the molecules changed their configuration at the stereogenic benzylic center. These experiments demonstrate that the phosphonate−phosphinate rearrangement follows exclusively a retentive course at the phosphorus atom and predominately a retentive course at the (benzylic) carbon atom.

Rearrangements of (±)-Dimethyl *N*-Boc-*N*-(1,2,3,4-tetrahydronaphthalen-1-yl)phosphoramidate. To study the effect of lowering the acidity of the benzylic hydrogen atom on the rearrangement, the (*S*)-phenylethylamine in phosphoramidate (*S*)-**8** was replaced by (±)-5,6,7,8-tetrahydro-naphthalen-1-ylamine **19** (Scheme 9). It was converted to *N*-Boc-protected phosphoramidate (±)-**21** using the procedures for the preparation of (*S*)-**8**. *s*-BuLi (1.4 equiv, reaction time: 70 min) or LiTMP (2.5 equiv, reaction time: 1 h) were used at −95 °C to induce a phosphoramidate−phosphonate rearrangements in THF. *s*-BuLi produced a complex mixture of compounds [molar ratio by ^{31}P NMR of (±)-**20**/(±)-**21**/(±)-**22**/(*S**,*R*$_P$*)-**23** and (*S**,*S*$_P$*)-**23**/presumably (±)-**24** 0.06:0.05:0.10:0.71 (1:1.79)]. We do not have an unequivocal proof for the presence of phosphinate (±)-**24** in the crude product. Surprisingly, phosphonate (±)-**22** which was not isolated was only a minor component and the diastereomeric phosphonamidates of **23** were the predominating components in the mixture. This is in strong contrast to the rearrangement of phosphoramidate (*S*)-**8** derived from 1-phenylethylamine, where the phosphonate (*R*)-**10** was formed in 88% and the phosphonamidate **14** in 7% yield. This change was presumably

Scheme 9. Preparation and Rearrangements of *N*-Boc-Protected Phosphoramidate (±)-21



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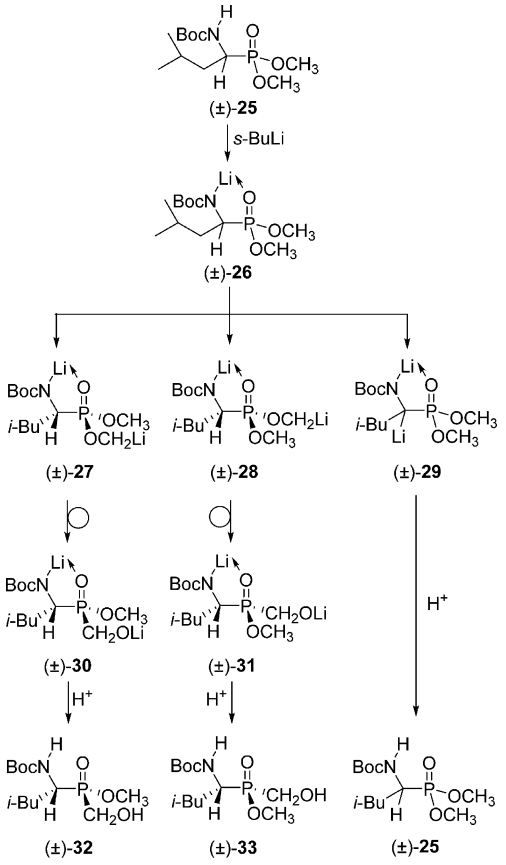
caused by the benzylic hydrogen atom, which is less acidic than a hydrogen atom at the methoxy group, and to a lesser extent by steric causes. When the reaction was repeated except that *s*-BuLi was replaced by LiTMP, only (S^*,R_P^*)- and (S^*,S_P^*)-**23** (the latter being more polar by TLC, ratio 1.43:1.0 by ^{31}P NMR) were formed, as expected. Neither starting material nor phosphoramidate (±)-**20** or phosphonate (±)-**22** or phosphinate could be detected by ^{31}P NMR spectroscopy. The phosphonamidates could be separated by flash column chromatography and crystallized. The more polar compound of **23** furnished crystals suitable for single-crystal X-ray structure analysis. The two stereogenic centers were found to have (S^*,S_P^*) configuration relatively. Consequently, the other diastereomer must have (S^*,R_P^*) configuration. These two experiments demonstrate that *N*-Boc-protected dimethyl phosphoramidates can be selectively metalated at the methoxy group and rearranged to hydroxymethylphosphonamidates. When phosphonamidate (S,R_P)-**23** was treated with excess *s*-BuLi (3.3 equiv) to undergo a phosphonate−phosphinate rearrangement to (±)-**24** after metalation at the benzylic position at −95 and −50 °C, only small amounts (37 and 24%) of starting material could be recovered by flash chormaotography. The major portion of the starting material was decomposed evidently.

Phosphonate−Phosphinate Rearrangement of Racemic *N*-Boc-Protected Dimethyl 1-Amino-3-methylbutylphosphonate. Finally, a simple *N*-Boc-protected dimethyl α-aminophosphonate, (±)-**25**, was studied as substrate for the phosphononate−phosphinate rearrangement (Scheme 10).

Scheme 10. Rearrangement of *N*-Boc-Protected Dimethyl α-Aminophosphonate (±)-25



This starting material was prepared easily by a literature procedure[17] from simple precursors and reacted under a variety of conditions with excess BuLi. It is clear that at first the nitrogen atom was metalated to give (±)-**26**. Although this *N*-Boc-protected aminophosphonate (±)-**25** has an acidic α-hydrogen atom, it was reasoned that it would become less acidic by metalation of nitrogen, possibly even less acidic than the hydrogen atoms of the methoxy groups. Furthermore, formation of a vicinal dianion was considered here highly unlikely, although known in a similar case,[18] but we were convinced of the opposite by later results. The second metalation, the deprotonation of a methoxy group of (±)-**26**, will produce α-oxymethyllithiums (±)-**27** and (±)-**28**, the former being possibly preferred, because the respective methoxy group is less shielded than the former by the isobutyl group. The supposedly short-lived and dipole-stabilized[19] oxymethyllithiums will immediately undergo phosphonate−phosphinate rearrangements to phosphinates (±)-**30** and (±)-**31**, respectively. A minimum of 2 equiv of base are necessary for quantitative transformation in principle. Acidic workup will produce a mixture of (±)-**32**, (±)-**33**, and (±)-**25** generated from (±)-**26** and (±)-**29**, respectively.

Therefore, (±)-**25** was reacted with excess LiTMP (2.5 equiv) or *s*-BuLi under a variety of conditions (Table 1). The ratio of starting phosphonate (±)-**25** and phosphinate(s) was determined by ^{31}P NMR spectroscopy in the crude product. There was only one resonance for phosphinates in the ^{31}P NMR spectra, indicating that either only one of the two possible diastereomeric phosphinates was formed or that both have the same chemical shift. LiTMP did not effect the phosphonate−phosphinate rearrangement of (±)-**25** (Entry 1). *s*-BuLi did not induce the rearrangement in diethyl ether (Entry 2) but in THF/DME (Entry 3) and THF (Entry 4). Flash chromatography furnished an oily phosphinate, (±)-**32** and/or (±)-**33**, of unknown configuration in about 20% yield at best, which was homogeneous by ^{1}H and ^{31}P NMR spectroscopy surprisingly. However, the two peaks in the ^{31}P NMR spectrum (δ: 52.6 and 50.4, ratio 96:4) were attributed to the two conformers of one diastereomeric phosphinate. Furthermore, we assume that the very polar phosphinates should have very similar polarity and should elute together. Unfortunately, the yield of the rearrangement could not be increased to values above 20%. The strong basic conditions induced side reactions, which consumed starting material and thus decreased the yield.

To ease the interpretation of the ^{1}H NMR spectrum and to determine the configuration of the isolated phosphinate, it was acetylated to give crystalline acetate (±)-**34** (Scheme 11). Single crystal X-ray structure analysis revealed that the two stereocenters had (R^*,S_P^*) configuration, supporting the notion that (±)-**27** is the intermediate oxymethyllithium formed preferentially. However, it was formed exclusively, unexpectedly. The high diastereoselectivity is noteworthy even if a small amount of (±)-**33** went unnoticed.

To check whether metalation of (±)-**26** to (±)-**29** is possible, a reaction mixture of (±)-**25** with *s*-BuLi by the standard procedure was quenched with AcOD. The starting phosphonate (±)-**25** was recovered by flash chromatography and investigated by ^{1}H NMR spectroscopy (400 MHz). Surprisingly, 32% of the molecules were deuterated at C-1, indicating that vicinal dianion (±)-**29** was generated indeed. It cannot undergo a phosphonate−phosphinate rearrangement, because the required metalation of a methoxy group will not be

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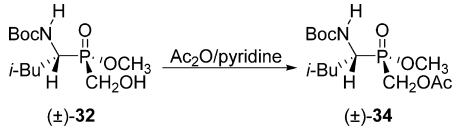
Table 1. Phosphonate−Phosphinate Rearrangement of (±)-25 at −78 °C for 2 h

entry	base/equiv	solvent	(±)-25: (±)-32[a]	yield (%)	recov. (±)-25
1	LiTMP/2.5	THF	only (±)-25	0	78
2	*s*-BuLi/2.5	Et_2O	only (±)-25	0	81
3	*s*-BuLi/2.2	THF/DME 4:1	2.6:1	5	13
4	*s*-BuLi/3	THF	1.9:1	19	42

[a]In crude product by ^{31}P NMR

Scheme 11. Acetylation of Hydroxymethylphosphinate (±)-32



(±)-32 (±)-34

feasible. This side reaction compromises the yield of the phosphinate undoubtedly.

CONCLUSIONS

In summary, we have demonstrated that (*S*)-dimethyl *N*-Boc-*N*-(1-phenylethyl)phosphoramidate underwent phosphate−phosphonate rearrangements. *s*-BuLi and LiTMP metalated the benzylic position or the OCH_3 group, respectively, giving preferably an *α*-aminophosphonate in the former case and a mixture of diastereomeric phosphonamidates in the latter case. These homogeneous compounds, when treated with *s*-BuLi, were converted to diastereomeric phosphinates (phosphonate−phosphinate rearrangement). The dimethyl phosphoramidate derived from 1,2,3,4-tetrahydronaphthalen-1-ylamine could only be induced to give phosphonates, but no phosphinates, attributed to the minor acidity of the benzylic proton compared to that one of the 1-phenylethylamine. The phosphonate−phosphinate rearrangement followed a retentive course, with partial epimerization because of a configurationally labile benzyllithium as intermediate. The *N*-Boc-protected dimethyl 1-amino-3-methylbutylphosphonate underwent a phosphonate−phosphinate rearrangement albeit in low yield, resulting from the metalation of one of the diastereomeric OCH_3 groups.

Experimental Section. $^1H/^{13}C$ (*J* modulated) NMR spectra were measured at 300 K at 400.13 MHz/100.61 MHz. $^{31}P\{^1H\}$ NMR spectra were recorded at 161.98 MHz. All chemical shifts (*δ*) are given in ppm. They were referenced either to residual $CHCl_3$ (δ_H 7.24)/toluene-d_8 (CHD_2: δ_H 2.09) or $CDCl_3$ (δ_C 77.0)/toluene-d_8 (CD_3: δ_C 21.04). IR spectra of films on a silicon disc[20] were recorded on a FT-IR spectrometer or by using ATR. Optical rotations were measured at 20 °C with a polarimeter in a 1 dm cell. Melting points are uncorrected.

Flash (column) chromatography was performed with silica gel 60 (230−400 mesh) and monitored by TLC, carried out on 0.25 mm thick plates, silica gel 60 F_{254}. Spots were visualized by UV and/or dipping the plate into a solution of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (23.0 g) and $Ce(SO_4)_2\cdot 4H_2O$ (1.0 g) in 10% aq H_2SO_4 (500 mL), followed by heating with a heat gun.

Analytical HPLC: Shimadzu EC 250/4 NUCLEOSIL 50−5, 2 mL/min, semipreparative HPLC: SemiPrep Superspher RSI 60, 40 mL/min.

Commercial *n*-BuLi and *s*-BuLi were not precooled before addition to reaction mixtures at low temperatures. The dropwise addition was performed slowly enough to maintain the temperature inside the flask.

*(S)-(−)-Dimethyl N-(1-phenylethyl)phosphoramidate [(S)-**16**].* A solution of bromine in dry CH_2Cl_2 (14.77 mL, 22 mmol, 1.49 M) was added dropwise to a stirred solution of trimethyl phosphite (2.73 g, 2.59 mL, 22 mmol) in dry CH_2Cl_2 (10 mL) under argon at −50 °C. After 30 min (*S*)-1-phenylethylamine (2.42 g, 2.58 mL, 20 mmol, 98% ee) and dry Et_3N (4.04 g, 5.53 mL, 40 mmol) were added and stirring was continued for 30 min at −50 °C and 2 h at room temperature. Water (9 mL) and HCl (16 mL, 2M) were added, and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc, then EtOAc/EtOH 5:2; R_f 0.42 for EtOAc) to yield phosphoramidate (*S*)-**16** (3.828 g, 84%) as colorless crystals; mp 53 °C (CH_2Cl_2/hexanes); $[\alpha]_D^{20}$ −47.8 (*c* 0.93, acetone). If the crude product was pure enough (as judged by ^1H NMR), it was used in the next step without flash chromatography.

IR (Si): *ν* 3216, 2951, 1455, 1236, 1035 cm^{-1}. ^1H NMR (400.13 MHz, $CDCl_3$): *δ* 7.36−7.21 (m, 5H), 4.31 (qdd, *J* = 15.7, 8.6, 6.8 Hz, 1H), 3.70 (d, *J* = 11.2 Hz, 3H), 3.49 (d, *J* = 11.2 Hz, 3H), 3.41 (dd, *J* = 11.1, 8.6 Hz, 1H), 1.49 (dd, *J* = 6.8, 0.7 Hz, 3H). ^{13}C NMR (100.61 MHz, $CDCl_3$): *δ* 145.0 (d, *J* = 4.6 Hz), 128.5 (2C), 127.1, 125.8 (2C), 52.9 (d, *J* = 5.4 Hz), 52.7 (d, *J* = 5.3 Hz), 51.4, 25.1 (d, *J* = 6.2 Hz). ^{31}P NMR (161.98 MHz, $CDCl_3$): *δ* 11.4. Anal. Calcd for $C_{10}H_{16}NO_3P$: C, 52.40; H, 7.04; N, 6.11. Found: C, 52.47; H, 6.83, N, 5.99.

*(S)-(−)-Dimethyl N-(t-butoxycarbonyl)-N-(1-phenylethyl)-phosphoramidate [(S)-**8**].* *s*-BuLi (13.5 mL, 18.85 mmol, 1.2 equiv, 1.4 M in cyclohexane) was added dropwise to a stirred solution of phosphoramidate (*S*)-**16** (3.60 g, 15.71 mmol) in dry THF (25 mL) under argon at −78 °C, followed by Boc_2O (3.77 g, 17.28 mmol, 1.1 equiv) dissolved in dry THF (4 mL) after 15 min. Stirring was continued for 1 h at −78 °C, then during slow warming to room temperature, and lastly for 1.5 h at room temperature. AcOH (25 mL, 1 M in CH_2Cl_2) was added to the reaction mixture. The organic phase was separated and the aqueous one was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc, R_f 0.67) to give *N*-Boc-protected phosphoramidate (*S*)-**8** (3.98 g, 77%) as a colorless oil; $[\alpha]_D^{20}$ −10.2 (*c* 1.3, acetone).

IR (Si): *ν* 2979, 1718, 1369, 1289, 1160, 1038 cm^{-1}. ^1H NMR (400.13 MHz, $CDCl_3$): *δ* 7.42−7.14 (m, 5H), 5.40 (qd, *J* = 13.8, 7.0 Hz, 1H), 3.79 (d, *J* = 11.6 Hz, 3H,), 3.70 (d, *J* = 11.8 Hz, 3H), 1.77 (d, *J* = 7.0 Hz, 3H), 1.28 (s, 9H). ^{13}C NMR (100.61 MHz, $CDCl_3$): *δ* 153.2 (d, *J* = 7.3 Hz), 142.1 (d, *J* = 3.1 Hz), 128.0 (2C), 126.8 (2C), 126.7, 82.5, 54.8 (d, *J* = 3.1 Hz), 54.3 (d, *J* = 6.1 Hz), 53.7 (d, *J* = 6.1 Hz), 27.9 (3C), 18.3. ^{31}P NMR (161.98 MHz, $CDCl_3$): *δ* 7.2. Anal. Calcd for $C_{15}H_{24}NO_5P$: C, 54.71; H, 7.35; N, 4.25. Found: C, 54.28, H, 7.23, N, 4.28.

*(R)-(+)-Dimethyl 1-(t-butoxycarbonylamino)-1-phenylethyl-phosphonate [(R)-**10**].* *s*-BuLi (4.86 mmol, 1.4 equiv, 3.5 mL, 1.4 M in cyclohexane) was added dropwise to a stirred solution of phosphoramidate (*S*)-**8** (1.144 g, 3.47 mmol) in dry THF (10 mL) at −95 °C under argon atmosphere. After the solution was stirred for 30 min, AcOH (1.9 mL, 5.7 mmol, 3 M in dry CH_2Cl_2) was added, followed by H_2O (10 mL) at room temperature. The organic phase was removed, and the aqueous one was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with water (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue (^{31}P NMR: (*S*)-**8**/(*R*)-**10**/(*S*,R_P)- and (*S*,S_P)-**14**/(*R*,R_P)- and (*R*,S_P)-**12**/(*S*)-**16** 0:88:7:3:2) was flash chromatographed (hexanes/EtOAc 1:3, R_f 0.44) to yield phosphonate (*R*)-**10** (0.843 g, 74%) as a colorless oil; $[\alpha]_D^{20}$ +2.7 (*c* 1.5, acetone).

IR (Si): *ν* 3443, 3278, 2977, 2957, 1730, 1495, 1251, 1167, 1031 cm^{-1}. ^1H NMR (400.13 MHz, $CDCl_3$; contained 2% by weight of

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EtOAc): δ 7.50−7.44 (m, 2H), 7.36−7.30 (m, 2H), 7.28−7.22 (m, 1H$_r$), 5.64 (br. d, J = 10.4 Hz, 1H), 3.55 (d, J = 10.4 Hz, 3H), 3.48 (d, J = 10.4 Hz, 3H), 2.03 (d, J = 16.2 Hz, 3H), 1.32 (br. s, 9H). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 154.1, 138.9, 128.1 (d, J = 2.3 Hz, 2C), 127.3 (d, J = 3.1 Hz), 126.9 (d, J = 4.6 Hz, 2C), 79.9, 57.8 (d, J = 148.4 Hz), 54.03 (d, J = 7.3 Hz), 54.0 (d, J = 7.3 Hz), 28.1 (3C), 21.2 (br. s). ^{31}P NMR (161.98 MHz, $CDCl_3$): δ 28.2. Anal. Calcd for $C_{15}H_{24}NO_5P$: C, 54.71; H, 7.35; N, 4.25. Found: C, 54.77; H, 7.28, N, 4.26.

*(S,R$_P$)-(−)- and (R,R$_P$)-(+)-Methyl N-t-butoxycarbonyl-N-(1-phenylethyl)-hydroxymethyl-phosphonamidate [(S,R$_P$)- and (S,S$_P$)-**14**].* *n*-BuLi (2.4 mL, 6 mmol, 2.5 M in cyclohexane) was added to a stirred solution of 1,1,6,6-tetramethylpiperidine (0.848 g, 1.0 mL, 6 mmol) in dry THF (3 mL) at −30 °C under an argon atmosphere. After 15 min, the solution was cooled to −95 °C and a solution of phosphoramidate (*S*)-**8** (0.988 g, 3 mmol) in dry THF (total of 3 mL) was added, followed by a solution of AcOH (0.540 g, 0.52 mL, 3 equiv) in dry THF (1 mL) 1 h later. The cooling bath was removed, and when the reaction mixture had reached room temperature, it was diluted with water (10 mL). The organic layer was separated, and the aqueous one was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with water (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexanes 5:2 for starting material; EtOAc for **14**, R_f 0.32 for EtOAc) to yield starting material (0.149 g, 15%) and a mixture of (*S*,*R*$_P$)- and (*S*,*S*$_P$)-**14** (0.545 g, 55%; ratio 60:40 by ^{31}P NMR) as a colorless viscous oil.

Similarly, (*S*)-**8** (0.908 g, 2.8 mmol) was reacted with LDA (2.5 equiv, prepared freshly from *i*Pr$_2$NH and 2.5 M *n*-BuLi). The ratio of starting material (*S*)-**8**/phosphonate (*R*)-**10**/phosphonamidates **14**/phosphinates **12** in crude product was 30:35:35:1 (by ^{31}P NMR). Flash chromatography (at first with EtOAc/hexanes 5:2 to recover starting material, then EtOAc) gave recovered starting material (*S*)-**8** (0.180 g, 20%), phosphonate (*R*)-**10** (0.181 g, 20%), and diastereomers **14** (0.247 g, 27%).

(***S*,*R*$_P$)-14**: Less polar diastereomer by HPLC, analytical HPLC (EtOAc/hexanes 5:2, (*S*,*R*$_P$)-**14**: t_R 6.01 min, (*S*,*S*$_P$)-**14**: t_R 7.25 min). (*S*,*R*$_P$)- and (*S*,*S*$_P$)-**14** were separated by semipreparative HPLC (EtOAc/hexanes 5:2).

(*S*,*R*$_P$)-**14**, obtained by semipreparative HPLC, was crystallized from CH_2Cl_2/hexanes at +4 °C by slow evaporation of solvent, mp 88−90 °C; $[\alpha]_D^{23}$ −35.0 (*c* 1.45, acetone); crystals were suitable for single crystal X-ray structure analysis. IR (Si): ν 3318, 2979, 1709, 1452, 1385, 1370, 1278, 1255, 1158, 1056, cm^{-1}. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.38−7.33 (m, 2H,), 7.30−7.22 (m, 2H), 7.21−7.14 (m, 1H), 5.37 (qd, J = 8.4, 7.1 Hz, 1H), 4.24 (ABP-system, J_{AB} = 14.7 Hz, J = 7.7, 3.5 Hz, 2H), 3.79 (br. s, 1H), 3.73 (d, J = 11.6 Hz, 3H), 1.75 (d, J = 7.1 Hz), 1.19 (s, 9H). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 154.6 (d, J = 9.9 Hz), 141.8 (d, J = 3.8 Hz), 128.0 (2C), 126.69, 126.66 (2C), 83.4, 59.6 (d, J = 143.0 Hz), 52.8, 51.8 (d, J = 7.7 Hz), 27.7 (3C), 18.3 (d, J = 2.5 Hz). ^{31}P NMR (161.98 MHz, $CDCl_3$): δ 31.7. Anal. Calcd for $C_{15}H_{24}NO_5P$: C, 54.71; H, 7.35; N, 4.25. Found: C, 54.73; H, 7.44; N, 4.21.

(*S*,*S*$_P$)-**14**, obtained by semipreparative HPLC, was crystallized from CH_2Cl_2/hexanes at +4 °C by slow evaporation of solvent, thin needles, mp 101−103 °C; $[\alpha]_D^{20}$ −5.5 (*c* 0.69, acetone). IR (Si): ν 3318, 2976, 1711, 1392, 1368, 1272, 1252, 1235, 1160, 1141, 1047 cm^{-1}. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.42−7.36 (m, 2H), 7.32−7.26 (m, 2H), 7.23−7.18 (m, 1H), 5.38 (qd, J = 9.9, 7.1 Hz, 1H), 4.14 (ABP-system, J_{AB} = 14.8 Hz, J = 7.1, 3.4 Hz, 2H), 3.79 (d, J = 11.1 Hz, 3H), 3.20 (br. s, 1H), 1.74 (d, J = 7.1 Hz), 1.26 (s, 9H). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 154.7 (d, J = 9.9 Hz), 141.9, 127.9 (2C), 126.9 (2C), 126.7, 83.4, 59.3 (d, J = 141.5 Hz), 53.1, 52.5 (d, J = 7.7 Hz), 27.9 (3C), 18.2 (d, J = 2.5 Hz). ^{31}P NMR (161.98 MHz, $CDCl_3$): δ 31.7. Anal. Calcd for $C_{15}H_{24}NO_5P$: C, 54.71; H, 7.35; N, 4.25. Found: C, 54.67; H, 7.51; N, 4.24.

*Conversion of Phosphonate (R)-**10** to Phosphinates (R,S$_P$)- and (R,R$_P$)-**12**, Respectively. Experiment with LiTMP.* *s*-BuLi (6.4 mmol, 2.5 equiv, 2.56 mL, 2.5 M in cyclohexane) was added to a stirred solution of 2,2,6,6-tetramethylpiperidine (0.904 g, 6.4 mmol, 1.08 mL) in dry THF (3.5 mL) at −30 °C under argon. After 15 min, the flask was cooled to −78 °C, and the solution of (*R*)-**10** (0.843 g, 2.56 mmol) in dry THF was added slowly. Stirring was continued for 18 h at −78 °C. The cooling bath was removed, and AcOH (0.472 g, 7.68 mmol, 2.6 mL of solution, 3 M in dry CH_2Cl_2), HCl (0.5 M, 10 mL), and EtOAc were added. The organic layer was separated, and the aqueous one was extracted with EOAc (2 × 15 mL). The combined organic layers were washed with water (20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product (^{31}P NMR: phosphonate (*R*)-**10**/phosphinates (*R*,*S*$_P$)- and (*R*,*R*$_P$)-**12** 88:12, by ^{1}H NMR: 81:19; by ^{1}H NMR: (*R*,*S*$_P$)-**12**/(*R*,*R*$_P$)-**12** 22:78) was flash chromatographed (hexanes/EtOAc 1:3) to recover only starting phosphonate (*R*)-**10** (0.543 g, 64%).

Experiment with 2.5 equiv of s-BuLi/TMEDA/Et$_2$O. *s*-BuLi (3.75 mmol, 2.5 equiv, 2.7 mL, 1.4 M in cyclohexane) was added dropwise to a stirred solution of (*R*)-**10** (0.483 g, 1.5 mmol) and dry TMEDA (0.436 g, 3.75 mmol, 0.57 mL, 2.5 equiv) in dry Et$_2$O (1.5 mL) at −78 °C under argon. After stirring for 2 h (at the end of the second hour, the temperature had risen to −60 °C), AcOH (0.45 g, 7.5 mmol, 0.43 mL, 5 equiv, 2.5 mL of solution, 3 M in dry CH_2Cl_2), HCl (10 mL, 0.25 M), and EtOAc (15 mL) were added. The layers were separated and the aqueous one was extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with water (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue [^{31}P NMR: starting phosphonate (*R*)-**10**/phosphinates (*R*,*S*$_P$)- and (*R*,*R*$_P$)-**12** (have same chemical shift) 63:37, by ^{1}H NMR: (*R*,*S*$_P$)-**12**/(*R*,*R*$_P$)-**12** 56:44] was purified by flash chromatography [EtOAc/EtOH 10:1, starting material R_f 0.49; diastereomers (*R*,*S*$_P$)- and (*R*,*R*$_P$)-**12** gave one spot of R_f 0.35] to yield mixture of phosphinates **12** [0.184 g, 37%; ratio of phosphinates (*R*,*S*$_P$)- and (*R*,*R*$_P$)-**12** 58:42 by ^{1}H NMR].

Phosphinate (*R*,*S*$_P$)-**12** was less polar than (*R*,*R*$_P$)-**12** by HPLC; analytical HPLC: EtOAc, (*R*,*S*$_P$)-**12**: t_R 6.99 min, (*R*,*R*$_P$)-**12**: t_R 8.83 min; separated by semipreparative HPLC using EtOAc as eluent.

Phosphinate (*R*,*S*$_P$)-**12** was crystallized by slow evaporation of solvent from a solution in CH_2Cl_2/hexanes at 4 °C to give very thin colorless crystals, mp 117−120 °C; $[\alpha]_D^{23}$ +25.1 (*c* 1.0, acetone). IR (Si): ν 3331, 2980, 1727, 1495, 1252, 1168, 1032 cm^{-1}. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.53−7.45 (m, 2H), 7.38−7.31 (m, 2H), 7.30−7.22 (m, 1H), 5.75 (very br. s, 1H), 3.88 (AB part of ABX-system, J_{AB} = 14.9 Hz, J = 2.8, 2.5 Hz, 2H), 3.66 (br. s, 1H), 3.49 (d, J = 9.9 Hz, 3H), 1.96 (d, J = 14.4 Hz, 3H), 1.35 (br. s, 9H). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 155.0 (d, J = 9.1 Hz), 135.9, 128.5 (2C), 127.7, 126.5 (2C), 80.6, 59.3 (d, J = 90.3 Hz), 57.5 (d, J = 99.4 Hz), 52.8 (d, J = 7.7 Hz), 28.23 (3C), 22.1 (br. s). ^{31}P NMR 161.98 MHz, $CDCl_3$): δ 50.13. Anal. Calcd for $C_{15}H_{24}NO_5P$: C, 54.71; H, 7.35; N, 4.25. Found: C, 54.46; H, 7.60; N, 4.21.

Phosphinate (*R*,*R*$_P$)-**12** was crystallized by slow evaporation of solvent from a solution in CH_2Cl_2/hexanes at 4 °C to give colorless crystals, mp 132−133 °C, suitable for single crystal X-ray structure analysis; $[\alpha]_D^{23}$ +15.6 (*c* 1.0, acetone). IR (Si): ν 3316, 2979, 1712, 1495, 1368, 1169, 1055, 1033 cm^{-1}. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.48−7.40 (m, 2H), 7.38−7.30 (m, 2H), 7.30−7.24 (m, 1H), 5.91 (br. s, 1H), 3.80 (AB-system, J = 14.8, 2.6, 0.0 Hz, 2H), 3.70 (d, J = 9.9 Hz, 3H), 3.5 (br. s, 1H), 1.97 (d, J = 14.2 Hz, 3H), 1.35 (br. s, 9H). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 154.9 (d, J = 12.2 Hz), 139.0, 128.5 (d, J = 1.5 Hz, 2C), 127.6 (d, J = 2.3 Hz), 126.4 (d, J = 3.1 Hz, 2C), 80.5, 59.4 (d, J = 91.0 Hz), 57.2 (d, J = 101.0 Hz), 53.2 (d, J = 7.7 Hz), 28.2 (3C), 21.8. ^{31}P NMR (161.98 MHz, $CDCl_3$): δ 50.20. Anal. Calcd for $C_{15}H_{24}NO_5P$: C, 54.71; H, 7.35; N, 4.25. Found: C, 54.68; H, 7.43; N, 4.25.

*Conversion of Phosphonamidates (S,R$_P$)- and (S,S$_P$)-**14** to Methyl (1-t-butoxycarbonylamino-1-phenylethyl)-(hydroxymethyl)-phosphinates (R,R$_P$)- and (S,R$_P$)-**12** and (R,S$_P$)-**12** and (S,S$_P$)-**12**, Respectively.* *s*-BuLi (2.90 mmol, 3.3 equiv, 2.1 mL, 1.4 M in cyclohexane) was added dropwise to a stirred solution of homogeneous (*S*,*R*$_P$)-**14** (0.291 g, 0.88 mmol) in dry THF (3 mL) at −95 °C under argon (the reaction mixture turned intensely yellow). After 1 h, the reaction was quenched with AcOH (0.349 g, 5.81 mmol, 6.6 equiv, 1.94 mL, 3 M solution in dry CH_2Cl_2) and HCl (5 mL, 0.25 M). The mixture was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under

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reduced pressure. The residue (^{31}P NMR: phosphinates **12**/starting phosphonamidate **14** 71:29, and impurities) was flash chromatographed (EtOAc/EtOH 10:1, starting material: R_f 0.74, phosphinates: 0.35) to yield recovered starting (S,R_P)-**14** (63 mg, 22%) and a mixture of phosphinates **12** (0.148 g, 51%; ^{1}H NMR: (R,S_P)-**12**/(S,S_P)-**12** 89:11; by HPLC: 92:8).

Similarly, phosphonate (S,S_P)-**14** (132 mg, 0.4 mmol) was reacted with *s*-BuLi; crude product: (S,S_P)**14**/**12** 67:33 by ^{1}H NMR; recovered starting material (68 mg, 52%), phosphinates **12** (33 mg, 25%, mixture by ^{1}H NMR of (S,R_P)-**12**/(R,R_P)-**12** 11:89; by HPLC: 12:88).

*(±)-Dimethyl N-(1,2,3,4-tetrahydronaphthalen-1-yl)-phosphoramidate [(±)-**20**].* (±)-1,2,3,4-Tetrahydro-naphthalen-1-yl-amine (2.94 g, 2.87 mL, 20 mmol) was converted to crude phosphoramidate (±)-**20** (4.72 g, 92%) as a crystalline product by the procedure used for the preparation of (*S*)-**16**. It was pure enough for the next step. An analytical sample was obtained by crystallization of crude product from CH_2Cl_2/hexanes as colorless crystals; mp 97−98 °C; R_f 0.38 (EtOAc).

IR (ATR): ν 3160, 2944, 2865, 1462, 1310, 1055, 1024, 1007, 976, cm^{-1}. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.51−7.45 (m, 1H), 7.19−7.11 (m, 2H), 7.08−7.02 (m, 1H), 4.37−4.27 (m, 1H), 3.76 (d, J = 11.1 Hz, 3H), 3.75 (d, J = 11.1 Hz, 3H), 2.85−2.65 (m, 3H), 2.12−2.00 (m, 1H), 1.92−1.72 (m, 3H). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 138.2 (d, J = 7.8 Hz), 137.1, 129.0, 128.5, 127.2, 126.1, 53.2 (d, J = 6.0 Hz, 2C), 50.1, 32.6 (d, J = 1.4 Hz), 29.1, 19.7. ^{31}P NMR (161.98 MHz, $CDCl_3$): δ 11.6. Anal. Calcd for $C_{12}H_{18}NO_3P$: C, 56.47; H, 7.11; N, 5.49. Found: C, 56.40; H, 6.84; N, 5.32.

*(±)-Dimethyl N-Boc-N-(1,2,3,4-tetrahydronaphthalen-1-yl)-phosphoramidate [(±)-**21**].* Crude phosphoramidate (±)-**20** (4.62 g, 18.1 mmol) was converted to crude phosphoramidate (±)-**21** by the procedure used for the preparation of (*S*)-**8**. Flash chromatography (CH_2Cl_2/hexanes 1:1, R_f 0.38) furnished *N*-Boc-protected phosphoramidate (±)-**21** (4.234 g, 66%) as a colorless oil.

IR (Si, NMR sample): ν 2954, 1719, 1284, 1160, 1045 cm^{-1}. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.25 (d, J = 7.3 Hz, 1H), 7.15−7.00 (m, 3H), 5.27 (td, J = 11.4, 6.8 Hz, 1H), 3.87 (d, J = 11.4 Hz, 3H), 3.79 (d, J = 11.9 Hz, 3H), 2.86−2.66 (m, 2H), 2.33−2.18 (m, 1H), 2.18−2.09 (m, 1H), 2.03−1.94 (m, 1H), 1.74 (qdd, J = 13.2, 4.8, 3.0 Hz, 1H), 1.19 (s, 9H). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 153.0 (d, J = 9.2 Hz), 137.8 (d, J = 3.8 Hz), 137.3, 128.7, 125.99, 125.98, 125.3, 82.3, 56.9 (d, J = 3.2 Hz), 54.6 (d, J = 6.1 Hz), 53.9 (d, J = 6.1 Hz), 29.7, 29.5, 27.6 (3C), 22.8. ^{31}P NMR (161.98 MHz, $CDCl_3$): δ 7.6. Anal. Calcd for $C_{17}H_{26}NO_5P$: C, 57.46; H, 7.37; N, 3.94. Found: C, 57.27; H, 7.02; N, 3.73.

(S,R_P*)-(±)- and (S*,S_P*)-(±)-Methyl N-Boc-N-(1,2,3,4-tetrahydronaphthalen-1-yl)-hydroxymethylphosphonamidate [(S*,R_P*)- and (S*,S_P*)-**23**]. Rearrangement of (±)-**21** with s-BuLi.* *s*-BuLi (3.97 mmol, 1.4 equiv, 2.8 mL, 1.4 M in cyclohexane) was added to a stirred solution of *N*-Boc-protected phosphoramidate (±)-**21** (1.007 g, 2.83 mmol) in dry THF (8.2 mL) at −95 °C under argon atmosphere. After stirring for 70 min, AcOH (2 mL, 2.45 M solution in dry CH_2Cl_2) was added, followed by stirring for 10 min at room temperature and addition of water (10 mL) and EtOAc (15 mL). The organic layer was separated, and the aqueous one was again extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with water (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give crude product (0.695 g, 69%). It was a mixture of phosphoramidate (±)-**20**/starting material (±)-**21**/phosphonate (±)-**22**/phosphonamidates (±)-**23** 0.06:0.05:0.10:0.71 [(S*,R_P*)-**23**:(S*,S_P*)-**23** 1:1.79], as determined by ^{31}P NMR.

*Rearrangement of (±)-**21** with TMPLi.* *n*-BuLi (2.51 mL, 6.27 mmol, 2.5 M in cyclohexane) was added dropwise to a solution of 2,2,6,6-tetramethylpiperidine (0.886 g, 1.06 mL, 6.27 mmol, 2.5 equiv) in dry THF (3 mL) at −30 °C under argon. After stirring for 10 min the solution was cooled to −95 °C and Boc-protected phosphoramidate (±)-**21** (0.891 g, 2.51 mmol) dissolved in dry THF (3 mL) was added. After 1 h AcOH (5.0 mL, 2.5 M in dry CH_2Cl_2) was added, followed by stirring for 10 min at room temperature. Water (10 mL) and EtOAc were added and the phases were separated. The aqueous phase was extracted again with EtOAc (2 × 10 mL). The combined organic layers were washed with water, dried (Na_2SO_4), and concentrated under reduced pressure to give a crystalline residue (0.860 g) being by ^{31}P NMR spectroscopy a mixture of (S*,R_P*)-and (S*,S_P*)-**23** in a ratio of 1.43:1 [(S*,R_P*)-**23**: 30.32 ppm, (S*,S_P*)-**23**: 30.70 ppm]. Neither starting material (±)-**21** nor phosphonate (±)-**22** or phosphinate (±)-**24** could be detected.

Flash chromatography [EtOAc/hexanes 2:1; R_f 0.35 for (S*,R_P*)-**23**, 0.29 for (S*,S_P*)-**23**] of the crude product gave homogeneous phosphonamidate (S*,R_P*)-**23** (0.474 g, 53%) as a crystalline solid and a mixture (0.218 g, 32%) of both diastereomers as a crystalline solid. (S*,R_P*)-**23** was crystallized from CH_2Cl_2 to give colorless crystals, mp 169−172 °C. The mixture of both diastereomers was again flash chromatographed (CH_2Cl_2/EtOAc 1:1; R_f 0.32 and 0.26, 57 cm × 2.5 cm) to give, besides homogeneous (±)-(S*,R_P*)-**23**, a mixture of (S*,R_P*)-**23** and (S*,S_P*)-**23** and a fraction with (S*,R_P*)-**23**/(S*,S_P*)-**23** 3:100, which furnished colorless crystals by slow evaporation of solvent from a solution in CH_2Cl_2/hexanes at room temperature; mp 121−122 °C; the crystals were suitable for single crystal X-ray structure analysis.

(**S*,R_P***)-**23**: IR (Si, NMR sample): ν 3318, 2936, 1709, 1274, 1234, 1158, 1047 cm^{-1}. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.28 (d, J = 7.3 Hz, 1H), 7.13−6.96 (m, 3H), 5.26 (td, J = 10.8, 7.4 Hz, 1H), 4.40 (td, J = 14.9, 8.3 Hz, 1H), 4.22 (ddd, J = 14.9, 4.0, 3.0 Hz, 1H), 3.77 (d, J = 11.4 Hz, 3H), 2.83−2.64 (m, 2H), 2.29−2.16 (m, 1H), 2.16−2.05 (m, 1H), 2.02−1.92 (m, 1H), 1.80−1.67 (m, 1H), 1.10 (s, 9H). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 154.5 (d, J = 10.7 Hz), 137.6 (d, J = 4.6 Hz), 137.5, 128.7, 126.2, 126.1, 125.5, 83.2, 59.3 (d, J = 142.3 Hz), 54.8 (d, J = 1.5 Hz), 51.7 (d, J = 7.7 Hz), 30.2, 29.6, 27.6 (3C), 22.8. ^{31}P NMR (161.98 MHz, $CDCl_3$): δ 31.7. Anal. Calcd for $C_{17}H_{26}NO_5P$: C, 57.46; H, 7.37; N, 3.94. Found: C, 57.25; H, 7.06; N, 3.72.

(**S*,S_P***)-**23**: IR (ATR, NMR sample): ν 3313, 2933, 1704, 1393, 1368, 1272, 1253, 1231, 1153, 1030 cm^{-1}. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.24 (d, J = 7.3 Hz, 1H), 7.15−7.05 (m, 2H), 7.02 (d, J = 6.8 Hz, 1H), 5.26 (q, J = 9.6 Hz, 1H), 4.17 (AB part of ABXY-system, J_{AB} = 14.9 Hz, J = 8.3 Hz (2 x), J = 4.3, 2.6 Hz, 2H), 3.91 (d, J = 11.1 Hz, 3H), 3.91−3.81 (m, 1H), 2.82−2.66 (m, 2H), 2.22−2.08 (m, 2H), 2.00−1.92 (m, 1H), 1.80−1.66 (m, 1H), 1.14 (s, 9H). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 154.8 (d, J = 10.7 Hz), 137.8 (d, J = 2.3 Hz), 137.5, 128.8, 126.0, 126.0, 125.3, 83.3, 59.3 (d, J = 139.2 Hz), 54.9, 52.9 (d, J = 6.9 Hz), 29.9, 29.7, 27.6 (3C), 22.8. ^{31}P NMR (161.98 MHz, $CDCl_3$): δ 32.0. Anal. Calcd for $C_{17}H_{26}NO_5P$: C, 57.46; H, 7.37; N, 3.94. Found: C, 57.52; H, 7.29; N, 3.91.

Experiments Performed To Study Conversion of Phosphonamidate (S,R_P*)-**23** to Phosphinate (±)-**24**.*

(1) *s*-BuLi (1.68 mmol, 3.3 equiv, 1.2 mL, 1.4 M in cyclohexane) was added dropwise to a stirred mixture of (S*,R_P*)-**23** (0.180 g, 0.51 mmol) in dry THF (1.5 mL) at −95 °C under argon. The mixture turned yellow. After 4 h, the reaction was quenched with AcOH (3.06 mmol, 6 equiv, 1.0 mL, 3 M solution in dry CH_2Cl_2) and concentrated under reduced pressure. Water (10 mL) and EtOAc were added to the residue. The organic layer was separated, and the aqueous one extracted with EtOAc (2 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. No phosphinate could be detected in the residue by ^{31}P NMR spectroscopy. The residue was flash chromatographed (EtOAc, starting material: R_f = 0.44) to recover starting material (S*,R_P*)-**23** (66 mg, 37%).

(2) *s*-BuLi (2.8 mmol, 3.3 equiv, 2 mL, 1.4 M in cyclohexane) was added dropwise to a stirred mixture of (S*,R_P*)-**23** (0.300 g, 0.84 mmol) in dry THF (3 mL) at −78 °C under argon. The mixture turned brown. It was stirred for 4 h at −78 °C, 2 h at −50 °C, then quenched with AcOH (5.1 mmol, 6 equiv, 1.7 mL, 3 M solution in dry CH_2Cl_2) and finally concentrated under reduced pressure. Water (10 mL) and EtOAc were added to the residue. The organic layer was separated and the aqueous one extracted with EtOAc (2 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concen-

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trated under reduced pressure. There was a broad singlet at 52.3 ppm in the ^{31}P NMR spectrum, which was tentatively assigned a phosphinate of unknown structure. The residue was flash chromatographed (EtOAc) to recover some impure (S*,R_P*)-**23** (72 mg, 24%). No phosphinate could be isolated.

*Phosphonate−Phosphinate Rearrangement of (±)-Dimethyl 1-(t-butoxycarbonylamino)-3-methylbutylphosphonate [(±)-**25**]; Preparation of (±)-Methyl 1-(t-butoxycarbonylamino)-3-methylbutyl-hydroxymethylphosphinate [(±)-**32**]. General Procedure (for Details See Table 1).* *N*-Boc-protected aminophosphonate (±)-**25**[17] (1−2 mmol), dried by coevaporation with toluene, was dissolved in dry THF or Et_2O (4 mL/mmol) or a mixture of dry THF/dimethoxyethane (4:1; 4 mL/mmol) under argon at room temperature. A strong base (LiTMP freshly prepared from *n*-BuLi (1.6 M)/TMPH; *s*-BuLi (1.4 M in cyclohexane)) was added slowly at −78 °C. The solution was stirred for 2 h, and then the reaction was quenched with acetic acid (3 equiv, 3 M in CH_2Cl_2) at low temperature. Excess 2 M HCl and water were added, and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc, R_f 0.19) to yield phosphinate (±)-**32** as a colorless oil.

IR (ATR): ν 3255, 2957, 1704, 1529, 1391, 1367, 1302, 1275, 1255, 1165, 1036 cm^{-1}. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 5.61 (d, J = 9.1 Hz, 1H), 4.50−3.91 (m, 2H), 3.89−3.80 (m, 2H), 3.77 (d, J = 10.1 Hz, 3H), 1.83−1.62 (m, 2H), 1.53−1.44 (m, 1H), 1.42 (b. s, 9H), 0.93 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 6.5 Hz, 3H). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 157.2, 81.1, 54.9 (d, J = 98.3 Hz), 51.9 (d, J = 7.4 Hz), 44.1 (d, J = 107.6 Hz), 34.4, 28.2 (3C), 24.3 (d, J = 10.3 Hz), 23.3, 20.8. ^{31}P NMR (161.98 MHz, $CDCl_3$; very likely two conformers): δ 52.6 (0.96P), 50.4 (0.04P). Anal. Calcd for $C_{12}H_{26}NO_5P$: C, 48.81; H, 8.87; N, 4.74. Found: C, 48.52; H, 8.58; N, 4.66.

*Quenching of Reaction with AcOD/D_2O and Isolation of Partially Deuterated Starting Material (±)-**25**.* When the rearrangement was quenched with AcOD (2.5 equiv dissolved in 0.5 mL D_2O and 2 mL THF), the partly deuterated starting material (45%) was isolated by flash chromatography (EtOAc, R_f 0.47); 30% of the molecules were deuterated at C-1 (by ^{1}H NMR). The ^{1}H and ^{31}P MR spectra were identical to the spectra for the nondeuterated compound except for the following. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 4.15−4.02 (m, 0.68H, CHP); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 38.39 (d, J = 2.6 Hz, 0.7C, CH_2CHP), 38.29 (d, J = 2.6 Hz, 0.3C, CH_2CDP). ^{31}P NMR (161.98 MHz, $CDCl_3$, very likely two conformers): δ 29.6 (0.86P), 29.0 (0.14P); the nondeuterated starting material showed a ratio of 85:15.

*Acetylation of Hydroxymethylphosphinate (±)-**32**.* Phosphinate (±)-**32** (0.055 g, 0.19 mmol) was dissolved in dry CH_2Cl_2 (1 mL). Dry pyridine (0.49 g, 0.5 mL, 6.19 mmol) and acetic acid anhydride (0.038 g, 0.04 mL, 0.37 mmol) were added at room temperature. The solution was stirred overnight, concentrated under reduced pressure (25 mbar), and finally dried for 3 h (0.5 mbar/60 °C). The residue was crystallized from CH_2Cl_2/hexanes to yield acetoxymethylphosphinate (±)-**34** (0.060 g, 95%) as colorless crystals suitable for single-crystal X-ray structure analysis; mp 80−81 °C.

IR (ATR): ν 3260, 2959, 1756, 1710, 1535, 1370, 1209, 1172, 1044, 913 cm^{-1}. ^{1}H NMR (400.13 MHz, $CDCl_3$; two conformers): δ 4.69 (d, J = 10.4 Hz, 0.9H), 4.62−4.50 (m, 0.1H), 4.42 (A part of ABX-system, dd, J = 14.6 Hz, J = 3.7 Hz, 1H), 4.36 (B part of ABX-system, dd, J = 14.6 Hz, J = 7.3 Hz, 1H), 4.17 (qd, J = 11.0 Hz, J = 4.0 Hz, 0.9H), 4.08−3.93 (m, 0.1H), 3.78 (d, J = 10.4 Hz, 3H), 2.12 (s, 3H, CH_3CO), 1.78−1.67 (m, 1H, CH), 1.63−1.47 (m, 2H, CH_2), 1.40 (s, 9H, $C(CH_3)_3$), 0.94 (d, J = 6.7 Hz, 3H), 0.91 (d, J = 6.5 Hz, 3H). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 170.1 (d, J = 6.8 Hz), 155.1 (d, J = 5.2 Hz), 80.3, 55.8 (d, J = 105.1 Hz), 52.3 (d, J = 7.4 Hz), 45.5 (d, J = 111.7 Hz), 36.3, 28.2 (3C), 24.4 (d, J = 11.2 Hz), 23.3, 21.1, 20.6. ^{31}P NMR (161.98 MHz, $CDCl_3$): δ 47.7 (0.9P), 46.0 (0.1P). To prove the presence of two conformers, ^{31}P NMR spectra were recorded in toluene-d_8 at 25 and 80 °C. ^{31}P NMR (161.98 MHz, toluene-d_8, 25 °C): δ 48.0 (0.94P), 46.0 (0.06P); ^{31}P NMR (161.98 MHz, toluene-d_8, 80 °C): δ 46.1. Anal. Calcd for $C_{14}H_{28}NO_6P$: C, 49.84; H, 8.37; N, 4.15. Found: C, 49.89; H, 8.21; N, 4.07.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H, ^{13}C, ^{31}P NMR spectra, HPLC chromatograms, and X-ray data including CIF files of four compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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