Transformation of Arylmethylamines into α-Aminophosphonic Acids via Metalated Phosphoramidates: Rearrangement of Partly Configurationally Stable N-Phosphorylated α-Aminocarbanions

Friedrich Hammerschmidt* and Martin Hanbauer

Institut für Organische Chemie der Universität Wien,Währingerstrasse 38, A-1090 Wien, Austria

frha@felix.orc.univie.ac.at

Received April 17, 2000

N-Benzyl phosphoramidate was protected at nitrogen with a TMS, *p*-toluenesulfonyl, Boc, lithium carboxylate, or diethoxyphosphinyl group and metalated with *s*-BuLi or LDA at −78 °C at the benzylic carbon. For the latter three protecting groups, the intermediate α-amino(phenylmethyl)-lithiums isomerized to N-protected α-aminophosphonates (phosphoramidate−aminophosphonate rearrangement). (*R*)-*N*-[1-$^2H_1$]Phenylmethyl phosphoramidate in combination with Boc or $(EtO)_2P$-(O) was used to demonstrate that metalation occurs with a high primary kinetic isotope effect (k_H/k_D 13−50) and migration of the diethoxyphosphinyl group with retention of configuration at carbon. Furthermore, the short-lived carbanion lithium pairs are partly configurationally stable as the aminophosphonates formed with the two protecting groups have enantiomeric excesses of 79 and 24%, respectively. When homochiral lithium amides derived from (*R*)-*N*-isopropyl-1-phenylethylamine and (*R,R*)-*N,N*-di(1-phenylethyl)amine were used to induce a phosphoramidate−aminophosphonate rearrangement, chiral nonracemic α-aminophosphonates were formed (ee 26−35%). Three racemic aminophosphonates were deprotected with hot 6 M HCl and purified by ion-exchange chromatography on Dowex 50W,H^+ to exemplify the transformation of phenyl-, *p*-tolyl-, and (1′-naphthyl)methylamine into aminophosphonic acids via lithiated phosphoramidates.

Introduction

α-Aminophosphonic acids serve as surrogates for α-amino acids, which play an important role in biological systems. The phosphonic acid group is considered to be an isosteric replacement for the carboxyl group. It also mimics the tetrahedral intermediate of reactions of carboxylic acid derivatives. Therefore, racemic and chiral, nonracemic phosphonic acid[1] analogues of proteinogenic and nonproteinogenic amino acids and peptides containing them have been prepared and tested for a variety of biological effects.[2] Recently, α-aminobenzylphosphonic acids were found to be potent inhibitors of human prostatic acid phosphatase.[3] (*R*)-Phosphatyrosine (phosphonic acid analogue of L-tyrosine) occurs naturally as a component of two hypotensive tripeptides.[4]

Despite the widespread interest in aminophosphonic acids, the number of available methods is still limited. The more general methods for the synthesis of chiral, nonracemic α-aminophosphonic acids, except chemical[1a] and enzymatic[5] resolution, are the enantioselective addition of phosphites to achiral imines,[6] addition of phosphites to homochiral imines,[7] acyliminium ions[8] and nitrones,[9] alkylation of α-lithiated homochiral imines derived from α-aminomethylphosphonic acid[10] and the transformation of chiral, nonracemic α-hydroxyphosphonates[11] via α-azidophosphonates.

We have been interested in the phosphate−phosphonate rearrangement and its reverse process for some time (Scheme 1).[12] Phosphates of general structure **1** with R^1 being Ar or, as found recently, alkyl and a suitable protecting group R^2 at phosphorus are metalated to give short-lived, configurationally stable α-oxyalkyllithium compounds (±)-**2**. They isomerize by migration of the dialkoxyphosphinyl group from oxygen to carbon to give phosphonates (±)-**3** and on workup α-hydroxyphosphonates (±)-**4**. This reaction is related to the Brook rearrangement.[13] We reasoned that by replacing oxygen by

* To whom correspondence should be addressed. Fax: (internat.) +43−1−4277−9521. Tel: +43-1-4277-52105.

(1) Reviews: (a) Dhawan, B.; Redmore, D. *Phosphorus Sulfur* **1987**, *32*, 119−144.; (b) Kukhar, V. P.; Soloshonok, V. A.; Solodenko, V. A. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1994**, *92*, 239−264.

(2) Kafarski, P.; Lejczak, B. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1991**, *63*, 193−215.

(3) Beers, S. A.; Schwender, C. F.; Loughney, D. A.; Malloy, E.; Demarest, K.; Jordan, *J. Bioorg. Med. Chem.* **1996**, *4*, 1693−1701.

(4) Kase, H.; Yamato, M.; Koguchi, T.; Okachi, R.; Kasai, M.; Shirahata, K., Kawamoto, I.; Shuto, K.; Karasawa, A.; Deguchi, T.; Nakayama, K. *Eur. Pat. Appl.* EP 0 061 172 A1, 1982; *Chem. Abstr.* **1983**, *98*, 107793.

(5) Solodenko, V. A.; Kasheva, T. N.; Kukhar, V. P.; Kozlova, E. V.; Mironenko, D. A.; Svedas, V. K. *Tetrahedron* **1991**, *47*, 3989−3998.

(6) Gröger, H.; Saida, Y.; Sasai, H.; Yamaguchi, K.; Martens, J.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 3089−3103.

(7) Smith, A. B., III; Yager, K. M.; Taylor, C. M. *J. Am. Chem. Soc.* **1995**, *117*, 10879−10888.

(8) Seebach, D.; Charczuk, R.; Gerber, C.; Renaud, P. *Helv. Chim. Acta* **1989**, *72*, 401−425.

(9) Huber, R.; Knierzinger, A.; Obrecht, J.-P.; Vasella, A. *Helv. Chim. Acta*, **1985**, *68*, 1730−1747. Huber, R.; Vasella, A. *Helv. Chim. Acta* **1987**, *70*, 1461−1476.

(10) Song, Y.; Niederer, D.; Lane-Bell, P. M.; Lam, L. K. P.; Crawley, S.; Palcic, M. M.; Pickard, M. A.; Pruess, D. L.; Vederas, J. C. *J. Org. Chem.* **1994,** *59*, 5784−5793. Groth, U.; Richter, L.; Schöllkopf, U. *Tetrahedron Lett.* **1992**, *48*, 117−122. Hanessian, S.; Bennani, Y. L. *Tetrahedron Lett.* **1990**, *31*, 6465−6465.

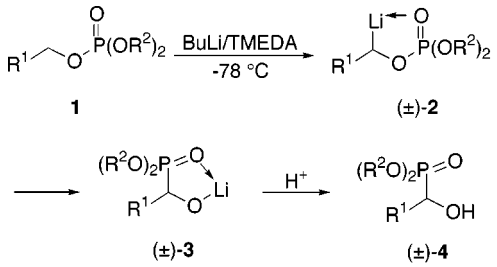
(11) Hammerschmidt, F.; Wuggenig, F. *Tetrahedron*: *Asymmetry* **1999**, *10*, 1709−1721. Gajda, T. *Tetrahedron*: *Asymmetry* **1994**, *5*, 1965−1972. Meier, C.; Laux, W. H. G.; Bats, J. W. *Liebigs Ann.* **1995**, 1963−1979.

(12) Hammerschmidt, F.; Schmidt, S. *Eur. J. Org. Chem.* **1999**, 3511−3518.

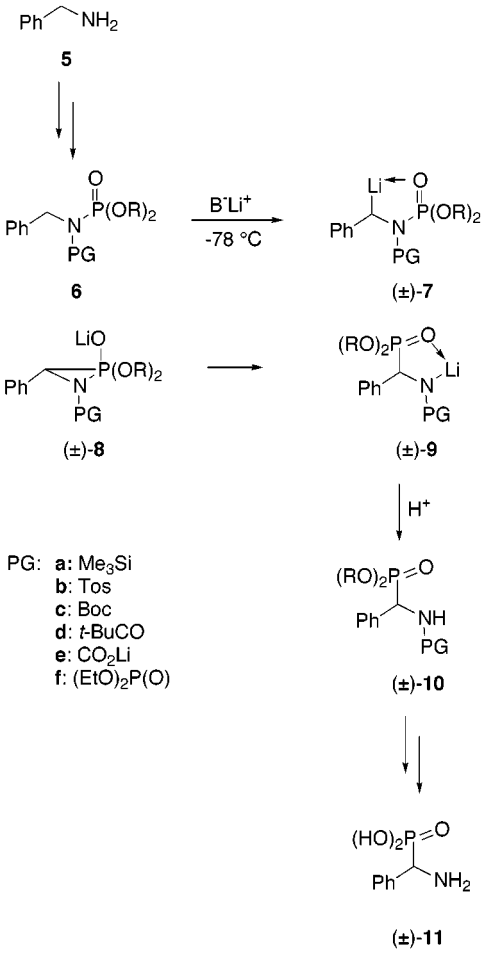
(13) Review: Brook, A. *Acc. Chem. Res.* **1974**, *7*, 77−84. Hoffmann, R.; Brückner, R. *Chem. Ber.* **1992**, *125*, 2731−2739.

10.1021/jo000585f CCC: $19.00
Published on Web 08/25/2000

Scheme 1



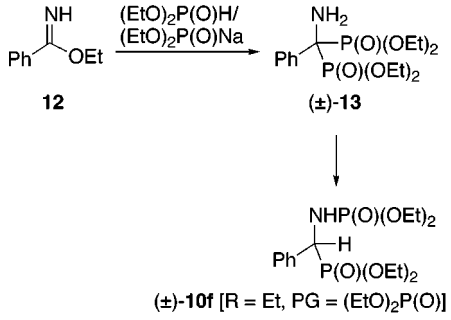
Scheme 2



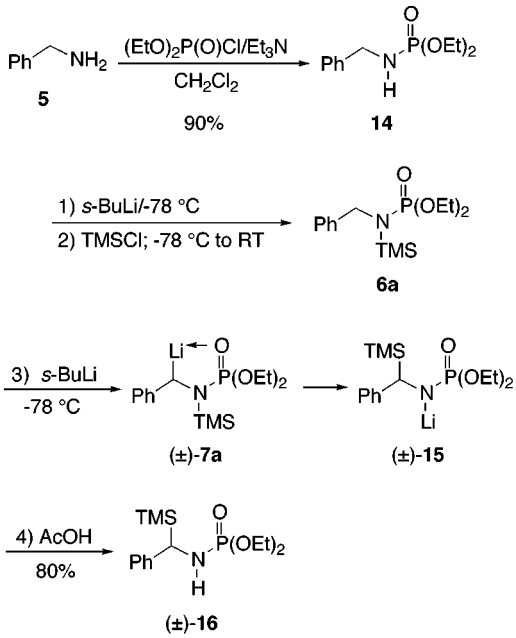
a protected nitrogen, it might be possible to prepare α-aminophosphonates. The proposed sequence starts with a primary amine **5** which is transformed into phosphoramidate **6** (Scheme 2). Metalation with a strong lithium base generates N-phosphorylated α-aminolithium compound (±)-**7**, which rearranges to lithiated α-aminophosphonate (±)-**9** and gives α-aminophosphonate (±)-**10** on workup. In analogy to the phosphate−phosphonate rerrangement, we propose the term phosphoramidate−aminophosphonate rearrangement for this isomerization, which so far has not been reported in the literature. The intermediates (±)-**7** are a new class of α-aminolithium compounds[14] having attracted much attention during the last years.

Pudovik and Zimin give in a review a few rare examples for the retro-reaction of the phosphoramidate−

Scheme 3



Scheme 4



aminophosphonate rearrangement, which they call aminophosphonate−amidophosphate rearrangement. One is given in Scheme 3. The intermediate α-aminobisphosphonate (±)-**13** isomerizes to α-aminophosphonate (±)-**10f**. Migration of the phosphinyl group generates a carbanionic species that is stabilized by a phenyl and a phosphonate group and protonated to furnish (±)-**10f**. To study the feasibility of the phosphoramidate−aminophosphonate rearrangement, we selected in the first place benzylamine (**5**) to ease deprotonation, Et for R and six different protecting groups for PG (see Scheme 2). Furthermore, we wanted to determine the configurational stability of a N-phosphorylated α-aminolithium compound **7** and the stereochemistry of the rearrangement at carbon. Finally, we hoped to get chiral, nonracemic α-aminophosphonates by use of homochiral bases.

Results and Discussion

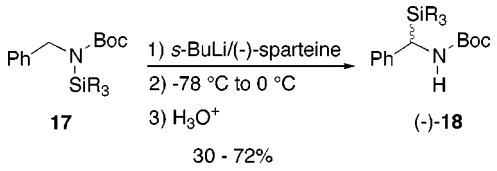
Trimethylsilyl as Protecting Group. Phosphoramidate **14** was prepared in high yield from benzylamine (**5**) and diethyl chlorophosphate (Scheme 4). Phosphoramidate **14**[16] was used to test the various protecting groups for the rearrangement. The trimethylsilyl group,

(14) Reviews: Gawley, R. E. *Current Org. Chem.* **1997**, *1*, 71−97. Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552−560.

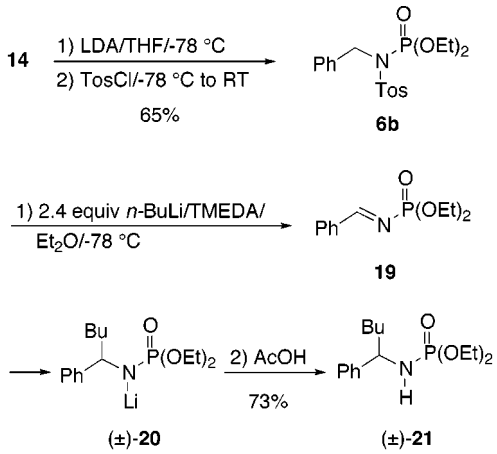
(15) Pudovik, A. N.; Zimin, M. G. *Pure Appl. Chem.* **1980**, *52*, 989−1011.

(16) Willeit, A.; Müller, E. P.; Peringer, P. *Helv. Chim. Acta* **1983**, *66*, 2467−2480.

Scheme 5



Scheme 6

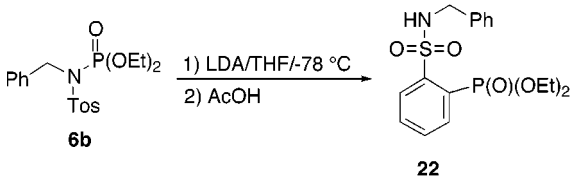


which can be manipulated easily, was introduced by silylation of the lithiated phosphoramidate with TMSCl. Because of the anticipated instability of the N-silylated phosphoamidate **6a** toward aqueous workup, it was not isolated. Instead, the reaction mixture was recooled to −78 °C and *s*-BuLi was added. The C-silylated phosphoramidate (±)-**16** was isolated in 80% overall yield for both steps. This result proves unambiguously that metalation of the N-silylated phosphoramidate generates an α-aminocarbanionic species (±)-**7a** in which the silyl group migrates exclusively in preference to the phosphinyl group (retro-aza-Brook rearrangement).[17] A similar reaction was found for Boc derivative **17** by Voyer and Barberis (Scheme 5).[18] The strong electron-withdrawing *p*-toluenesulfonyl group is ideally suited to both acidify the hydrogens α to nitrogen and to stabilize the negative charge on nitrogen after migration of phosphorus was tested next.

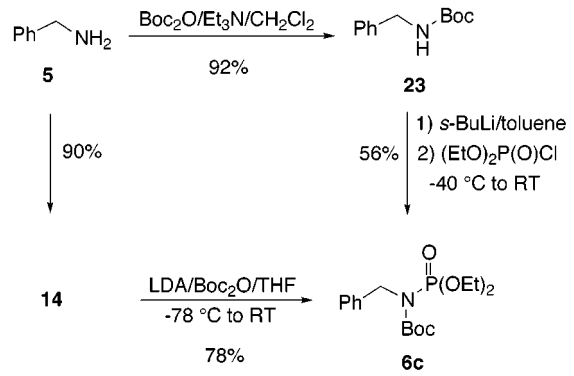
***p*-Toluenesulfonyl as Protecting Group.** The *N*-tosyl amide **6b** was prepared easily from phosphoramidate **14** according to Scheme 6. Treatment of **6b** with 2.4 equiv of *n*-BuLi/TMEDA produced phosphoramidate (±)-**21** in 73% yield. Its formation starts very likely with the generation of imine **19** by elimination (E2 or E1cB) of *p*-toluenesulfinate from **6b**. Excess *n*-BuLi adds to the C=N bond to give lithiated phosphoramidate (±)-**20**, which is protonated on workup. *s*-BuLi gives an analogous product in 54% yield having complex NMR spectra as a 1:1 mixture of two diastereomers is formed. When the trifluoromethylsulfonyl group was substituted for the *p*-toluenesulfonyl group, the product pattern did not change. LDA did not effect elimination of *p*-toluenesulfinate, but metalation of the *p*-tolyl ring ortho to the sulfonyl group (Scheme 7). A 1,4-migration of phosphorus and protonation furnished crystalline sulfonamide **22**.

Boc as Protecting Group. Two entries to *N*-Boc-protected phosphoramidate **6c** were developed (Scheme

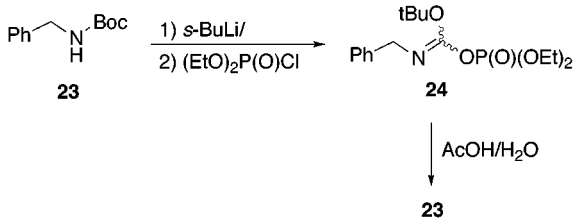
Scheme 7



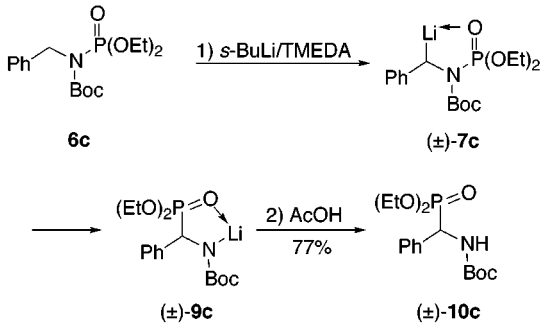
Scheme 8



Scheme 9



Scheme 10

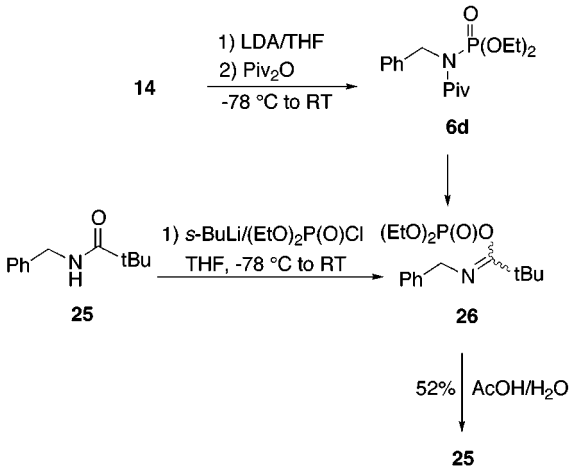


8). First, benzylamine (**5**) was protected with $(Boc)_2O$/Et_3N[19] in dichloromethane followed by phosphorylation of the lithiated *N*-Boc amine. Second, the two steps were interchanged, which gave a better overall yield. Possibly, the lithiated carbamate was phosphorylated not only at nitrogen but to a small extent also at oxygen (Scheme 9). The sensitive enol phosphate **24** hydrolyzed on workup to regenerate the starting material. We have no evidence for a 1,3-phosphinyl shift in **6c**[20] to give enol phosphate **24**.

The rearrangement of phosphoramidate **6c** with 1.5 equiv of *s*-BuLi/TMEDA was a smooth reaction (Scheme 10). It was finished in 30 min in diethyl ether and furnished α-aminophosphonate (±)-**10c**[21] in 77% yield.

(17) Honda, T.; Mori, M. *J. Org. Chem.* **1996**, *61*, 1196−1197.
(18) Barberis, N.; Voyer, N. *Tetrahedron Lett.* **1998**, *39*, 6807−6810.
(19) Kanazawa, A. M.; Correa, A.; Denis, J.-N.; Luche, M. J.; Greene, A. E. *J. Org. Chem.* **1993**, *58*, 255−257.
(20) Zwierzak, A.; Pilichowska, S. *Synthesis* **1982**, 920−924.
(21) Genet, J. P.; Mallart, S.; Greck, C.; Piveteau, E. *Tetrahedron Lett.* **1991**, *32*, 2359−2362.

Scheme 11



The introduction of the Boc group and the phosphoramidate−aminophosphonate rearrangement can also be carried out as a one-pot reaction in 70% overall yield.

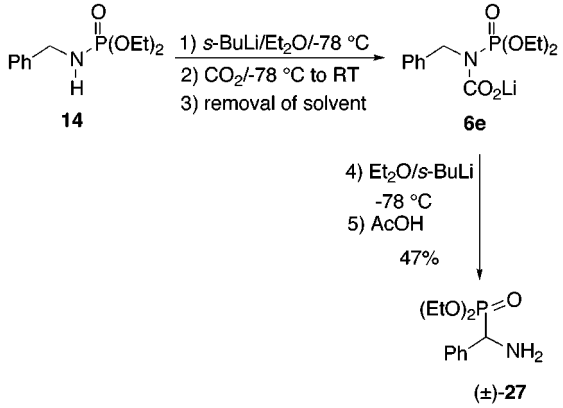
Pivaloyl as Protecting Group. The satisfying results with the Boc group induced us to study also the pivaloyl group as protecting group. When pivalamide **25**[22] was treated with *s*-BuLi and diethyl chlorophosphate, or when phosphoramidate **14** was treated with LDA and then Piv_2O, only pivalamide **25** was isolated (Scheme 11). This finding can be explained by assuming that in the first case the desired product **6d** isomerized to the presumably thermodynamically more stable enol phosphate **26**, which is hydrolyzed on aqueous workup. In the second case, the lithiated pivalamide is phosphorylated at oxygen. To circumvent the possible rearrangement of the *N*-pivaloyl phosphoramidate **6d** at room temperature, Piv_2O was added to the metalated phosporamidate. The reaction mixture was kept at −78 °C for 1.5 h before the addition of *s*-BuLi to induce the phosphoramidate-aminophosphonate rearrangement. Unfortunately, no aminophoshonate could be detected, which is possibly caused by an N to O migration of the phosphinyl group in the *N*-pivaloyl phosphoramidate **6d** even at −78 °C.

Carboxyl as Protecting Group. Katritzky et al. found that carboxylation of lithiated benzyl alcohol and benzylamine can be used to facilitate metalation α to the heteroatom.[23] We also tried this method, because the unprotected amino group is formed immediately on workup (Scheme 12).

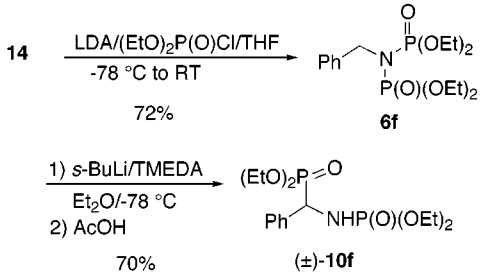
The lithiated phosphoramidate was carboxylated by simply replacing the argon atmosphere by CO_2 and allowing the reaction mixture to warm to room temperature. The solvent and excess CO_2 were removed in vacuo (0.3 mm). The solid lithium salt **6e** of the carbamidic acid was dissolved in diethyl ether and treated with *s*-BuLi at −78 °C. Addition of acetic acid and extractive workup furnished the aminophosphonate (±)-**27**[24] in 47% yield, which was not optimized.

Diethoxyphosphinyl Group as Protecting Group. At last, a second diethoxyphosphinyl group was placed on the nitrogen to test it as a protecting group. Phosphorylation of the lithiated phosphoramidate with diethyl chlorophosphate gave bisphosphoramidate **6f**[6] in 72% yield (Scheme 13). It was rearranged under the standard conditions (diethyl ether, *s*-BuLi/TMEDA, −78 °C) in 70% yield to the highly polar aminophosphonate (±)-**10f**.[26]

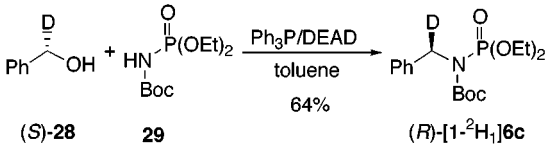
Scheme 12



Scheme 13



Scheme 14



From the five protecting groups tested the Boc group is best, because it can be handled very easily. In practice, a phosphoramidate of an arylmethylamine can be N-protected with Boc, metalated, and rearranged in a one-pot sequence. The crude product of the *N*-Boc α-aminophosphonate can be deprotected in refluxing 6 M HCl to give α-aminophosphonic acid as will be shown later.

Configurational Stability of N-Phosphorylated α-Amino(phenylmethyl)lithium and Stereochemistry of Its Phosphoramidate−Aminophosphonate Rearrangement at Carbon. The phosphoramidates derived from homochiral α-deuteriobenzylamine with a Boc or a diethoxyphosphinyl group at nitrogen were prepared (Scheme 14). The first one was obtained from deuterated phenylmethanol (*S*)-**28**,[27] which was converted to phosphoramidate (*R*)-[1-$^2H_1$]**6c** by a Mitsunobu reaction using Ph_3P/DEAD/*N*-Boc phosphoramidate **29**.[28]

(22) Martinez, A. G.; Alvarez, R. M.; Vilar, E. T.; Fraile, A. G.; Hanack, M.; Subramanian, L. R. *Tetrahedron Lett.* **1989**, *30*, 581−582.

(23) Katritzky, A. R.; Fan, W.-Q.; Akutagawa, K. *Synthesis* **1987**, 415−417.

(24) Rogozhin, S. V.; Davankov, V. A.; Belov, Y. P. *Izv. Akad. Nauk. SSSR Ser. Khim.* **1973**, 955−956; *Chem. Abstr.* **1973**, *79*, 42610k.

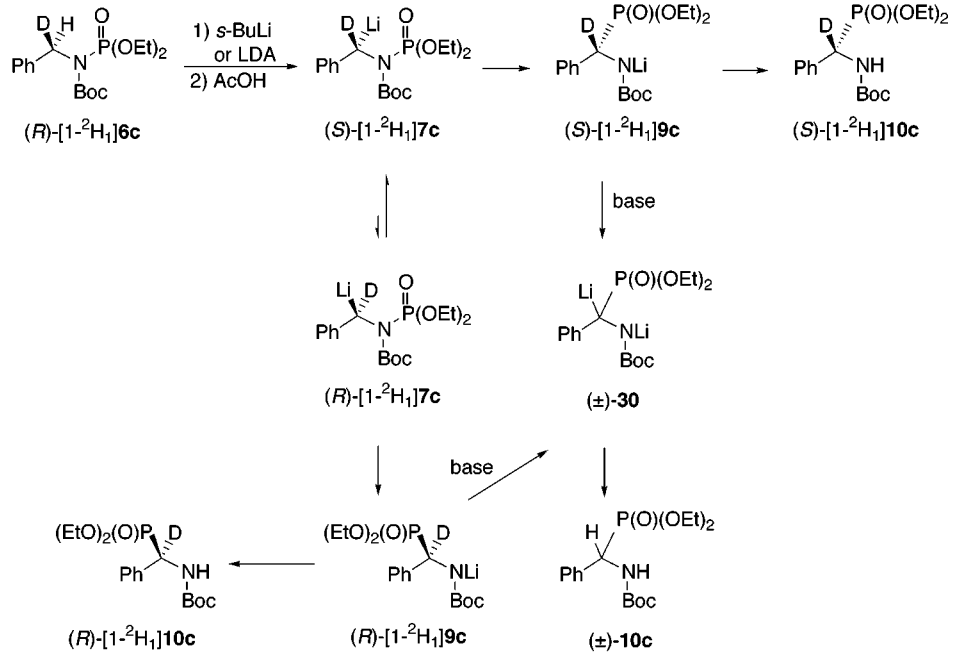
(25) Naumann, C.; Kocis, P. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1994**, *91*, 169−178.

(26) Zimin, M. G.; Dvoinishnikova, T. A.; Konovalova, I. V.; Pudovik, A. N. *Izv. Akad. Nauk. SSSR Ser. Khim.* **1978**, 499−500; *Chem. Abstr.* **1978**, *88*, 190978n.

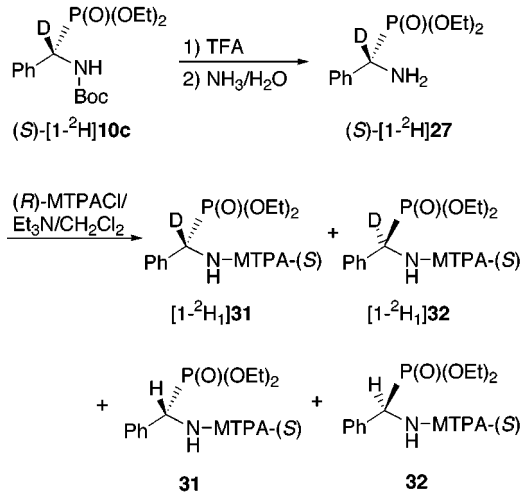
(27) Wightman, R. H.; Staunton, J.; Battersby, A. R.; Hanson, K. R. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2355−2364.

(28) Slusarska, E.; Zwierzak, A. *Liebigs Ann. Chem.* **1986**, 402−405.

Scheme 15



Scheme 16



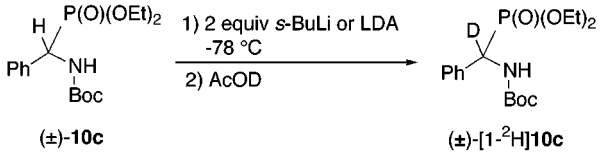
We assume a clean inversion for the substitution process. The deuterated phosphoramidate was metalated with 2 equiv of *s*-BuLi/TMEDA or LDA in diethyl ether or THF. The resulting phosphoramidate **10c** was formed in 74% and 81% yield, respectively. (Scheme 15; only products obtained by removal of protium are shown). The ee, the yield, and the deuterium content (36% and 67% D) are collected in Table 1. The enantiomeric excess was determined by derivatizing α-aminophosphonate (*S*)-[1-$^2H_1$]**27** obtained by treating (*S*)-[^{2}H]**10c** with TFA in dichloromethane with (*R*)-MTPACl (Scheme 16).[29] The mixture of deuterated and nondeuterated diastereomeric amides **31** and **32** was investigated by NMR spectroscopy. The 250 MHz ^{1}H NMR spectrum showed two very close doublets of doublets (δ = 5.445 and 5.461, each with J = 9.8, 20.6 Hz) of equal intensity for the two diastereomeric PCH of **31** and **32**. This is indicating that the nondeuterated species in the mixture is racemic. The CH_3O substituents of the (*S*)-MTPA groups of the deuterated and nondeuterated diastereomers appeared as two quartets (δ = 3.48 and 3.37, $J_{H,F}$ = 1.6 Hz) of different intensity. Therefore, the deuterated species of the aminophosphonate must in part be chiral, nonracemic.

Table 1. Phosphoramidate−Aminophosphonate Rearrangement of (*R*)-[1-$^2H_1$]6c Induced by *s*-BuLi or LDA in Et_2O or THF

entry	base (equiv)	solvent	yield	ee (%)	^{2}H (%)
1	*s*-BuLi (2.0)	Et_2O	74	37	36[a]
2	LDA (2.0)	THF	81	61	67[a]
3	*s*-BuLi (0.9)	Et_2O	58	43	90[b]
4	LDA (0.9)	THF	56	72	98[b]
5	LDA (0.9)	Et_2O	44	79	96[b]

[a] Determined by ^{1}H NMR spectroscopy. [b] Determined by MS.

Scheme 17



Three more experiments were carried out with (*R*)-[1-$^2H_1$]**6c** using only 0.9 equiv of base, which caused a significant drop in yield, but an increase of the deuterium content to 90% (in diethyl ether as solvent) for *s*-BuLi and 98% (in THF as solvent) and 96% (in diethyl ether as solvent) for LDA (Table 1, entries 3−5). This finding can be explained by the fact that excess base metalates the rearranged products (*R*)- and (*S*)-[1-$^2H_1$]**9c**. The dilithiated species **30** is configurationally not stable and gives racemic, nondeuterated aminophosphonate (±)-**10c** on quenching with AcOH. That this is actually happening is proven by metalation of (±)-**10c** with 2 equiv of *s*-BuLi or LDA and quenching with AcOD (Scheme 17). The isolated aminophosphonate (±)-[1-^{2}H]**10c** was partly deuterated (91% for *s*-BuLi, 28% for LDA) which is formed via dilithiated species. The extent of deuteration reflects in part the difference in the basicity between *s*-BuLi and LDA.

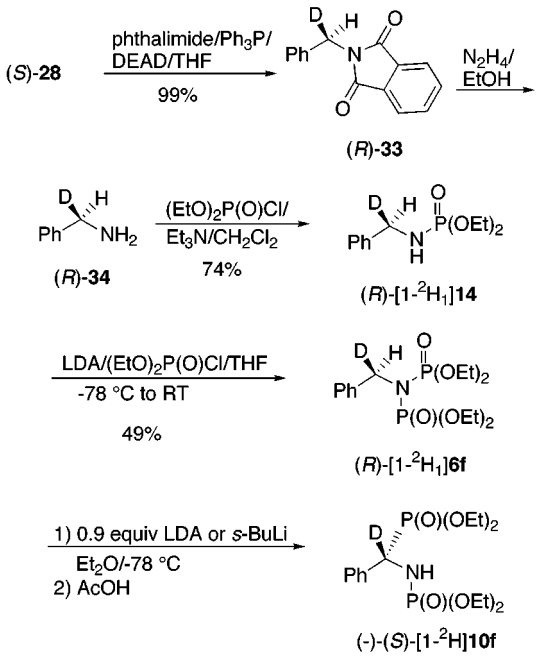
(29) Review: Parker, D. *Chem. Rev.* **1991**, *91*, 1441−1457. Hammerschmidt, F.; Li, Y.-F. *Tetrahedron* **1994**, *50*, 10253−10264.

Assuming that a second lithiation does not interfere, when 0.9 equiv of base are used, the deuterium contents of 98% and 96% are the result of a high primary kinetic isotope effect for metalation of the phosphoramidate (*R*)-[1-$^2H_1$]**6c** ($k_H/k_D \geq 50$ or 25) (see Scheme 15). The lithiated species (*S*)-[1-$^2H_1$]**7c** can rearrange before or after the inversion of the configuration. When no excess base is present, (*S*)- and (*R*)-[1-$^2H_1$]**9c** are not metalated and end up as (*S*)- and (*R*)-[1-$^2H_1$]**10c**. The ratio of the latter reflects the ratio of (*S*)- and (*R*)-[1-$^2H_1$]**7c**. The drop in ee from a maximum of 98% to 72% or 79%, respectively, is caused by partial racemization of the intermediate carbanion (*S*)-[1-$^2H_1$]**7c** before 1,2-migration of the phosphorus. With a deuterium content of 98% and 96% an ee of 96% and 92% is possible at best, because the nondeuterated species generated by metalation of (*R*)-[1-$^2H_1$]**6c** has (*R*)-configuration. The experimental ee value of 72% and 79% demonstrate, that roughly 10% of the lithiated phosphoramidate invert their configuration, independent of the solvent used (THF, diethyl ether). This result shows that the α-amino(phenylmethyl)lithium **7c** is nearly as configurationally stable as the α-oxy(phenylmethyl)lithium where only 3.5% of the molecules invert their configuration. As the isolated α-aminophosphonate **10c** is laevorotatory and therefore has (*S*)-configuration, the rearrangement occurs with retention of configuration at carbon as with the oxygen analogue [the change of configuration from (*R*) to (*S*) is a consequence of the change of priorities according to the rules developed by Cahn, Prelog, and Ingold].[30]

The homochiral bisphosphoramidate (*R*)-[1-$^2H_1$]**6f** was prepared as well and rearranged to study the influence of the diethoxyphosphinyl group compared to Boc as protecting group at nitrogen on the configurational stability of the metalated species (Scheme 18). (*S*)-[1-$^2H_1$]-Benzyl alcohol was again used as starting material. It was transformed into (*R*)-[1-$^2H_1$]benzylamine [(*R*)-**34**] via phthalimide (*R*)-**33**, which was obtained by Mitsunobu reaction.[31] Two consecutive phosphorylations furnished bisphosphoramidate (*R*)-[1-$^2H_1$]**6f**, which was subjected to a phosphoramidate-aminophosphonate rearrangement. To minimze a possible *C*-metalation of the *N*-lithiated intermediate α-aminophosphonate as given for the Boc-protected analogue in Scheme 15, only 0.9 equiv of *s*-BuLi or LDA were used. The results show that metalation occurs with a primary kinetic isotope effect of ≥25 or ≥13. As a small amount of second metalation is very likely, the determined values are lower limits. Surprisingly, the enantiomeric excesses of 4% and 24% are much lower than the ones obtained with Boc as protecting group (compare Scheme 16). Therefore, the intermediate metalated bisphosphoramidate is configurationally less stable than the corresponding lithiated *N*-Boc phoshoramidate. Only a small portion of the molecules retain their configuration.

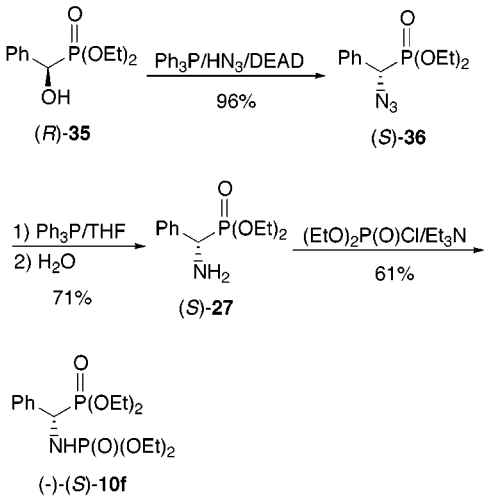
To determine the absolute configuration and the enantiomeric excess of (−)-[1-$^2H_1$]**10f**, we tried to deblock it at nitrogen to correlate it with diethyl α-aminophenylmethylphosphonate,[24] but all attempts with various concentrations of hydrochloric acid at different temperatures were unsuccessful. So *N*-phosphorylated α-aminophosphonate (−)-(*S*)-**10f** was prepared from known

Scheme 18



(*S*)-[1-^{2}H]**10f**	yield (%)	ee (%)	^{2}H (%, by MS)
s-BuLi	47	4	96
LDA	47	24	93

Scheme 19

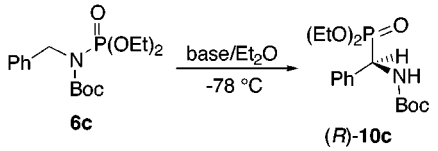


α-hydroxyphosphonate (*R*)-**35**[30] of ≥98% ee by the sequence given in Scheme 19. When the Mitsunobu reaction was carried out in toluene as solvent at room temperature, azide (*S*)-**36** was formed in high yield with partial racemization (ee 86%) as proven by NMR spectroscopy of (*R*)-MTPA amide of (*S*)-**27**. When toluene was replaced by a mixture of toluene/THF (4:1), the substitution was a clean inversion process and furnished an azide with an ee ≥98%. The data of *N*-phosphorylated derivative (−)-(*S*)-**10f** of α-aminophosphonate (*S*)-**27** were used to assign the absolute configuration of (−)-[1-$^2H_1$]**10f** and determine its enantiomeric excess. As the rearrangement of bisphosphoramidate (*R*)-[1-$^2H_1$]**6f** produces aminophosphonate (*S*)-[1-^{2}H]**10f**, the migration of the diethoxyphosphinyl group occurs with retention of configuration, although partial racemization is heavily interfering.

(30) Hammerschmidt, F.; Hanninger, A. *Chem. Ber.* **1995**, *128*, 823−830.

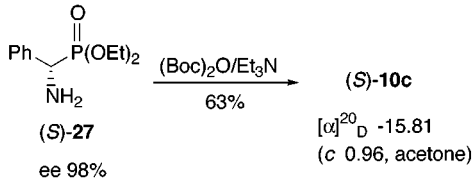
(31) Reviews: Mitsunobu, O. *Synthesis* **1981**, 1−28. Hughes, D. L. *Organic Reactions* **1992**, *42*, 335−656.

Scheme 20

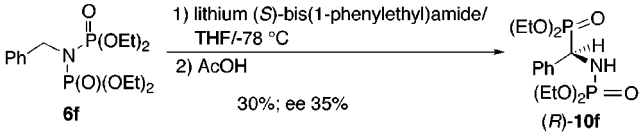


base: A: (-)-sparteine/*s*-BuLi
B: lithium (*R*)-*N*-isopropyl-*N*-1-phenylethylamide
C: lithium (*R*,*R*)-*N*,*N*-bis(1-phenylethyl)amide

(*R*)-**10c**	yield (%)	$[\alpha]^{20}_D/c$ (in acetone)	ee (%)
base A	30	+2.07/1.02	13
base B	65	+2.01/1.00	13
base C	55	+4.16/1.01	26



Scheme 21

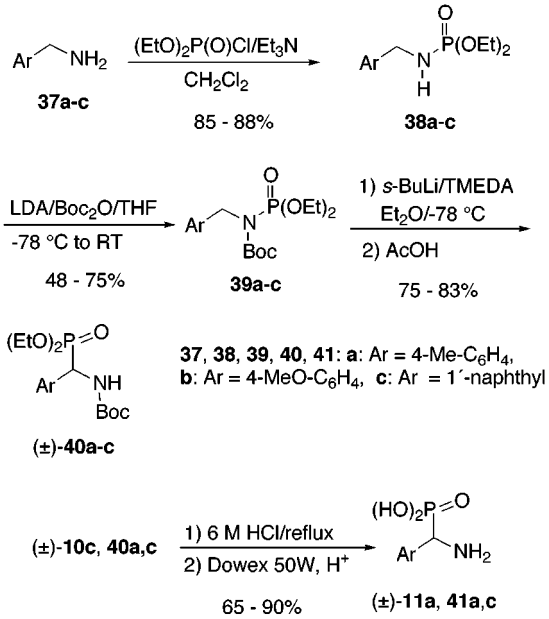


Enantioselective Phosphoramidate−Aminophosphonate Rearrangement. To increase the attractiveness of this rearrangement, an enantioselective version is desirable. Therefore, we conducted a few exploratory experiments using homochiral bases for the metalation (Scheme 20). When **6c** was deprotonated with (−)-sparteine/^{s}BuLi[32] or lithium amide[33] bases such as B and C, chiral, nonracemic aminophosphonate (R)-**10c** was formed in moderate yields. As the enantiomeric excess is at best 26% and as it is known that the intermediate metalated species racemizes only to a small extent, the enantioselectivity of deprotonation must be low. To ease the determination of the enantiomeric excess of (*R*)-**10c** by use of optical rotation, a reference sample of (*S*)-**10c** was prepared from (S)-**27** of 98% ee. For comparison the ee of the sample of (*R*)-**10c** obtained with base C was also determined by ^{1}H and ^{31}P NMR spectroscopy of the corresponding Mosher amide to be 28% and 24%, respectively.

At last bisphosphoramidate **6f** was subjected to a phosphoramidate−aminophosphonate rearrangement with lithium (*S*,*S*)-*N*,*N*-bis(1-phenylethyl)amide in THF as solvent (Scheme 21). Although the yield was onyl 30%, the ee was 35%, which is significantly higher than with the Boc-protected phosphoramidate **6c**. As the intermediate *N*,*N*-bisphosphorylated α-amino(phenylmethyl)lithium is configurationally less stable than the *N*-Boc *N*-phosphorylated counterpart and additionally THF was used instead of diethyl ether, an ee of about 24% can be expected at best even if metalation is highly enantioselective (93%, see Scheme 19). Therefore, we assume that the major portion of the chiral, nonracemic α-aminophosphonate (*R*)-**10f** is formed by an enantioselective rearrangement. The (*S*)-ion pair complexed with (*S*,*S*)-*N*,*N*-bis(1-phenylethyl)amine seems to rearrange more easily than the (*R*)-ion pair complexed with the same amine. Furthermore, the (*R*)-ion pair inverts its configuration more easily than it rearranges.

These findings are encouraging. As there are many homochiral bases known, the ee can probably be increased to an acceptable level.

Scheme 22



Preparation of (±)-α-Amino(arylmethyl)phosphonic Acids. To demonstrate the usefulness of the rearrangement for the preparation of α-aminophosphonic acids from arylmethylamines, phosphoramidates **38a**−**c**, prepared in the same way as **14**, were *N*-Boc protected to give phosphoramidates **39a**−**c** (Scheme 22). These were isolated to fully characterize them and were then subjected to the phosphoramidate-aminophosphonate rearrangement, although the two steps can be carried out as a one pot reaction. The reaction time was 30 min for **39a** and **39b** and 4 h for **39c** and the yields varied from 75 to 83%. The free α-aminophosphonic acids were easily obtained by refluxing the protected precursors (±)-**10c**, **40a**,**c** with 6 M HCl, followed by purification by ion exchange chromatography on Dowex 50W,H$^+$. The aminophosphonic acids (±)-**11c**, **41a**,**c** were eluted with water and were crystalline, high melting compounds. They were derivatized in a buffer system with 3,5-dinitrobenzyloxy carbonyl chloride (DNZ−Cl) or 2,4-dinitrofluorobenzene (DNP−F) and used to evaluate their enantioseparation by HPLC employing quinine-derived chiral anion exchangers.[34] The resolution values for the DNZ derivatives are much higher than for the DNP derivatives and range from 5 to 9. The ee of chiral, nonracemic α-arylmethylphosphonic acids we are plan-

(32) Review: Hoppe, D.; Hense, T. *Angew. Chem.* **1997**, *109*, 2376−2410; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282−2316.
(33) Review: Cox, P. J.; Simpkins, N. S. *Tetrahedron*: *Asymmetry* **1991**, *2*, 1−26.
(34) Zarbl, E.; Lämmerhofer, M.; Hammerschmidt, F.; Wuggenig, F.; Hanbauer, M.; Maier, N. M.; Sajovic, L.; Lindner, W. *Anal. Chim. Acta* **2000**, *404*, 169−177.

ning to prepare by enantioselective metalation can thus be determined easily. At present, we are trying to extend the rearrangement to α-substituted arylmethyl- and allylamines.

Conclusions

We have demonstrated that arylmethylamines can be easily transformed into N-protected phosphoramidates, the Boc group being the best protecting group. These derivatives of the amines are metalated by *s*-BuLi/TMEDA or LDA. The α-amino(arylmethyl)lithiums isomerize with retention of configuration to N-protected α-aminophosphonates (phosphoramidate−aminophosphonate rearrangement). As demostrated for the metalated species derived from benzylamine, such carbanionic intermediates are partly configurationally stable, which is strongly influenced by the N-protecting group of the phosphoramidate. Experiments to extend the methodology to aliphatic amines are under way.

Experimental Section

All starting materials were obtained from commercial suppliers and were generally used without further purification. Melting points were determined without correction. IR spectra of liquid samples were measured as films between NaCl plates or on a silicon[35] disk. Spots on TLC plates were visualized by UV and/or dipping the plate into a solution of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (24 g) and $Ce(SO_4)_2\cdot 4H_2O$ (1 g) in 10% H_2SO_4 in water (500 mL), followed by heating with a hot gun. Spots of free aminophosphonic acids on TLC plates (silica, 6:3:1 *i*-PrOH/H_2O/concentrated ammonia) were visualized by dipping into a solution of ninhydrin (32 mg) in ethanol (16 mL) containing 2,4,6-trimethylpyridine (1 mL) and AcOH (3 mL) and heating with a hot gun. (*S*)-MTPACl [JPS Chimie; $[\alpha]^{20}_D$ +136.5 (*c* 5.2, CCl_4), ee >99.5%] was used for derivatization of α-aminophosphonates.

THF was distilled prior to use from K and diethyl ether from $LiAlH_4$. TMEDA and solvents were refluxed over drying agent, distilled and stored over molecular sieve; toluene (Na; 4 Å), pyridine (CaH_2; 4 Å), CH_2Cl_2 (P_4O_{10}; 4 Å), MeOH (Mg; 3 Å). Et_3N p.A. was dried over KOH.

Phosphorylation of Amines with Diethyl Chlorophosphate (General Procedure A). Diethyl chlorophosphate (2.9 mL, 3.5 g, 20 mmol) was added dropwise to a cooled (0 °C) and stirred solution of of benzylamine (**5**) or arylmethylamine **37a**−**c** (22 mmol) and triethylamine (3.4 mL, 2.4 g, 24 mmol) in dry CH_2Cl_2 under argon. Stirring was continued at room temperature until completion of reaction (3 h, TLC: 8:1 CH_2Cl_2/EtOAc). The reaction mixture was extracted with 1 M HCl and a saturated aqueous solution of $NaHCO_3$. The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by bulb to bulb distillation.

Preparation of N-Protected Phosphoramidates 6, 39a−c from Phosphoramidates 14, 38a−c (General Procedure B). A solution of *s*-BuLi (4.6 mL, 6 mmol, 1.3 M, in cyclohexane) was added to a stirred and cooled (bath temperature −20 °C) solution of *i*-Pr_2NH (0.84 mL, 0.61 g, 6.0 mmol) in dry THF (10 mL) under argon. After 10 min, the solution was cooled to −78 °C and phosphoramidate **14** or **38a**−**c** (5.0 mmol, in 5 mL of dry THF) was added, followed by the electrophile [Boc_2O, Piv_2O, *p*-$MeC_6H_4SO_2Cl$, $(CF_3SO_2)_2O$, $(EtO)_2P(O)Cl$, dissolved in 5 mL of dry THF] 10 min later. The reaction mixture was allowed to warm slowly to room temperature in the bath (16 h, TLC: 8:1 CH_2Cl_2/EtOAc for Boc, Piv, Tos and Tf; 1:8 CH_2Cl_2/EtOAc for bisphosphoramidate) and then concentrated in vacuo. Water and CH_2Cl_2 were added to the residue and the mixture was shaken vigorouly. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with 0.5 M HCl, a saturated solution of $NaHCO_3$, dried (Na_2SO_4), and concentrated in vacuo. The residue was flash chromatographed to furnish **6** or **39a-c**.

Rearrangement of N-Protected Phosphoramidates 6 and 39a−c (General Procedure C). *s*-BuLi (1.2 mL, 1.5 mmol, 1.3 M in cyclohexane) was added to a cooled (−78 °C) and stirred solution of N-protected phosphoramidate **6 or 38a**−**c** (1.0 mmol) and TMEDA (0.23 mL, 0.21 g, 1.5 mmol) in dry diethyl ether (5 mL) under argon. When the starting material was consumed (30 min for *N*-Boc derivatives, TLC: 2:1 hexanes/EtOAc; 3 h for bisphosphoramidate, TLC 1:8 CH_2Cl_2/EtOAc), AcOH (4 mL, 8 mmol; 2 M solution in diethyl ether) was added. The reaction mixture was concentrated in vacuo. After addition of water, the product was extracted four times with CH_2Cl_2. The combined organic layers were washed with water, dried (Na_2SO_4), and concentrated in vacuo. The product was purified by flash chromatography.

Preparation and Rearrangement of N-Protected Phosphoramidates 6 and 39a−c as a One-Pot Procedure with *s*-BuLi (General Procedure D). *s*-BuLi (1.9 mL, 2.4 mmol, 1.3 M solution in cyclohexane) was added dropwise to a cooled (−78 °C) and stirred solution of phosphoramidate **14** (2 mmol) in dry diethyl ether (5 mL) under argon, followed by $(Boc)_2O$ (0.48 g, 2.2 mmol) after 10 min. When the starting material was consumed (about 3 h, TLC 8:1 CH_2Cl_2/EtOAc), TMEDA (0.46 mL, 3 mmol) and *s*-BuLi (3.0 mmol) were added and stirring was continued for 30 min. AcOH (8 mL, 16 mmol; 2 M solution in diethyl ether) was added and the mixture was concentrated in vacuo. The isolation of the product was the same as given in general procedure C.

Rearrangement of N-Protected Phosphoramidate 6 with LDA or Homochiral Lithium Amide Bases (General Procedure E). A solution of *s*-BuLi (1.2 mL, 1.5 mmol, 1.3 M in cyclohexane) was added to a stirred and cooled (bath temperature −20 °C) solution of *i*-Pr_2NH (0.21 mL, 0.15 g, 1.5 mmol) or homochiral *N*-isopropyl-*N*-1-phenylethylamine or *N*,*N*-bis(1-phenylethyl)amine in dry THF or diethyl ether (5 mL) under argon. After 10 min, the solution was cooled to −78 °C, and the phosphoramidate **6** (1 mmol, dissolved in 5 mL of dry THF or diethyl ether) was added. Stirring was continued for 30 min for *N*-Boc-protected phosporamidates (TLC 2:1 hexanes/EtOAc) and 3.5 h for bisphosphoramidates (TLC 1:8 CH_2Cl_2/EtOAc). AcOH (4 mL of a 2 M solution in diethyl ether) was added and the reaction mixutre was concentrated in vacuo. The workup and purification was as given in general procedure C.

Removal of Boc from *N*-Boc Aminophosphonates 10c and Preparation of Mosher Amides from α-Aminophosphonates 27 (General Procedure F). A solution of *N*-Boc aminophosphonate **10c** (0.3 mmol) in a mixture of dry CH_2Cl_2 (1 mL) and CF_3CO_2H (1 mL) was stirred at room temperature (3 h, TLC 10:1 CH_2Cl_2/MeOH). The reaction mixture was concentrated in vacuo, and CH_2Cl_2, water, and concentrated ammonia (5 drops) were added. The organic layer was separated, and the aqueous one was extracted with CH_2Cl_2. The combined organic phases were washed with water, dried (Na_2SO_4), and concentrated in vacuo. The crude product was directly used for the preparation for the Mosher amide or was purified by flash chromatography.

A mixture of crude α-aminophosphonate **27** (0.1 mmol) and (*R*)-MTPACl (0.25 mmol) in dry Et_3N (2 mL) and dry CH_2Cl_2 (1 mL) was stirred at room temperature (16 h, TLC 10:1 CH_2Cl_2/MeOH). Water (a few drops) was added, and the reaction mixture was concentrated in vacuo. The residue was taken up in CH_2Cl_2, washed with 2 M HCl, a saturated solution of $NaHCO_3$ and dried (Na_2SO_4). Evaporation of the solvent left the crude product which was purified by flash chromatography.

Complete Deprotection of N-Protected α-Aminophosphonates 10c, 40a and 40c To Prepare α-Aminophosphonic Acids 11c, 41a, and 41c (General Procedure G). A stirred mixture of protected α-aminophosphonate (1 mmol) and HCl (20 mL, 6 M) was refluxed (16 h, TLC 6:3:1 i-PrOH/H_2O/concentrated ammonia). The cold reaction mixture was concentrated in vacuo and the residue was dried in a vacuum

(35) Mikenda, W. *Vib. Spectrosc.* **1992**, *3*, 327−330.

desiccator over KOH. The crude product was purified by ion exchange chromatogrphy (Dowex 50W x 4, H^+, 50−100 mesh), using water as eluent. Ninhydrin positive fractions were pooled, concentrated by rotary evaporation to a small volume and freeze-dried to leave a sufficiently pure, crystalline product **11** or **41**. The analytical sample was crystallized from water.

Diethyl *N*-Phenylmethylphosphoramidate (14). Benzylamine (**5**) (2.3 mL, 2.3 g, 22 mmol) yielded according to general procedure A 4.40 g (90%) of phosphoramidate **14** as a colorless liquid: bp 140 °C/0.15 mm (lit.[16] bp 120 °C/0.05 mm).

Diethyl *N*-4-Toluenesulfonyl-*N*-phenylmethylphosphoramidate (6b). Phosphoramidate **14** (1.2 g, 5 mmol) yielded according to general procedure B 1.30 g (65%) of tosylamide **6b** as a colorless oil: R_f 0.64 (8:1 CH_2Cl_2/EtOAc); IR (Si) 1353, 1268, 1020 cm^{-1}; ^1H NMR (250.1 MHz, $CDCl_3$) δ 1.21 (dt, J = 1.1, 7.0 Hz, 6H), 2.36 (s, 3H), 3.97 (m, 4H), 4.66 (d, J = 11.4 Hz), 7.21 (m, 5H), 7.41 (m, 2H), 7.70 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.52 (d, J = 7.4 Hz), 21.13, 51.60 (d, J = 2.3 Hz), 63.81 (d, J = 5.5 Hz), 127.32, 127.54 (2C), 127.83 (2C), 128.43 (2C), 128.89 (2C), 136.40, 136.98, 143.65. Anal. Calcd for $C_{18}H_{24}NO_5P$ (397.43): C, 54.40; H, 6.09; N, 3.52. Found: C, 54.66; H, 5.98, N, 3.42.

Diethyl *N*-*tert*-Butoxycarbonyl-*N*-phenylmethylphosphoramidate (6c). Method 1. A solution of *s*-BuLi (4.6 mL, 6.0 mmol, 1.3 M in cyclohexane) was added to a cooled (bath temperature −40 °C) solution of *N*-Boc benzylamine (**23**)[19] (1.04 g, 5 mmol) in dry toluene (10 mL) under argon. Stirring was continued for 15 min. Diethyl chlorophosphate (0.87 mL, 1.04 g, 6.0 mmol, dissolved in 5 mL of dry toluene) was added. The reaction mixture was allowed to warm slowly to room temperature and was stirred until the starting material was consumed (16 h, TLC: 8:1 CH_2Cl_2/EtOAc). CH_2Cl_2 and a saturated solution of NH_4Cl were added. The organic phase was separated and the aqueous one was extracted twice with CH_2Cl_2. The combined organic layers were washed with 0.5 M HCl and a saturated solution of $NaHCO_3$, dried with Na_2SO_4 and concentrated in vacuo. The residue was flash chromatographed to yield 0.98 g (56%) of **6c** as a viscous oil; R_f 0.57 (8:1 CH_2Cl_2/EtOAc).

Method 2. Phosphoramidate **14** (1.20 g, 5 mmol) was transformed by general procedure B into 1.33 g (78%) of **6c** as a viscous oil: IR (Si) 1720 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$) δ 1.30 (dt, J = 1.1, 7.0 Hz, 6H), 1.48 (s, 9H), 4.05 (m, 4H), 4.74 (d, J = 11.2 Hz), 7.31 (m, 3H), 7.45 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.95 (d, J = 6.9 Hz), 27.94, 49.49 (d, J = 3.8 Hz), 63.26 (d, J = 6.1 Hz), 82.30, 127.10, 127.99 (2C), 128.13 (2C), 138.85, 153.57 (d, J = 6.1 Hz).

Tetraethyl *N*-*N*-Phenylmethylbis(phosphoramidate) (6f). Phosphoramidate **14** (1.20 g, 5 mmol) was transformed by general procedure B into 1.34 g (72%) of **6f**[25] as a viscous oil: R_f 0.24 (1:3 CH_2Cl_2/EtOAc); IR (Si) 1262, 1026 cm^{-1}; ^1H NMR (250.1 MHz, $CDCl_3$) δ 1.22 (dt, J = 0.6, 7.0 Hz, 12H), 3.99 (m, 8H), 4.52 (t, J = 13.8 Hz, 2H), 7.25 (m, 3H), 7.49 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.86 (d, J = 3.1 Hz), 15.90 (d, J = 3.1 Hz), 50.58, 63.23 (d, J = 2.3 Hz), 63.27 (d, J = 2.3 Hz), 127.38, 127.88 (2C), 128.83 (2C), 138.44.

Diethyl *N*-(1-Trimethylsilylphenylmethyl)phosphoramidate (16). Phosphoramidate **14** (243 mg, 1 mmol) furnished according to general procedure D, except that Boc_2O was replaced by TMSCl and that the reaction mixture was allowed to warm slowly at the end to room temperature, 0.252 g (80%) of (±)-**16** as a crystalline product: mp 78−79 °C (hexanes); IR (Si) 1232, 1033 cm^{-1}; ^1H NMR (250.1 MHz, $CDCl_3$) δ −0.02 (s, 9H), 0.85 (dt, J = 0.9, 7.1 Hz, 3H), 1.27 (dt, J = 0.9, 7.1 Hz, 3H), 3.11 (br dd, J = 10.1, 13.9 Hz, 1H), 3.47 (m, 1H), 3.66 (t, J = 10.5 Hz, 2H); 3.79 (m, 1H), 3.99 (m, 2H), 7.09 (m, 3H), 7.23 (m, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ −4.01, 15.40 (d, J = 7.8 Hz), 16.03 (d, J = 7.4 Hz), 47.80 (d, J = 5.1 Hz), 61.90 (d, J = 4.6 Hz), 61.99 (d, J = 5.1 Hz), 125.32, 125.83 (2C), 127.82 (2C), 142.82. Anal. Calcd for $C_{14}H_{24}NO_3PSi$ (315.42): C, 53.31; H, 7.67; N, 4.44. Found: C, 53.60; H, 7.96, N, 4.41.

(±)-Diethyl 1-(*tert*-Butoxycarbonylamino)phenylmethylphosphonate [(±)-10c]. Phosphoramidate **6c** (0.34 g, 1 mmol) gave by general procedure C 0.265 g (77%) of crystalline (±)-**10c**: Rf 0.15 (2:1 hexanes/EtOAc); mp 119−121 °C (hexanes) (lit.[21] mp 118−120 °C).

(±)-Diethyl 1-(Diethoxyphosphinylamino)phenylmethylphosphonate [(±)-10f]. Bisphosphoramidate **6f** (0.380 g, 1 mmol) furnished by general procedure C 0.267 g (70%) of (±)-**10f** as a colorless oil: R_f 0.08 (1:8 CH_2Cl_2/EtOAc); IR (Si) 1240, 1029 cm^{-1}; ^1H NMR (250.1 MHz, $CDCl_3$) δ 0.97 (dt, J = 0.9, 7.1 Hz, 3H), 1.03 (dt, J = 0.7, 7.1 Hz, 3H), 1.19 (dt, J = 0.9, 7.1 Hz, 3H),1.26 (dt, J = 0.6, 7.0 Hz, 3H), 3.60 (m, 2H), 3.88 (m, 5H), 4.07 (m, 2H), 4.44 (dt, J = 10.6, 23.2 Hz, 1H), 7.30 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.66 (d, J = 7.7 Hz), 15.98 (d, J = 7.6 Hz), 16.06 (d, J = 6.1 Hz), 16.32 (d, J = 6.1 Hz), 52.98 (d, J = 154.5 Hz), 62.34 (d, J = 4.6 Hz), 62.39 (d, J = 5.4 Hz), 62.97 (d, J = 6.9 Hz), 63.26 (d, J = 6.9 Hz), 127.79 (d, J = 6.1 Hz, 2C), 128.00 (d, J = 3.1 Hz), 128.37 (d, J = 2.3 Hz, 2C), 136.69.

Reaction of *n*-BuLi/TMEDA with Tosylated Phosphoramidate 6b: (±)-Diethyl 1-Phenylpentylphosphonate [(±)-21]. Phosphoramidate **6b** (397 mg, 1 mmol) was treated with *n*-BuLi (2.4 mmol, 1.5 mL, 1.6 M solution in hexane)/TMEDA (0.36 mL, 279 mg, 2.4 mmol) according to general procedure C. Flash chromatography (1:1 hexanes/EtOAc; R_f 0.16) and bulb-to-bulb distillation (130−140 °C/0.3 mm) gave 217 mg (73%) of (±)-**21** as a colorless oil: IR (Si) 3209, 1232, 1033 cm^{-1}; ^1H NMR (250.1 MHz, $CDCl_3$) δ 0.80 (t, J = 6.9 Hz, 3H), 0.97 (dt, J = 0.9, 7.1 Hz, 3H), 1.21 (m, 4H), 1.24 (dt, J = 0.9, 7.1 Hz, 3H), 1.68 (m, 2H), 3.38 (br.t, J = 9.3 Hz, 1H), 3.54 (m, 1H), 3.81 (m, 1H), 3.98 (m, 3H), 7.22 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 13.62, 15.51 (d, J = 7.8 Hz), 15.89 (d, J = 7.4 Hz), 22.08, 28.03, 38.59 (d, J = 7.4 Hz), 55.86, 61.64 (d, J = 4.6 Hz), 61.66 (d, J = 5.1 Hz), 126.08 (2C), 126.71, 128.06 (2C), 144.22 (d, J = 2.8 Hz). Anal. Calcd for $C_{15}H_{26}NO_3P$ (299.35): C, 60.19; H, 8.75; N, 4.68. Found: C, 60.21; H, 8.70, N, 4.46.

***N*-Phenylmethyl-2-diethoxyphosphinyl-4-methylbenzenesulfonamide (22).** *N*-Tosyl phosphoramidate **6b** (0.40 g, 1 mmol) was treated with LDA according to general procedure E. Flash chromatography (2:1 hexanes/EtOAc, R_f 0.35) of the crude product furnished 0.27 g (68%) of **22** as crystalline solid: mp 78−80 °C (hexanes); IR (Si) 3142, 1021 cm^{-1}; ^1H NMR (250.1 MHz, $CDCl_3$) δ 1.33 (t, J = 0.7, 7.1 Hz, 6H), 2.41 (s, 3H), 4.07 (d, J = 6.2 Hz, 2H), 4.17 (m, 4H), 7.14 (m, 5H), 7.37 (br.d, J = 8.2 Hz, 1H), 7.66 (dd, J = 1.4, 13.9 Hz, 1H), 7.95 (br.t, J = 6.8 Hz), 7.99 (dd, J = 6.2, 8.2 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 16.00 (d, J = 6.4 Hz), 21.10, 47.16, 63.12 (d, J = 5.5 Hz), 126.01 (d, J = 187.1 Hz), 127.02, 127.67 128.02 (2C), 130.31 (d, J = 12.4 Hz), 132.36 (d, J = 2.8 Hz), 135.08 (d, J = 6.0 Hz), 136.46, 140.73 (d, J = 10.1 Hz), 142.12 (d, J = 12.9 Hz). Anal. Calcd for $C_{18}H_{24}NO_5PS$ (397.43): C, 54.40; H, 6.09; N, 3.52. Found: C, 54.63; H, 6.18, N, 3.40.

Carboxylation and Rearrangement of Phosphoramidate 14. *s*-BuLi (0.88 mL, 1.14 mmol, 1.3 M, in cyclohexane) was added to a stirred and cooled (bath temperature −78 °C) solution of phosphoramidate **14** (0.24 g, 1 mmol) in dry diethyl ether (5 mL). After the solution was stirred for 5 min, the argon atmosphere was replaced by a CO_2 atmosphere, the cooling bath was removed, and stirring was continued for 20 min. The solvent was removed at the oil pump (0.3 mm), and the flask was filled with argon. Dry diethy ether (5 mL) was added to the residue, followed by *s*-BuLi (0.96 mL, 1.2 mmol, 1.3 M in cyclohexane) after cooling of the solution to −78 °C. When the reaction was complete (4 h, TLC 19:1 CH_2Cl_2/MeOH), AcOH (1.15 mL, 2.3 mmol, 2 M solution in diethyl ether) was added. The solvent was removed and the residue was diluted with CH_2Cl_2 and water. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with water, dried (Na_2SO_4) and concentrated in vacuo. The residue was flash chromatographed (19:1 CH_2Cl_2/MeOH, R_f 0.29) to yield 115 mg (47%) of (±)-**27** as a colorless oil: ^1H NMR (250.1 MHz, $CDCl_3$) δ 1.16 (t, J = 7.0 Hz, 3H), 1.26 (t, J = 7.3 Hz, 3H), 1.75 (br.s, 2H), 3.85 (m, 1H), 3.96 (m, 1H), 4.03 (m, 2H), 4.24 (d, J = 17.1 Hz, 1H), 7.28 (m, 1H), 7.34 (m, 2H), 7.44 (m, 2H).

(+)-Diethyl (*R*)-*N*-*tert*-Butoxycarbonyl-*N*-[1-$^2H_1$]-phenylmethylphosphoramidate (*R*)-[1-$^2H_1$]6c. DEAD (0.7 mL, 0.77 g, 4.4 mmol) was added dropwise to a cooled (0 °C) and stirred solution of Ph_3P (1.15 g, 4.4 mmol), *N*-Boc phosphoramidate **29**[25] (1.11 g, 4.4 mmol) and (*S*)-**28**[27] (0.44 g, 4.0 mmol) in dry toluene (20 mL) under argon. The cooling bath was removed and the reaction mixture was stirred for 16 h and then concentrated in vacuo. Hexanes (20 mL) were added and the mixture was stirred vigorously. The crystalline solid was removed and the mother liquor was rotary evaporated. Flash chromatography (2:1 hexanes/EtOAc, R_f 0.36) gave 0.89 g (64%) of (*R*)-[1-$^2H_1$]**6c** as a colorless oil: ^2H ≥98% (by ^1H NMR); $[\alpha]^{20}_D$ +0.36 (*c* 33.1, acetone); ^1H NMR (250.1 MHz, $CDCl_3$) δ 1.25 (dt, J = 0.9, 7.1 Hz, 6H), 1.43 (s, 9H), 4.01 (m, 4H), 4.68 (d, J = 11.4 Hz, 1H), 7.26 (m, 3H), 7.39 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.98 (d, J = 6.9 Hz), 27.97, 49.26 (dt, J = 3.0, 21.9 Hz), 63.28 (d, J = 5.4 Hz), 82.32, 127.16, 128.06 (2C), 128.18 (2C), 138.81, 153.62. ^{31}P NMR (162.0 MHz, $CDCl_3$) δ 3.39. Anal. Calcd for $C_{16}H_{25}DNO_5P$ (344.35): C, 55.81; H + D, 7.61; N, 4.07. Found: C, 56.09; H + D, 7.60, N, 4.04.

(*R*)-*N*-[1-$^2H_1$]Phenylmethylphthalimide [(*R*)-33]. DEAD (0.83 g, 0.75 mL, 4.8 mmol) was added dropwise to a stirred and cooled (0 °C) solution of phthalimide (1.26 g, 4.8 mmol), of Ph_3P (1.26 g, 4.8 mmol) and (*S*)-**28** (0.44 g, 4.0 mmol) in dry THF (20 mL) under argon. The cooling bath was removed and stirring was continued at room temperature (4 h, TLC: 2:1 hexanes/EtOAc). Then water (1 mL) was added and the reaction mixture was filtered through a column of silica (60 g), eluting with CH_2Cl_2. The eluate was concentrated in vacuo and the crude product was flash chromatographed (2:1 hexanes/EtOAc, R_f 0.42) to yield 958 mg (99%) of (*R*)-**33** as a crystalline product: mp 116−117 °C [lit.[26] for (±)-**33** mp 116 °C (hexane)], ≥98% D (^1H NMR); $[\alpha]^{20}_D$ +0.12 (*c* 8.50, acetone).

(*R*)-[1-$^2H_1$]Phenylmethylamine [(*R*)-34]. Phthalimide (*S*)-**33** (0.81 g, 3.3 mmol) was deprotected by a literature procedure[26] to yield 358 mg (100%) of (*R*)-**34** as a yellowish oil that was used for the next step without further purification.

Diethyl (*R*)-*N*-[1-$^2H_1$]Phenylmethylphosphoramidate [(*R*)-[1-$^2H_1$]14]. Crude amine (*R*)-**34** (0.27 g, 2.5 mmol) was transformed using general procedure A into 452 mg (74%) of (*R*)-[1-$^2H_1$]**14** as a colorless liquid: bp 145 °C/0.2 mm; ≥98% D (^1H NMR); $[\alpha]^{20}_D$ −0.62 (*c* 13.96, acetone); ^1H NMR (250.1 MHz, $CDCl_3$) δ 1.27 (t, J = 7.1 Hz, 6H), 3.02 (t, J = 7.5, 1H), 4.03 (m, 5H), 7.28 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.96 (d, J = 6.9 Hz), 44.87 (t, J = 20.9 Hz), 62.14 (d, J = 5.5 Hz), 127.13 (3C), 128.34 (2C), 139.47 (d, J = 6.0 Hz); ^{31}P NMR (162.0 MHz, $CDCl_3$) δ 9.76.

Tetraethyl (*R*)-*N*-[1-$^2H_1$]Phenylmethylbis(phosphoramidate) [(*R*)-[1-$^2H_1$]6f]. Phosphoramidate (*R*)-[1-$^2H_1$]**14** (0.42 g, 1.7 mmol) was transformed by general procedure B into 318 mg (49%) of (*R*)-[1-$^2H_1$]**6f** as a viscous oil: R_f 0.27 (1:8 CH_2Cl_2/EtOAc); ≥98% ^2H (^1H NMR); $[\alpha]^{20}_D$ −0.33 (*c* 5.99, acetone); ^1H NMR (250.1 MHz, $CDCl_3$) δ 1.23 (dt, J = 0.6, 7.1 Hz, 12H), 4.00 (m, 8H), 4.52 (t, J = 13.5 Hz, 1H), 7.26 (m, 3H), 7.50 (m, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 15.83 (d, J = 3.7 Hz), 15.91 (d, J = 3.7 Hz), 50.02 (t, J = 21.6 Hz), 63.21 (d, J = 2.3 Hz), 63.28 (d, J = 2.3 Hz), 127.38, 127.97 (2C), 128.83 (2C), 138.38; ^{31}P NMR (162.0 MHz, $CDCl_3$) δ 5.15.

Diethyl (*S*)-1-Azidophenylmethylphosphonate [(*S*)-36]. To a stirred and cooled (0 °C) solution of (*R*)-**35**[30] [0.32 g, 1.3 mmol; $[\alpha]^{20}_D$ +37.31 (*c* 1.04, $CHCl_3$)] and Ph_3P (0.47 g, 1.8 mmol) in a mixture of dry toluene (8 mL) and dry THF (2 mL) under argon HN_3 (1.12 mL, 1.8 mmol, 1.6 M in toluene) was added, immediately followed by DEAD (0.29 mL, 0.32 g, 1.8 mmol). The cooling bath was removed and stirring was continued until the reaction was finished (1 h, TLC 3:1 CH_2Cl_2/EtOAc). MeOH (0.3 mL) was added and the solvent was removed in vacuo. Hexanes (15 mL) were added to the residue and the mixture was stirred vigorously for 16 h. The crystalline material was filtered off and the mother liquor was concentrated. Flash chromatography (8:1 CH_2Cl_2/EtOAc, R_f 0.38) yielded 338 mg (96%) of (*S*)-**36** as a colorless oil: $[\alpha]^{20}_D$ −40.17 (*c* 1.16, $CHCl_3$); ee 98% when the reaction was carried out in dry toluene in the same way, 146 g (47%) of (*S*)-**36** resulted; $[\alpha]^{20}_D$ −35.11 (*c* 1.17, $CHCl_3$); ee 86%; IR (Si) 2104 cm^{-1}; ^1H NMR (250.1 MHz, $CDCl_3$) δ 1.21 (dt, J = 0.5, 7.1 Hz, 3H), 1.26 (dt, J = 0.5, 7.1 Hz, 3H), 4.03 (m, 4H), 4.70 (d, J = 16.7 Hz, 1H), 7.39 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 16.16 (d, J = 6.0 Hz), 16.27 (d, J = 5.5 Hz), 61.49 (d, J = 158.1 Hz), 63.33 (d, J = 5.1 Hz), 63.43 (d, J = 5.5 Hz), 128.16 (d, J = 6.0 Hz, 2C), 128.57 (d, J = 1.8 Hz, 2C), 128.72 (d, J = 2.8 Hz), 132.16 (d, J = 3.7 Hz). Anal. Calcd for $C_{11}H_{16}N_3O_3P$ (269.22): C, 49.07; H, 5.62; N, 15.61. Found: C, 49.14; H, 5.85, N, 15.47.

Diethyl (*S*)-1-Aminophenylmethylphosphonate [(*S*)-27]. A solution of (*S*)-**36** [0.41 g, 1.5 mmol, $[\alpha]^{20}_D$ −35.11 (*c* 1.17, $CHCl_3$)] and Ph_3P (0.65 g, 2.5 mmol) in dry THF (10 mL) was stirred under argon at room temperature until completion of reaction (19 h, TLC 19:1 CH_2Cl_2/MeOH).[37] Water (1 mL) was added, and the mixture was refluxed for 3 h (TLC 1:8 CH_2Cl_2/EtOAc). The mixture was concentrated in vacuo. Flash chromatography (1:8 CH_2Cl_2/EtOAc, R_f 0.14) of the residue yielded 337 mg (92%) of (*S*)-**27** as a colorless oil: $[\alpha]^{20}_D$ −16.30 (*c* 1.49, MeOH) [lit.[24] $[\alpha]^{20}_D$ −15.60 (*c* 1.0, MeOH)]; when azide with $[\alpha]^{20}_D$ +40.17 (*c* 1.16, $CHCl_3$) was reduced by the same procedure, an amine of $[\alpha]^{20}_D$ −18.72 (*c* 1.26, MeOH) resulted; the ^1H NMR spectrum is identical with that of (±)-**27**.

Diethyl (*S*)-1-(Diethoxyphosphinylamino)phenylmethylphosphonate [(*S*)-10f]. Diethyl chlorophosphate (0.12 mL, 138 mg, 0.8 mmol) was added dropwise to a cooled (0 °C) and stirred solution of (*S*)-**27** [0.13 g, 0.53 mmol, $[\alpha]^{20}_D$ −16.30 (*c* 1.49, MeOH)] and Et_3N (0.18 mL, 1.2 mmol) in dry CH_2Cl_2 (5 mL) under argon. The cooling bath was removed and the mixture was refluxed (4 h, TLC 10:1 CH_2Cl_2/MeOH). The cooled solution was washed with 2 M HCl and a saturated solution of $NaHCO_3$, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography of the residue furnished 139 mg (69%) of (*S*)-**10f** as a colorless oil: $[\alpha]^{20}_D$ −17.06 (*c* 1.08, acetone); aminophosphonate (*S*)-**27** with $[\alpha]^{20}_D$ −18.72 (*c* 1.26, MeOH) gave (*S*)-**10f** with $[\alpha]^{20}_D$ −19.54 (*c* 0.99, acetone); the spectroscopic data of (*S*)-**10f** are identical with those of (±)-**10f**.

Diethyl (*S*)-1-(*tert*-Butoxycarbonylamino)phenylmethylphosphonate [(*S*)-10c]. α-Aminophosphonate (*S*)-**27** (0.15 g, 0.61 mmol, ee 98%) was reacted with Et_3N (2 equiv) and Boc_2O (1.1 equiv) by the procedure given for the preparation for (*S*)-**10f.** Flash chromatography (5:1 CH_2Cl_2/EtOAc, R_f 0.23) furnished 134 mg (63%) of (*S*)-**10c** as a crystalline solid: mp 137−138 °C (hexanes) [lit.[21] for (±)-**10c** 118−120 °C]; $[\alpha]^{20}_D$ −15.81 (*c* 0.96, acetone); the spectroscopic data are identical with that of (±)-**10c**.

Diethyl *N*-(4-Methylphenyl)methylphosphoramidate (38a). Amine **37a** (2.8 mL, 2.7 g, 22 mmol) yielded according to general procedure A 4.41 g (86%) of phosphoramidate **38a** as a colorless liquid that solidified on storage at +4 °C: bp 145 °C/0.15 mm; IR (Si) 3226, 1239, 1032 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$) δ 1.26 (t, J = 7.0 Hz, 6H), 2.29 (s, 3H), 3.07 (dt, J = 6.5, 10.5 Hz, 1H), 4.01 (m,6H), 7.13 (AA′BB′system, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.00 (d, J = 7.7 Hz), 20.09, 44.91, 62.12 (d, J = 5.4 Hz), 127.13 (2C), 129.02 (2C), 136.55 (d, J = 6.1 Hz), 136.77; ^{31}P NMR (162.0 MHz, $CDCl_3$) δ 9.65. Anal. Calcd for $C_{12}H_{20}NO_3P$ (257.26): C, 56.03; H, 7.84; N, 5.44. Found: C, 55.79; H, 7.72, N, 5.34.

Diethyl *N*-(4-Methoxyphenyl)methylphosphoramidate (38b). Amine **37b** (2.9 mL, 3.0 g, 22 mmol) yielded according to general procedure A 4.67 g (85%) of phosphoramidate **38b** as a colorless liquid: bp 175 °C/0.15 mm; IR (Si) 3233, 1249, 1032 cm^{-1}; ^1H NMR (250.1 MHz, $CDCl_3$) δ 1.26 (dt, J = 0.7, 7.1 Hz, 6H), 3.01 (dt, J = 6.3, 10.5 Hz, 1H), 3.75 (s, 3H), 4.01 (m, 6H), 7.01 (AA′BB′ system, 4H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 16.01 (d, J = 6.9 Hz), 44.69, 55.10, 62.13 (d, J = 5.5 Hz), 113.76 (2C), 128.44 (2C), 131.73 (d, J = 6.4 Hz), 158.75; ^{31}P NMR (162.0 MHz, $CDCl_3$) δ 9.70. Anal. Calcd for $C_{12}H_{20}NO_4P$ (273.26): C, 52.75; H, 7.38; N, 5.13. Found: C, 52.01; H, 7.35, N, 4.86.

Diethyl *N*-(1′-Naphthyl)methylphosphoramidate (38c). Amine **37c** (3.2 mL, 3.4 g, 22 mmol) yielded according to

(36) Kim, J.-M.; Bogdan, M. A.; Mariano, P. S. *J. Am. Chem. Soc.* **1993**, *115*, 10591−10595.
(37) Öhler, E.; Kotzinger, S. *Liebigs Ann. Chem.* **1993**, 269−280.

general procedure A 5.17 g (88%) of phosphoramidate **38c**: bp 175 °C/0.15 mm; mp 61−63 °C; IR (Si) 3220, 1235, 1032 cm^{-1}; ^1H NMR (250.1 MHz, $CDCl_3$) δ 1.28 (dt, J = 0.7, 7.1 Hz, 6H), 3.02 (dt, J = 6.4, 9.1 Hz, 1H), 4.04 (m, 4H), 4.54 (dd, J = 6.9, 8.7 Hz, 2H), 7.48 (m, 4H), 7.82 (m, 2H), 8.06 (m, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 16.04 (d, J = 6.9 Hz), 43.12, 62.31 (d, J = 5.5 Hz), 123.09, 125.24, 125.33, 125.71, 126.20, 128.12, 128.64, 130.98, 133.69, 134.84 (d, J = 6.9 Hz); ^{31}P NMR (162.0 MHz, $CDCl_3$) δ 9.46. Anal. Calcd for $C_{15}H_{20}NO_4P$ (293.30): C, 61.43; H, 6.87; N, 4.78. Found: C, 61.33; H, 6.71, N, 4.73.

Diethyl *N*-*tert*-Butoxycarbonyl-*N*-(4-methylphenyl)-methylphosphoramidate (39a). Phosphoramidate **38a** (1.30 g, 5 mmol) was transformed by general procedure B into 1.22 g (68%) of **39a** as a colorless oil: R_f 0.40 (10:1 CH_2Cl_2/EtOAc); IR (Si) 1720 cm^{-1}; ^1H NMR (250.1 MHz, $CDCl_3$) δ 1.25 (dt, J = 0.9, 7.1 Hz, 6H), 1.43 (s, 9H), 2.29 (s, 3H), 4.00 (m, 4H), 4.65 (d, J = 11.4 Hz), 7.18 (AA′BB′ system, 4H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 15.92 (d, J = 6.9 Hz), 20.96, 27.94, 49.20 (d, J = 3.2 Hz), 63.16 (d, J = 5.5 Hz), 82.17, 128.05 (2C), 128.76 (2C), 135.80, 136.62, 153.55 (d, J = 6.4 Hz). ^{31}P NMR (162.0 MHz, $CDCl_3$) δ 3.46. Anal. Calcd for $C_{17}H_{28}NO_5P$ (357.38): C, 57.13; H, 7.90; N, 3.92. Found: C, 57.16; H, 7.70, N, 3.77.

Diethyl *N*-*tert*-Butoxycarbonyl-*N*-(4-methoxyphenyl)-methylphosphoramidate (39b). Phosphoramidate **38b** (1.40 g, 5 mmol) was transformed by general procedure B into 1.41 g (75%) of **39b** as a colorless oil: R_f 0.31 (10:1 CH_2Cl_2/EtOAc); the analytical sample was bulb to bulb distilled, bp 185 °C/0.2 mm; IR (Si) 1720 cm^{-1}; ^1H NMR (250.1 MHz, $CDCl_3$) δ 1.24 (dt, J = 0.9, 7.1 Hz, 6H), 1.43 (s, 9H), 3.75 (s, 3H), 3.97 (m, 4H), 4.62 (d, J = 11.4 Hz), 7.08 (AA′BB′ system,. 4H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 15.89 (d, J = 7.4 Hz), 27.93, 48.84 (d, J = 3.2 Hz), 55.04, 63.07 (d, J = 5.5 Hz), 82.12, 113.40 (2C), 129.63 (2C), 131.08, 153.52 (d, J = 6.0 Hz); ^{31}P NMR (162.0 MHz, $CDCl_3$) δ 3.42. Anal. Calcd for $C_{17}H_{28}NO_6P$ (373.38): C, 54.69; H, 7.56; N, 3.75. Found: C, 54.94; H, 7.67, N, 3.97.

Diethyl *N*-*tert*-Butoxycarbonyl-*N*-(1′-naphthyl)methylphosphoramidate (39c). Phosphoramidate **38c** (1.50 g, 5 mmol) was transformed by general procedure B into 0.94 g (48%) of **39c** as a colorless oil; R_f 0.35 (10:1 CH_2Cl_2/EtOAc); IR (Si) 1723 cm^{-1}; ^1H NMR (250.1 MHz, $CDCl_3$) δ 1.27 (dt, J = 0.9, 7.1 Hz, 6H), 1.41 (s, 9H), 4.09 (m, 4H), 5.24 (d, J = 11.2 Hz, 2H), 7.46 (m, 4H), 7.72 (bd, J = 7.8 Hz, 2H), 7.83 (m, 1H), 8.06 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.04 (d, J = 6.9 Hz), 27.90, 47.23, 63.65 (d, J = 6.1 Hz), 82.48, 122.89, 123.59, 125.21, 125.44, 125.87, 127.39, 128.58, 130.79, 133.53, 133.96, 153.73 (d, J = 6.1 Hz); ^{31}P NMR (162.0 MHz, $CDCl_3$) δ 3.55. Anal. Calcd for $C_{20}H_{28}NO_5P$ (393.42): C, 61.06; H, 7.17; N, 3.56. Found: C, 61.34; H, 7.17, N, 3.48.

(±)-1-Aminophenylmethylphosphonic Acid [(±)-11c]. Phosphoramidate **14** (243 mg, 1 mmol) was transformed by general procedure D into aminophosphonate (±)-**10c**, which was deproteced as crude product by general procedure G: yield 124 mg (63% overall yield starting from **14**) of (±)-**11c** as a crystalline solid; R_f 0.49, mp 279−281 °C (water) [lit.[38] 280−282 °C (water/EtOH)].

(±)-1-Amino-(4-methylphenyl)methylphosphonic Acid [(±)-41a]. Phosphoramidate **39a** (357 mg, 1 mmol) was transformed by general procedure C into aminophosphonate (±)-**40a** which was deprotected as crude product by general procedure G; yield: 152 mg (75% overall yield starting from **39a**) of (±)-**41a** as a crystalline solid: R_f 0.61, mp 274−276 °C (water) [lit.[38] 274−277 °C (water/EtOH)].

(±)-1-Amino-(1′-naphthyl)methylphosphonic Acid [(±)-41c]. Phosphoramidate **39c** (393 mg, 1 mmol) was transformed by general procedure C into aminophosphonate (±)-**40c** which was deprotected as crude product by general procedure G; yield: 117 mg (49% overall yield starting from **39c**) of (±)-**41c** as a crystalline solid: R_f 0.72, mp 268−270 °C (water) [lit.[39] 270 °C (water/MeOH)].

Acknowledgment. We are grateful to the Fonds zur Förderung der wissenschafltichen Forschung (project no. P13017-CHE and 6537C).

JO000585F

(38) Lukszo, J.; Tyka, R. *Synthesis* **1977**, 239−240.
(39) Hoffmann, H.; Förster, H. *Monatsh. Chem.* **1968**, *99*, 380−388.