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Asymmetric synthesis of 2*H*-aziridine phosphonates, and α- or β-aminophosphonates from enantiomerically enriched 2*H*-azirines

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Abstract—A simple and efficient method for asymmetric synthesis of 2*H*-azirine-2-phosphonates **6** is described. The key step is a base-mediated Neber reaction of *p*-toluenesulfonyloximes **4** derived from phosphonates. Triethylamine **5**, alkaloids **7** and solid-phase bound achiral **8** or chiral amines **9** are used. Reduction of 2*H*-azirines **6** with sodium borohydride in ethanol gives *cis*-aziridine-phosphonates **10**. Ring opening of aziridines **10** and **11** leads to the formation of enantiomerically enriched β-**12** and **14** and α-aminophosphonates **13** and **15**. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

2*H*-Azirine ring systems represent an important class of compounds because of their high reactivity.[1] They can be used as key intermediates in organic synthesis in the preparation of acyclic functionalized amino derivatives[2a–c] and heterocycles[2d–h] since all three bonds of the azirine ring can be cleaved, depending on the experimental conditions used. In particular, 2*H*-azirines containing a carboxylic ester group (**I**, Fig. 1) are constituents of naturally occurring antibiotics[1a] and are excellent reagents for the preparation of functionalized aziridines[1,3] and α-[3b,4a–e] and β-amino acid derivatives.[3b,4f–h] Furthermore, fosfomycin **IIIa** (X=O) (Fig. 1), a three ring heterocycle containing a phosphorus substituent is a broad spectrum antibiotic,[5a,b] which has been used in vitro[5c,d] and clinically.[5e] It is also known that phosphorus substituents regulate important biological functions,[6] and that molecular modifications involving the introduction of organophosphorus functionalities could increase their biological activity in a similar manner to that reported for other pharmaceuticals.[6] Some procedures for the synthesis of 2*H*-azirines have been reported,[1] and enantiomerically enriched 2*H*-azirine carboxylates **I** have been prepared from chiral *N*-substituted aziridine 2-carboxylic esters,[7a,b] and by using the Neber reaction.[7c,d] However, despite the potential utility of 2*H*-azirines,[1] these three-membered heterocycles directly substituted with a phosphorus containing functional group have received little attention.[8]

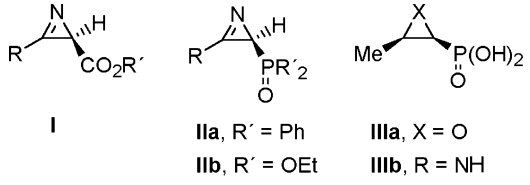

Figure 1.

For these reasons, the development of new processes for the asymmetric synthesis of functionalized azirines containing a phosphorus substituent at the 2 position (**II**, Fig. 1) may represent an important tool in organic synthesis because these heterocycles are expected to play a similar role to that of their isosteric analogues **I**, and therefore could be used as starting materials for the preparation of phosphorus substituted aziridines **IIIb** and in the enantioselective synthesis of α- and β-aminophosphorus derivatives. α-Aminophosphonates[9] can be considered as surrogates for α-amino acids,[10a] and have been used as haptens for the generation of catalytic antibodies,[10b,c] as antibacterial agents,[10d,e] and as nucleosides,[10f] or as phosphapeptide enzyme inhibitors,[10g–k] whereas β-aminophosphonate derivatives, some of them naturally occurring,[9b,11a–c] have been used for the preparation of hydroxy derivatives,[12a–c] of peptide-based enzyme inhibitors[12d–g] and as agrochemicals[12h] or pharmaceuticals.[12i–k]

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In this context, we have described new methods for the preparation of five-[13] and six-membered[14] phosphorus substituted nitrogen heterocycles from functionalized phosphine oxides and phosphonates and the synthetic uses of amino phosphorus derivatives as starting materials for the preparation of acyclic compounds[15] and phosphorus-containing heterocycles.[16] Recently, we disclosed the first asymmetric synthesis of 2*H*-azirines derived from phosphine oxides (**IIa**, R′ = Ph, Fig. 1) by an alkaloid-mediated Neber reaction of tosyl oximes[17] and their use for the preparation of phosphorylated oxazoles[18a,b] and pyrazines.[18c] A recent publication[19a] reporting the preparation of regioisomeric mixtures of 2-aryl substituted 2*H*-azirine-2-phosphonates and 2*H*-azirine-3-phosphonates from the Swern oxidation of enantiopure substituted aziridines and some reactions of both regioisomers, prompted us to report our own results[20] concerning the solution- and solid-phase-asymmetric synthesis of 2*H*-azirine-phosphonates containing alkyl and aryl substituents in the 2-position **IIb** from easily available *p*-toluenesulfonyloximes containing a phosphonate group (**IV**, X = Ts, Scheme 1) by means of triethylamine, alkaloids and polymer-bound achiral and chiral amines. The presence of phosphorus substituents in these substrates (**IIb**) increases the synthetic value of these compounds because they may be used as building blocks for the stereoselective preparation of enantiomerically enriched aziridines (**IIIb**), α-(**V**) and β-aminophosphorus derivatives (**VI**).[1,9–11]

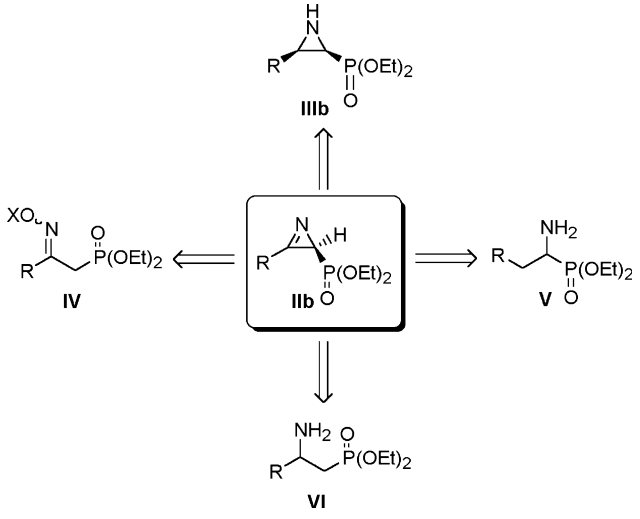
2. Results and discussion

2.1. Solution and solid-phase synthesis of azirines 6

The asymmetric synthesis of 2*H*-azirine phosphine oxides has been described using the modified Neber reaction of *p*-toluenesulfonyloximes derived from phosphine oxides with alkaloids.[17] Now we wish to extend the process to azirines derived from phosphonates. The preparation of the requisite functionalised β-*p*-toluenesulfonyloxime phosphonate **4a** ($R^1 = CH_3$, X = Ts) was accomplished by a simple reaction of β-ketoxime phosphonate **3a** ($R^1 = CH_3$, X = H), easily prepared from allene **1**,[21] with *p*-toluenesulfonyl chloride in pyridine. Compound **4a** was isolated as a mixture of the *E*- and *Z*-isomers. The ^{31}P NMR spectrum of **4a** (*E*- and *Z*-isomers) showed two absorptions at $\delta_P = 21.4$ and 19.8 ppm in an approximate isomer ratio of 60:40 as evidenced by the relative peak areas for each compound, in which the high-field chemical shift corresponds to the *Z*-isomer **4a**. Both isomers can be separated (by flash chromatography). The ^1H NMR spectrum of **4a** (*E*-isomer) gave a well-resolved doublet for the methylene protons ($\delta_{CH2} = 2.73$ ppm, $^2J_{PH} = 21.9$ Hz) and a singlet at $\delta_{CH3} = 2.06$ ppm, while the ^{13}C NMR showed absorptions at $\delta_C = 33.4$ ppm ($^1J_{PC} = 135.8$ Hz) and $\delta_{CH3} = 21.4$ ppm assignable to the carbon bonded to the phosphorus atom and the methyl group. Conversely, the *Z*-isomer **4a** showed clearly different absorptions, namely a doublet at $\delta_{CH2} = 2.97$ ppm ($^2J_{PH} = 23.7$ Hz) for the methylene protons as well as a high-field signal for the methyl group at $\delta_{CH3} = 2.05$ ppm, while in the ^{13}C NMR the methylene group resonates at $\delta_C = 29.2$ ppm ($^1J_{PC} = 133.9$ Hz) and the absorption of the methyl group is shifted to a lower field ($\delta_{CH3} = 21.5$ ppm) relative to that of the *E*-isomer.

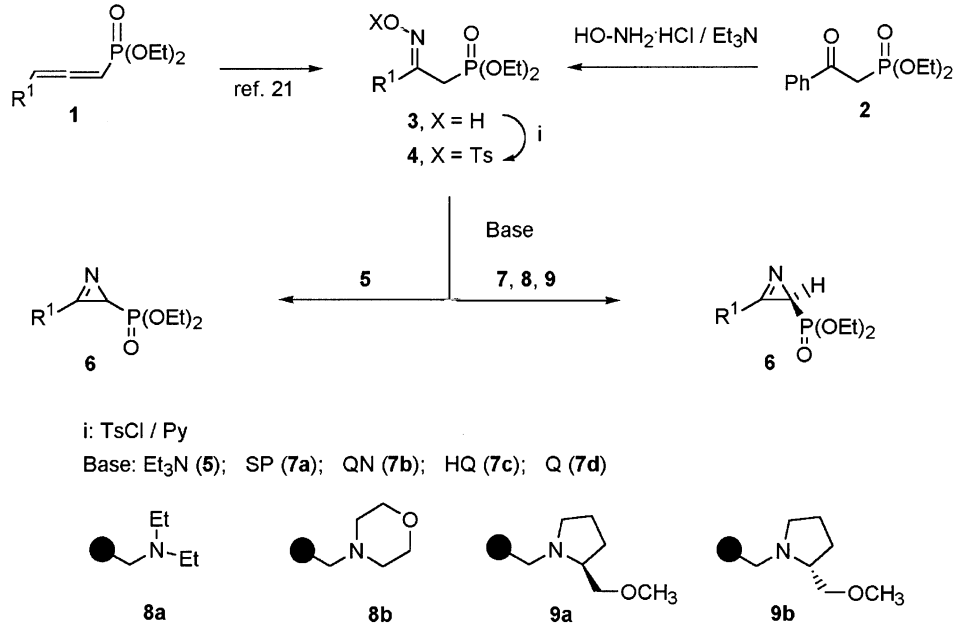
The base-mediated modified Neber reaction[22] of *p*-toluenesulfonyl oximes was explored. 2-Methyl-2*H*-azirine phosphonate **6a** ($R^1 = CH_3$) was generated regioselectively and good yield by treatment of β-ketoxime **4a** ($R^1 = CH_3$, X = Ts), with triethylamine **5** (see Scheme 2, Table 1, entry 1). Spectroscopic data were in agreement with the assigned structure of compound **6a**. Mass spectrometry of **6a** showed the molecular ion peak, while in the ^{31}P NMR spectrum the phosphonate group resonated at $\delta_P = 23.1$ ppm. The ^1H and ^{13}C NMR spectra showed well-resolved doublets at $\delta = 1.72$ ppm ($^2J_{PH} = 39.3$ Hz) for the hydrogen directly bonded to the phosphonate group, and at $\delta_C = 22.5$ ppm ($^1J_{PC} = 214.5$ Hz) for the carbon atom directly bonded to the phosphorus (C-2). In a similar manner, 2*H*-azirine **6b** ($R^1 = C_2H_5$) was prepared from β-ketoxime **4b** ($R^1 = C_2H_5$, X = Ts) and triethylamine (see Scheme 2, Table 1, entry 2). Nevertheless, the preparation of *p*-toluenesulfonyloxime **4c** ($R^1 = C_6H_5$, X = Ts) was accomplished in a simple two-step procedure involving the condensation of hydroxylamine with β-keto-phosphonate **2** and subsequent reaction of functionalized β-oxime **3c** ($R^1 = C_6H_5$, X = H) with *p*-toluenesulfonyl chloride in pyridine. Compound **4c** was only isolated as the *E*-isomer **4c**. 3-Aryl-2*H*-azirine **6c** ($R^1 = C_6H_5$) was obtained from functionalized β-ketoxime **4c**. Treatment of this oxime **4c** with triethylamine **5** led to the formation of diethyl 3-aryl-2*H*-azirine-2-phosphonate **6c** ($R^1 = C_6H_5$), (see Scheme 2, Table 1, entry 3).

This process can also be extended to the asymmetric synthesis of 2*H*-azirines **6** (ee 2–72%)[23] when chiral bases **7** are used. Firstly, a mixture of both isomers *E*- and *Z*-*p*-toluenesulfonyloximes **4** was used. Alkaloids such as sparteine (SP) **7a**, quinidine (QN) **7b**, hydroquinidine (HQ) **7c** or quinine (Q) **7d** were used in



Scheme 1.

a stoichiometric fashion (see Scheme 2, Table 1, entries 4–13) and good results were also obtained with substoichiometric amounts of quinidine **7b** (0.05–0.25 equiv.) in the presence of potassium carbonate (5–10 equiv.) and at high dilution (see Scheme 2, Table 1, entries 14–19). The use of only one isomer, either *E*- or *Z*-*p*-toluenesulfonyl oxime **4a**, did not increase the enantioselectivity of the process, whereas a positive nonlinear effect, (+)-NLE, was found when employing quinidine/quinine mixtures of known composition.[24] The absolute configuration of azirines **6a**,**b** was established by reduction to aziridines and ring opening leading to the formation of the known optically active α- and β-amino phosphonates (see later) and in the case of 3-phenyl-2*H*-azirine phosphonate **6c** by correlation with optically active azirine.[19b] From a synthetic point



Scheme 2.

Table 1. Synthesis of 2*H*-azirine phosphonates **6**

Entry	Compound	Base	Dilution	R^1	Yield (%)[a]	Ee[b]
1	**6a**	**5**	1/5	CH_3	70	–
2	**6b**	**5**	1/5	C_2H_5	79	–
3	**6c**	**5**	1/5	C_6H_5	69	–
4	**6a**	**7a**	1/5	CH_3	87	2 (*S*)
5	**6a**	**7b**	1/5	CH_3	94	20 (*S*)
6	**6a**	**7c**	1/5	CH_3	97	11 (*S*)
7	**6a**	**7d**	1/5	CH_3	93	8 (*R*)
8	**6b**	**7b**	1/5	C_2H_5	95	24 (*S*)
9	**6b**	**7c**	1/5	C_2H_5	92	22 (*S*)
10	**6b**	**7d**	1/5	C_2H_5	94	10 (*R*)
11	**6c**	**7b**	1/5	C_6H_5	85	65 (*S*)
12	**6c**	**7c**	1/5	C_6H_5	81	53 (*S*)
13	**6c**	**7d**	1/5	C_6H_5	79	39 (*R*)
14	**6a**	**7b**	1/10	CH_3	84	33 (*S*)
15	**6a**	**7b**	1/20	CH_3	72	42 (*S*)
16	**6a**	**7b**	1/20	CH_3	69[c], 63[d]	37 (*S*), 2 (*S*)
17	**6c**	**7b**	1/20	C_6H_5	77	72 (*S*)
18	**6c**	**7b**	1/100	C_6H_5	77	63 (*S*)
19	**6c**	**7b**	1/20	C_6H_5	69[e]	66 (*S*)
20	**6c**	**7b**	1/20	C_6H_5	49[f]	69 (*S*)

[a] Yield of isolated purified compound **6**.
[b] Ee was determined by HPLC on a chiral stationary phase.
[c] Yield of isolated compound **6a** using 0.25 equiv. of **7b** and 10 equiv. of K_2CO_3.
[d] Yield of isolated compound **6a** using 0.1 equiv. of **7b** and 5 equiv. of K_2CO_3 in a 'one-pot' reaction from oxime **3a**.
[e] Yield of isolated compound **6c** using 0.25 equiv. of **7b** and 5 equiv. of K_2CO_3.
[f] Yield of isolated compound **6c** using 0.05 equiv. of **7b** and 5 equiv. of K_2CO_3 in a 'one-pot' reaction from oxime **3c**.

of view, it is noteworthy that azirines **6** can also be prepared from oximes **3c** ($R^1 = C_6H_5$, X = H), when they are treated with *p*-toluenesulfonyl chloride in the presence of amine **5** (see Scheme 2, Table 1, entries 16 and 20).

We next wished to explore whether these heterocycles **6** could also be prepared in solid-phase by using an amine-supported resin,[26] since new polymer-supported reagents have attracted growing interest because they can provide attractive and practical methods for combinatorial chemistry and solid-phase synthesis for the preparation of heterocycles and small molecules.[27,28] 2*H*-Azirines **6** were generated regioselectively in good yield by treatment of β-ketoximes **4** with polymer-supported amines derived from diethylamine **8a** and morpholine **8b** in benzene at 50°C (see Scheme 2, Table 2, entries 1–3). Amine-supported resins **8a**,**b** can be recovered after handling of the resins with triethylamine. This process can also be extended to the solid-phase asymmetric synthesis of 2*H*-azirines **6** when chiral polymer-supported bases derived from (*S*)-(+)-**9a** and (*R*)-(−)-(methoxymethyl)-pyrrolidine **9b** are used. These chiral polymer-supported amines **9a**,**b** were used as chiral bases in the modified Neber reaction of *p*-toluenesulfonyl oximes **4**, in a similar manner to that reported before for achiral amine resins **8a**,**b** to give enantiomerically enriched 2*H*-azirines **6** (ee 3–15%)[23] (Scheme 2, Table 2, entries 4–8). The synthetic use of the enantiomerically enriched 2*H*-azirine phosphonates **6** was then studied.

2.2. Reduction of azirines 6. Synthesis of aziridine phosphonates 10 and α- 13, 15 and β-aminophosphonates 12, 14

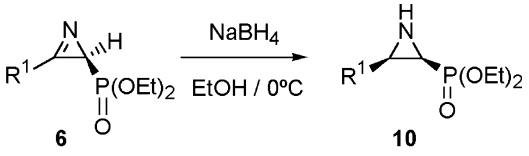
Reduction of the N–C double bond of azirines can be achieved with hydrides,[1a,17] and in our case this reaction could have two applications. On one hand, the process could represent a new entry to enantiomerically enriched aziridine phosphonates; and on the other hand, the reduction of azirines followed by ring opening could be used for the determination of the absolute configuration of azirines **6**. For this reason, we explored the reduction of azirines. Reduction of enantiomerically enriched azirine phosphonates **6** with sodium borohydride in ethanol led exclusively to the formation of *cis*-aziridines containing a phosphonate group in the 2-position **10** in very good yields (Scheme 3, Table 3, entries 1–3). No trace of the *trans*-aziridine could be observed by ^{31}P NMR. The stereochemical assignment was based on the large ring proton coupling constant observed for **10a** ($R^1 = CH_3$, $^3J_{HH} = 6.1$ Hz), while in the case of *trans*-isomers a lower coupling constant has been reported ($^3J_{HH} = 2.3$–4.0 Hz).[4e,17]

Furthermore, no loss of chirality was observed. The exclusive formation of *cis*-aziridines **10** suggests that, due to the high exocyclic dihedral angle of the sp^3 hybridized saturated carbon and the presence of the bulky phosphorus group, the approach of the hydride to the imine carbon–nitrogen double bond of the cyclic compound from behind the plane is more favourable than from the opposite face of the imine group.

Table 2. Solid-phase synthesis of 2*H*-azirine phosphonates **6**

Entry	Compound	Base	R^1	Yield (%)[a]	Ee[b]
1	**6b**	**8a**	C_2H_5	87	–
2	**6a**	**8a**	CH_3	47[c], 82[d]	–
3	**6b**	**8b**	C_2H_5	98[d]	–
4	**6a**	**9a**	CH_3	83[d]	7 (*S*)
5	**6b**	**9a**	C_2H_5	50	15 (*R*)
6	**6b**	**9b**	C_2H_5	43	11 (*S*)
7	**6c**	**9a**	C_6H_5	60	3 (*S*)
8	**6c**	**9b**	C_6H_5	88	8 (*R*)

[a] Yield of isolated purified compound **6**.
[b] Ee was determined by HPLC on a chiral stationary phase.
[c] Carried out with polymer-supported amine **8a** recycled after use in entry 1.
[d] Yield of compound **6** based on recovered starting tosyloxime.



Scheme 3.

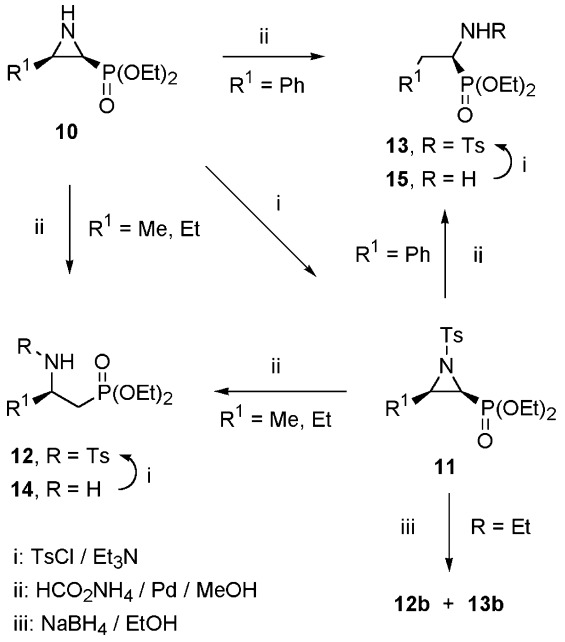
Table 3. Aziridines **10** and tosyl aziridines **11**

Entry	Compound	R^1	Yield (%)[a]
1	**10a**	CH_3	81
2	**10b**	C_2H_5	82
3	**10c**	C_6H_5	91
4	**11a**	CH_3	80
5	**11b**	C_2H_5	85
6	**11c**	C_6H_5	84

[a] Yield of isolated purified compounds **10** and **11**.

Ring opening of the aziridines was then studied to ascertain whether these substrates could be useful synthons for the preparation of aminophosphonates. Racemic and enantiomerically enriched *cis* 3-alkyl-2*H*-aziridine-2-phosphonate **10a** ($R^1 = CH_3$) and **10b** ($R^1 = C_2H_5$) were treated with sodium borohydride in refluxing ethanol, but the starting aziridines **10a**,**b** were recovered unchanged. The aziridines were then substituted with a *p*-toluenesulfonyl group at the nitrogen atom in order to increase their reactivity.[3] Thus, the reaction of inactive and optically active *cis*-aziridine phosphonates **10** with *p*-toluenesulfonyl chloride in dichloromethane at room temperature in the presence of triethylamine led to the formation of racemic and enantiomerically enriched *N*-*p*-toluenesulfonyl-*cis*-aziridine phosphonates **11** in excellent yields (Scheme 4, Table 3, entries 4–6).

Ring opening of these aziridines **11** with sodium borohydride was studied. Treatment of enantiomerically enriched (+)-(2*S*,3*R*)-*cis*-*N*-*p*-toluenesulfonyl-2*H*-aziridine phosphonate **11b** ($R^1 = C_2H_5$, ee 24%, $[\alpha]_D^{20}$:



Scheme 4.

+2.4, *c* 1.00, CH_2Cl_2) with sodium borohydride in refluxing ethanol led to the formation of a mixture (1:1) of both (+)-(*R*)-*N*-*p*-toluenesulfonyl β-amino phosphonate **12b** ($R^1=C_2H_5$, ee 24%, $[\alpha]_D^{20}$ +3.9, *c* 0.38, CH_3OH)[29] and (−)-(*S*)-*N*-*p*-toluenesulfonyl α-amino phosphonate **13b** ($R^1=C_2H_5$, ee 24%, $[\alpha]_D^{20}$ −0.8, *c* 0.24, CH_3OH)[30] (Scheme 4, Table 4, entry 3). Spectroscopic data were in agreement with the assigned structure of compounds **12b** and **13b**. The formation of both aminophosphonates **12b** and **13b** could be explained by ring opening of both N–C2 and N–C3 single bonds of the aziridine **11b**.

We next explored the regioselective ring opening of aziridines **11** in order to obtain *N*-protected α- **12** and β-amino phosphonates **13**. Hydrogenolysis of *N*-substituted aziridines **11** was studied with different reducing agents and the best results were observed by catalytic transfer hydrogenation with palladium.[31–33] Reduction of enantiomerically enriched (+)-(2*S*,3*R*)-3-alkyl-*N*-substituted aziridines **11a** ($R^1=CH_3$) and **11b** ($R^1=C_2H_5$) with ammonium formate and palladium on carbon in refluxing methanol (2 h) gave optically active (+)-(*R*)-*N*-*p*-toluenesulfonyl β-amino phosphonates **12a** ($R^1=CH_3$) and **12b** ($R^1=C_2H_5$) in good yields and retention of configuration at the stereogenic center (Scheme 4, Table 4, entries 1 and 2). The formation of these compounds **12a**,**b** in the case of alkyl substituted aziridines **11** could be explained by regioselective ring opening of the N–C2 single bond of the ring. The configuration of β-amino phosphonates **12** was correlated with enantiomerically pure β-amino phosphonates prepared by the Karanewsky method from α-amino alcohols.[29] In addition, this correlation allowed us to establish the absolute configuration of azirines **6** and aziridines **10** and **11**.

However, in a similar manner to that reported for racemic aziridine phosphonates with aryl substituents in the 2-position,[32b] a different behaviour was observed in the case of the ring opening of enantiomerically enriched (−)-(2*S*,3*R*)-3-phenyl-*N*-substituted aziridine **11c** ($R^1=C_6H_5$) by catalytic transfer hydrogenation with ammonium formate and palladium on carbon, to afford optically active (+)-(*S*)-*N*-*p*-toluenesulfonyl α-amino phosphonate **13c** ($R^1=C_6H_5$) in good yield (Scheme 4, Table 4, entry 4), through selective cleavage of the N–C3 bond of aziridine **11c**. Regioselective reductive opening of *N*-tosyl-aziridine carboxylates containing aryl and alkyl substitutes in the 2-position to give α- and β-*N*-tosylamino carboxylates has also been reported.[35]

Table 4. Tosyl β-aminophosphonates **12**, tosyl α-aminophosphonates **13**, β-aminophosphonates **14** and α-aminophosphonate **15**[a]

Entry	Compound	R^1	Yield (%)
1	**12a**	CH_3	74
2	**12b**	C_2H_5	76
3	**13b**	C_2H_5	34[b]
4	**13c**	C_6H_5	89
5	**14a**	CH_3	66
6	**14b**	C_2H_5	81
7	**15c**	C_6H_5	72

[a] Yield of isolated purified compounds **12**, **13**, **14** and **15**.
[b] Yield of isolated compound **13b** obtained as a mixture of **12b** and **13b** after ring opening of aziridine **11b** with sodium borohydride.

Finally, the regioselective ring opening of aziridines **11** was extended to the less reactive *N*-unsubstituted aziridines derived from phosphonates **10** in order to obtain *N*-unprotected β-**14** and α-amino phosphonates **15**. Catalytic transfer hydrogenation in the presence of Pd(0)/C and ammonium formate of enantiomerically enriched (+)-(2*S*,3*R*)-3-alkyl-*N*-substituted aziridines **10a** ($R^1=CH_3$) and **10b** ($R^1=C_2H_5$) gave optically active (+)-(*R*)-β-amino phosphonates **14a** ($R^1=CH_3$) and **14b** ($R^1=C_2H_5$) in good yields (Scheme 4, Table 4, entries 5 and 6). The configuration of these β-amino phosphonates **14a**,**b** was established by reaction with *p*-toluenesulfonyl chloride in the presence of pyridine (0°C), and correlation of the corresponding *N*-tosylated compounds **12a**,**b** with enantiomerically pure compounds.[29] In a similar manner to that reported before, when aziridine **10c** ($R^1=C_6H_5$) containing an aryl substituent in the 2-position was reduced (HCO_2NH_4/Pd(0)/C), a selective cleavage of the N–C3 bond of aziridine **10c** took place to give optically active (+)-(*S*)-α-amino phosphonate **15c** ($R^1=C_6H_5$) in good yield (Scheme 4, Table 4, entry 7).

3. Conclusion

In conclusion, this account describes a simple, mild, and convenient strategy for solution- and solid-phase asymmetric synthesis of 2*H*-azirines substituted with a phosphonate group in the 2-position **6** from easily available oximes **4** and bases such as triethylamine **5**,

alkaloids **7** as well as achiral **8** and chiral polymer-bound amines **9**. These three-membered heterocycles are very useful intermediates in the formation of enantiomerically enriched *cis*-aziridine phosphonates **10** and **11**, *N*-protected **12** and **13** and *N*-unsubstituted α- and β-aminophosphonates **14** and **15**. Substituted azirines and aziridines as well as α- and β-aminophosphonates are important building blocks in organic synthesis[1,3] and in the preparation of biologically active compounds of interest in medicinal chemistry.[9–12]

4. Experimental

4.1. General

Solvents for extraction and chromatography were technical grade. All solvents used in reactions were freshly distilled from appropriate drying agents before use: CH_2Cl_2 (P_2O_5); *n*-hexane and diethyl ether (sodium benzophenone ketyl); ethyl acetate (K_2CO_3); $CHCl_3$ (P_2O_5); toluene (CaH_2); dioxane (Na, benzophenone). All other reagents were recrystallized or distilled as necessary. All reactions were performed under an atmosphere of dry nitrogen. Analytical TLC was performed with silica gel 60 F_{254} plates. Visualization was accomplished by UV light and $KMnO_4$ solution. Flash chromatography was carried out using silica gel 60 (230–400 mesh). Melting points are uncorrected. ^{1}H (300 MHz), ^{13}C (75 MHz) and ^{31}P NMR (120 MHz) spectra were recorded using tetramethylsilane (TMS) (0.00 ppm) or chloroform (7.26 ppm) as an internal reference in $CDCl_3$ or D_2O solutions for ^{1}H NMR spectra or chloroform (77.0 ppm) as an internal reference in $CDCl_3$ solutions for ^{13}C NMR, and phosphoric acid (85%) for ^{31}P NMR spectra. Chemical shifts (δ) are given in ppm; multiplicities are indicated by s (singlet), d (doublet), dd (double–doublet), t (triplet), q (quadruplet) or m (multiplet). Coupling constants *(J)* are reported in hertz. Low-resolution mass spectra (MS) were obtained at 50–70 eV by electron impact (EI) or chemical ionization (CI). Data are reported in the form *m*/*z* (intensity relative to base = 100). Infrared spectra (IR) were taken on a IRFT spectrometer, and were obtained as solids in KBr or as neat oils in NaCl. Peaks are reported in cm^{-1}. $[\alpha]_D^{20}$ were taken on a polarimeter using a Na/HaI lamp. Enantiomeric ratios were determined by HPLC with Daicel Chiralpak AD-H (4.6×250 mm) at 25°C using MS detection by chemical ionization (CI). Oximes **3a**,**b**, **4a**,**b**,[17,21] and polymer-supported amines **9a**,**b**[18a] were synthesized according to literature procedures.

4.2. Diethyl (2-hydroxyimino-2-phenylethyl)phosphonate, 3c

To an ice-bath cooled solution of ketone **2** (1.28 g, 5 mmol) in $CHCl_3$ (15 mL), there was added $NH_2OH{\cdot}HCl$ (0.42 g, 6 mmol) and then Et_3N (0.83 mL, 6 mmol) under a nitrogen atmosphere. The mixture was stirred 20 h at rt, washed three times with HCl 1N, once with water and extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under vacuum. The crude mixture was purified by flash chromatography (SiO_2 in 2:1 hexane/AcOEt) to yield oxime **3c** (1.00 g, 74%) as *E*/*Z* mixture in 95:5 ratio. Pale yellow oil. ^{1}H NMR: δ 8.26 (s, 1H, OH), 7.67–7.64 (m, 2H, H-arom), 7.32–7.26 (m, 3H, H-arom), 4.01 (m, 4H, OCH_2), 3.46 (d, $^2J_{PH}$ = 23.6 Hz, 2H, CH_2-P, *E*-isomer), 3.42 (d, $^2J_{PH}$ = 23.5 Hz, 2H, CH_2-P, *Z*-isomer), 1.15 (m, 6H, CH_3) ppm; ^{13}C NMR: δ 150.0 (d, $^2J_{PC}$ = 10.5 Hz, C=N, *Z*-isomer), 148.9 (d, $^2J_{PC}$ = 11.1 Hz, C=N, *E*-isomer), 135.1–126.2 (C-arom), 62.1 (CH_2O), 25.6 (d, $^1J_{PC}$ = 138.0 Hz, CH_2-P, *Z*-isomer), 24.6 (d, $^1J_{PC}$ = 137.0 Hz, CH_2-P, *E*-isomer), 15.8 (CH_3) ppm; ^{31}P NMR: δ 23.0 (*E*-isomer), 26.5 (*Z*-isomer) ppm; IR (NaCl): 3276, 3065, 2985, 1660, 1443, 1205, cm^{-1}; MS (CI) *m*/*z* 272 [(M^++1), 28]. Anal calcd for $C_{12}H_{18}NO_4P$: C, 53.14; H, 6.69; N, 5.16. Found: C, 53.32; H, 6.65; N, 5.19%.

4.3. Diethyl (2-phenyl-2-*p*-toluenesulfonyliminoethyl) phosphonate, 4c

To an ice-bath cooled solution of oxime **3c** (1.36 g, 5 mmol) in pyridine (2.42 mL, 30 mmol), there was added tosyl chloride (freshly recrystallized from hexane, 1.05 g, 5.5 mmol) under N_2 atmosphere, and the mixture was stirred 1–3 h at rt, washed three times with HCl 6N, once with water and extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under vacuum. The crude mixture was purified by flash chromatography (SiO_2 in 2:1 hexane/AcOEt) to yield tosyl oxime **4c** (0.74 g, 35%) as *E*-isomer. Low yield is due to Beckmann rearrangement of tosyl oxime **4c** during chromatography to yield α-phosphorylated acetylaniline. The crude product can be employed in the Neber reaction. Yellow oil. ^{1}H NMR: δ 7.86 (d, $^3J_{HH}$ = 8.4 Hz, 2H, H-arom), 7.59 (d, $^3J_{HH}$ = 8.4 Hz, 2H, H-arom), 7.39–7.26 (m, 5H, H-arom), 3.98 (m, 4H, OCH_2), 3.41 (d, $^2J_{PH}$ = 23.7 Hz, 2H, CH_2-P), 2.36 (s, 3H, CH_3), 1.12 (m, 6H, CH_3) ppm; ^{13}C NMR: δ 158.0 (d, $^2J_{PC}$ = 9.1 Hz, C=N), 145.3 (Cipso-arom), 132.4–122.9 (C-arom), 132.3 (d, $^3J_{PC}$ = 10.1 Hz, Cipso-arom), 62.9 (CH_2O), 35.6 (d, $^1J_{PC}$ = 133.0 Hz, CH_2-P), 21.5 (CH_3) 16.0 (CH_3) ppm; ^{31}P NMR: δ 20.3 ppm; IR (NaCl): 3084, 2978, 2932, 1679, 1600, 1208, cm^{-1}; MS (CI) *m*/*z* 426 [(M^++1), 17]. Anal calcd for $C_{19}H_{24}NO_6PS$: C, 53.64; H, 5.69; N, 3.29; S, 7.54. Found: C, 53.45; H, 5.72; N, 3.28; S; 7.62%.

4.4. General procedure for the synthesis of 2*H*-azirine-2-phosphonates, 6

Method A. *Stoichiometric solution synthesis*: To a solution of tosyl oxime **4** (1 mmol) in benzene (5 mL) was added amine **5** or **7** (1.1 mmol). The mixture was stirred 8 h at rt under a N_2 atmosphere, washed three times with HCl 1N and extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was evaporated. The crude mixture was purified by microdistillation or flash chromatography to yield azirines **6**. Method B. *Catalytic solution synthesis*: To a solution of tosyl oxime **4** (1 mmol) in benzene (20 mL) was added chiral amine **7** (0.05–025 mmol), and then, potassium carbonate (K_2CO_3, 5–10 mmol). The mixture was stirred 24 h at rt under a N_2 atmosphere, washed

three times with HCl 1N and extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was evaporated. The crude mixture was purified by microdistillation or flash chromatography to yield azirines **6**. Chiral amines can be recovered from aqueous layer by treatment with NaOH 2N, precipitation and filtering. Method C. *Solid-phase synthesis*: To a suspension of resin-supported amine **8a**–**b** or **9a**–**b** (ca. 0.5 mmol, 1.1 equiv.) in benzene (8.0 ml) was added tosyl oxime **4** (0.45 mmol, 1 equiv.). The mixture was shaken at 50°C for 5 to 6 days under a N_2 atmosphere after which time the polymer was filtered and washed with CH_2Cl_2 (5 ml), Et_2O (5 ml), CH_2Cl_2 (5 ml) and Et_2O (5 ml). The filtrate was evaporated under vacuum. Purification of the crude product by flash-chromatography (silica gel AcOEt–hexanes 1:2) afforded 2*H*-azirines **6**. Resin-supported amines **8a**–**b** and **9a**–**b** were recovered by washing successively with MeOH, TEA, CH_2Cl_2, MeOH, TEA, CH_2Cl_2, MeOH, TEA, and CH_2Cl_2.

4.4.1. Diethyl (3-methyl-2*H*-azirin-2-yl)phosphonate, 6a. (A) Prepared as described in the general procedure (method A), 133.7 mg (70%) was obtained as a colorless oil from tosyl oxime **4a** and amine **5**. Purified by microdistillation. bp = 90–95°C at 10^{-2} mmHg. (B) As described in the general procedure (method C), 70.5 mg (82%) was obtained from tosyl oxime **4a** and recovered resin-supported amine **8a**. See Ref. 16a for spectroscopic data.

4.4.2. Diethyl (3-ethyl-2*H*-azirin-2-yl)phosphonate, 6b. (A) Prepared as described in the general procedure (method A), 162.0 mg (79%) was obtained as a colorless oil from tosyl oxime **4b** and amine **5**. Purified by microdistillation. bp = 95–100°C at 10^{-2} mmHg. (B) As described in the general procedure (method C), 80.3 mg (87%) was obtained from tosyl oxime **4b** and resin-supported amine **8a**. (C) As described in the general procedure (method C), 90.4 mg (98%) was obtained from tosyl oxime **4b** and resin-supported amine **8b**. ^{1}H NMR: δ 4.09 (m, 4H, OCH_2), 2.82 (q, $^3J_{HH}$ = 7.5 Hz, 2H, CH_2), 1.72 (d, $^2J_{PH}$ = 39.4 Hz, 1H, CH-P), 1.29 (m, 9H, CH_3) ppm; ^{13}C NMR: δ 164.7 (d, $^2J_{PC}$ = 3.5 Hz, C=N), 61.6 (CH_2O), 21.9 (d, $^1J_{PC}$ = 214.5 Hz, CH-P), 20.5 (CH_2), 15.8 (d, $^3J_{PC}$ = 2.0 Hz, CH_3), 7.8 (CH_3) ppm; ^{31}P NMR: δ 23.2 ppm; IR (NaCl): 2998, 1785, 1646, 1241, 1043 cm^{-1}; MS (EI) *m*/*z* 206 [(M^++1), 4]. Anal calcd for $C_8H_{16}NO_3P$: C, 46.83: H, 7.86; N, 6.83. Found: C, 46.77: H, 7.88; N, 6.85%.

4.4.3. Diethyl (3-phenyl-2*H*-azirin-2-yl)phosphonate, 6c. Prepared as described in the general procedure (method A), 174.6 mg (69%) was obtained as an oil from tosyl oxime **4c** and amine **5**. Purified by flash-chromatography (SiO_2 in 2:1 hexane/AcOEt). ^{1}H NMR: δ 7.90–7.87 (m, 2H, H-arom), 7.59–7.52 (m, 3H, H-arom), 4.19–4.02 (m, 4H, OCH_2), 2.11 (d, $^2J_{PH}$ = 39.1 Hz, 1H, CH-P), 1.31 (m, 3H, CH_3) 1.22 (m, 3H, CH_3) ppm; ^{13}C NMR: δ 160.6 (d, $^2J_{PC}$ = 4.0 Hz, C=N), 133.9–129.3 (m, C-arom), 62.5 (CH_2O), 62.3 (CH_2O), 23.9 (d, $^1J_{PC}$ = 214.0 Hz, CH-P), 16.2 (CH_3) ppm; ^{31}P NMR: δ 22.4 ppm; IR (NaCl): 3058, 1765, 1692, 1261, 1036 cm^{-1}; MS (EI) *m*/*z* 253 (M^+, 4). Anal. calcd for $C_{12}H_{16}NO_3P$: C, 56.92; H, 6.37; N, 5.53. Found: C, 56.77; H, 6.36; N, 5.52%.

4.4.4. Diethyl (−)-(*S*)-(3-methyl-2*H*-azirin-2-yl)phosphonate, 6a. (A) Prepared as described in the general procedure (method A), 166.2 mg (87%) was obtained from tosyl oxime **4a** and amine **7a**, ee 2%; $[\alpha]_D^{20}$ −2.0 (*c* 0.75, CH_2Cl_2). (B) As described in the general procedure (method A), 179.5 mg (94%) was obtained from tosyl oxime **4a** and amine **7b**, ee 20%; $[\alpha]_D^{20}$ −18.8 (*c* 0.75, CH_2Cl_2). (C) As described in the general procedure (method A), 185.3 mg (97%) was obtained from tosyl oxime **4a** and amine **7c**, ee 11%; $[\alpha]_D^{20}$ −10.6 (*c* 1.10, CH_2Cl_2). (D) As described in the general procedure (method A), 160.4 mg (84%) was obtained from tosyl oxime **4a** and amine **7b** using a dilution of 1:10, ee 33%; $[\alpha]_D^{20}$ −31.0 (*c* 0.85, CH_2Cl_2). (E) As described in the general procedure (method A), 137.5 mg (72%) was obtained from tosyl oxime **4a** and amine **7b** using a dilution of 1:20, ee 42%; $[\alpha]_D^{20}$ −39.2 (*c* 1.23, CH_2Cl_2). (F) As described in the general procedure (method B), 131.8 mg (69%) was obtained from tosyl oxime **4a** and amine **7b**, ee 37%; $[\alpha]_D^{20}$ −34.8 (*c* 0.89, CH_2Cl_2). (G) As described in the general procedure (method B), 120.3 mg (63%) was obtained in a one pot reaction from oxime **3a** and amine **7b**, ee 2%; $[\alpha]_D^{20}$ −1.6 (*c* 0.90, CH_2Cl_2). (H) As described in the general procedure (method C), 71.3 mg (83%) was obtained from tosyl oxime **4a** and resin-supported amine **9a**, ee 7%; $[\alpha]_D^{20}$ −2.9 (*c* 0.66, CH_2Cl_2).

4.4.5. Diethyl (+)-(*R*)-(3-methyl-2*H*-azirin-2-yl)phosphonate, 6a. (A) Prepared as described in the general procedure (method A), 177.6 mg (93%) was obtained from tosyl oxime **4a** and amine **7d**, ee 8%; $[\alpha]_D^{20}$ +7.7 (*c* 1.20, CH_2Cl_2).

4.4.6. Diethyl (+)-(*R*)-(3-ethyl-2*H*-azirin-2-yl)phosphonate, 6b. (A) Prepared as described in the general procedure (method A), 192.7 mg (94%) was obtained from tosyl oxime **4b** and amine **7d**, ee 10%; $[\alpha]_D^{20}$ +11.1 (*c* 0.80, CH_2Cl_2). (B) As described in the general procedure (method C), 46.1 mg (50%) was obtained from oxime **4b** and resin-supported amine **9a**, ee 15%; $[\alpha]_D^{20}$ +2.5 (*c* 0.40, CH_2Cl_2).

4.4.7. Diethyl (−)-(*S*)-(3-ethyl-2*H*-azirin-2-yl)phosphonate, 6b. (A) Prepared as described in the general procedure (method A), 194.8 mg (95%) was obtained from tosyl oxime **4b** and amine **7b**, ee 24%; $[\alpha]_D^{20}$ −27.1 (*c* 0.75, CH_2Cl_2). (B) As described in the general procedure (method A), 188.6 mg (92%) was obtained from tosyl oxime **4b** and amine **7c**, ee 22%; $[\alpha]_D^{20}$ −23.9 (*c* 0.75, CH_2Cl_2). (C) As described in the general procedure (method C), 39.7 mg (43%) was obtained from tosyl oxime **4b** and resin-supported amine **9b**, ee 11%; $[\alpha]_D^{20}$ −4.0 (*c* 0.40, CH_2Cl_2).

4.4.8. Diethyl (−)-(*S*)-(3-phenyl-2*H*-azirin-2-yl)phosphonate, 6c. (A) Prepared as described in the general procedure (method A), 215.1 mg (85%) was obtained from tosyl oxime **4c** and amine **7b**, ee 65%;

$[\alpha]_D^{20}$ −132.1 (*c* 0.70, CH_2Cl_2). (B) As described in the general procedure (method A), 204.9 mg (81%) was obtained from tosyl oxime **4c** and amine **7c**, ee 53%; $[\alpha]_D^{20}$ −107.0 (*c* 0.30, CH_2Cl_2). (C) As described in the general procedure (method A), 194.8 mg (77%) was obtained from tosyl oxime **4c** and amine **7b** using a dilution of 1:20, ee 72%; $[\alpha]_D^{20}$ −144.4 (*c* 0.70, CH_2Cl_2). (D) As described in the general procedure (method A), 194.8 mg (77%) was obtained from tosyl oxime **4c** and amine **7b** using a dilution of 1:100, ee 63%; $[\alpha]_D^{20}$ −127.1 (*c* 0.68, CH_2Cl_2). (E) As described in the general procedure (method B), 174.6 mg (69%) was obtained from tosyl oxime **4c** and amine **7b**, ee 66%; $[\alpha]_D^{20}$ −132.3 (*c* 0.92, CH_2Cl_2). (F) As described in the general procedure (method B), 124.0 mg (49%) was obtained in a one pot reaction from oxime **3c** and amine **7b**, ee 69%; $[\alpha]_D^{20}$ −138.3 (*c* 1.10, CH_2Cl_2). (G) As described in the general procedure (method C), 68.3 mg (60%) was obtained from tosyl oxime **4c** and resin-supported amine **9a**, ee 3%; $[\alpha]_D^{20}$ −9.4 (*c* 0.53, CH_2Cl_2).

4.4.9. Diethyl (+)-(*R*)-(3-phenyl-2*H*-azirin-2-yl)phosphonate, 6c. (A) As described in the general procedure (method A), 199.9 mg (79%) was obtained from tosyl oxime **4c** and amine **7d**, ee 39%; $[\alpha]_D^{20}$ +79.0 (*c* 1.20, CH_2Cl_2). (B) As described in the general procedure (method C), 100.2 mg (88%) was obtained from oxime **4c** and resin-supported amine **9b**, ee 8%; $[\alpha]_D^{20}$ +6.0 (*c* 0.50, CH_2Cl_2).

4.5. General procedure for reduction of azirines 6 to aziridines 10

To an ice-bath cooled solution of azirine **6** (1 mmol) in EtOH (5 mL), was added $NaBH_4$ (0.12 g, 3 mmol) under a N_2 atmosphere. After 1–2 h, was added CH_2Cl_2, and the reaction mixture was washed three times with water. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was evaporated. The crude mixture was purified by flash chromatography to yield aziridines **10**.

4.5.1. Diethyl (3-methyl-aziridin-2-yl)phosphonate, 10a. Prepared according to the general procedure from azirine **6a** (0.192 g) to yield aziridine **10a** (0.156 g, 81% yield). Purified by flash-chromatography (SiO_2 in AcOEt and 9:1 AcOEt/MeOH). Colorless oil. ^{1}H NMR: δ 4.10 (m, 4H, OCH_2), 2.26 (dq, $^3J_{HH}=6.1$ Hz, $^3J_{HH}=5.8$ Hz, 1H, CH), 1.85 (dd, $^2J_{PH}=15.2$ Hz, $^3J_{HH}=6.1$ Hz, 1H, CH-P), 1.54 (s, 1H, NH), 1.42 (d, $^3J_{HH}=5.8$ Hz, 3H, CH_3), 1.29 (m, 6H, CH_3) ppm; ^{13}C NMR: δ 61.8 (CH_2O), 31.2 (d, $^2J_{PC}=2.5$ Hz, CH), 28.1 (d, $^1J_{PC}=199.4$ Hz, CH-P), 16.1 (CH_3), 14.4 (d, $^3J_{PC}=2.5$ Hz, CH_3) ppm; ^{31}P NMR: δ 25.5 ppm; IR (NaCl): 3433, 3271, 2985, 1659, 1248, 1056, 1024 cm^{-1}; MS (EI) *m*/*z* 194 [(M^++1), 3]. Anal calcd for $C_7H_{16}NO_3P$: C, 43.52: H, 8.35; N, 7.25. Found: C, 43.41; H, 8.37; N, 7.23%.

4.5.2. Diethyl (+)-(2*S*,3*R*)-(3-methyl-aziridin-2-yl)phosphonate, 10a. Prepared according to the general procedure from enantiomerically enriched (ee 20%) azirine (−)-(*S*)-**6a**. ee 20%; $[\alpha]_D^{20}$ +7.9 (*c* 0.75, CH_2Cl_2).

4.5.3. Diethyl (3-ethyl-aziridin-2-yl) phosphonate, 10b. Prepared according to the general procedure from azirine **6b** (0.210 g) to yield aziridine **10b** (0.182 g, 88% yield). Purified by flash-chromatography (SiO_2 in AcOEt and 9:1 AcOEt/MeOH). Colorless oil. ^{1}H NMR: δ 4.09 (m, 4H, OCH_2), 2.15 (dt, $^3J_{HH}=6.0$ Hz, $^3J_{HH}=6.1$ Hz, 1H, CH), 1.90 (dd, $^2J_{PH}=15.1$ Hz, $^3J_{HH}=6.0$ Hz, 1H, CH-P), 1.72 (dq, $^3J_{HH}=7.3$ Hz, $^3J_{HH}=6.1$ Hz, 2H, CH_2), 1.34 (s, 1H, NH), 1.29 (m, 6H, CH_3), 1.03 (t, $^3J_{HH}=7.3$ Hz, 3H, CH_3) ppm; ^{13}C NMR: δ 61.8 (CH_2O), 37.8 (CH), 28.0 (d, $^1J_{PC}=201.4$ Hz, CH-P), 22.4 (d, $^3J_{PC}=2.5$ Hz, CH_2) 16.0 (CH_3), 11.7 (CH_3) ppm; ^{31}P NMR: δ 25.6 ppm; IR (NaCl): 3462, 3270, 2992, 1659, 1241, 1043, 1024 cm^{-1}; MS (EI) *m*/*z* 208 [(M^++1), 2]. Anal calcd for $C_8H_{18}NO_3P$: C, 46.37; H, 8.76; N, 6.76. Found: C, 46.54; H, 8.75; N, 6.78%.

4.5.4. Diethyl (+)-(2*S*,3*R*)-(3-ethyl-aziridin-2-yl)phosphonate, 10b. Prepared according to the general procedure from enantiomerically enriched (ee 24%) azirine (−)-(*S*)-**6b**. ee 24%; $[\alpha]_D^{20}$ +0.8 (*c* 0.74, CH_2Cl_2).

4.5.5. Diethyl (3-phenyl-aziridin-2-yl)phosphonate, 10c. Prepared according to the general procedure from azirine **6c** (0.254 g) to yield aziridine **10c** (0.214 g, 84% yield). Purified by flash chromatography (SiO_2 in AcOEt and 9:1 AcOEt/MeOH). Pale green-yellow oil. ^{1}H NMR: δ 7.41–7.16 (m, 5H, H-arom), 3.83–3.71 (m, 3H, OCH_2), 3.57–3.42 (m, 2H, CH, OCH_2), 2.31 (dd, $^2J_{PH}=17.9$ Hz, $^3J_{HH}=6.5$ Hz, 1H, CH-P), 1.62 (s, 1H, NH), 1.08 (m, 6H, CH_3) ppm; ^{13}C NMR: δ 128.7–125.4 (C-arom), 61.9 (CH_2O), 61.5 (CH_2O), 37.6 (CH), 31.4 (d, $^1J_{PC}=208.0$ Hz, CH-P), 16.1 (CH_3), ppm; ^{31}P NMR: δ 22.5 ppm; IR (NaCl): 3441, 3270, 3065, 2985, 1659, 1252, 1052, 1022 cm^{-1}; MS (EI) *m*/*z* 256 [(M^++1), 2]. Anal calcd for $C_{12}H_{18}NO_3P$: C, 56.47; H, 7.11; N, 5.49. Found: C, 56.62; H, 7.09; N, 5.48%.

4.5.6. Diethyl (−)-(2*S*,3*R*)-(3-phenyl-aziridin-2-yl)phosphonate, 10c. Prepared according to the general procedure from enantiomerically enriched (ee 65%) azirine (−)-(*S*)-**6c**. ee 65%; $[\alpha]_D^{20}$ −22.6 (*c* 0.62, CH_2Cl_2).

4.6. General procedure for the synthesis of tosyl aziridines 11

To an ice-bath cooled solution of aziridine **10** (1 mmol) in CH_2Cl_2 was added, under a N_2 atmosphere, tosyl chloride (freshly recrystallized from hexane, 0.23 g, 1.2 mmol), and then Et_3N (0.17 mL, 1.2 mmol). The mixture was stirred 3–4 h at rt, washed three times with HCl 1N, once with water and extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was evaporated. The crude mixture was purified by flash chromatography to yield tosyl aziridines **10**.

4.6.1. Diethyl [3-methyl-1-(*p*-toluenesulfonyl)aziridin-2-yl)]phosphonate, 11a. Prepared according to the general procedure from aziridine **10a** (0.194 g) to yield aziridine **11a** (0.278 g, 80% yield). Purified by flash-chromatography (SiO_2 in hexane/AcOEt). Colorless oil. ^{1}H NMR: δ

7.78 (d, $^3J_{HH}=8.2$ Hz, 2H, H-arom), 7.29 (d, $^3J_{HH}=8.2$ Hz, 2H, H-arom), 4.14–3.80 (m, 4H, OCH_2), 2.95 (m, 1H, CH), 2.73 (dd, $^2J_{PH}=13.4$ Hz, $^3J_{HH}=7.5$ Hz, 1H, CH-P), 2.39 (s, 3H, CH_3), 1.40 (d, $^3J_{HH}=6.0$ Hz, 3H, CH_3), 1.23 (t, $^3J_{HH}=7.1$ Hz, 3H, CH_3), 1.15 (t, $^3J_{HH}=7.1$ Hz, 3H, CH_3) ppm; ^{13}C NMR: δ 144.9 (C-arom), 134.3 (C-arom), 129.6–128.1 (C-arom), 62.9 (CH_2O), 62.5 (CH_2O), 39.1 (CH), 36.5 (d, $^1J_{PC}=205.5$ Hz, CH-P), 21.5 (CH_3), 16.2 (CH_3), 16.1 (CH_3), 13.0 (CH_3) ppm; ^{31}P NMR: δ 17.0 ppm; IR (NaCl): 3065, 2936, 1613, 1396, 1163, 973 cm^{-1}; MS (EI) m/z 347 (M^+, 3). Anal calcd for $C_{14}H_{22}NO_5PS$: C, 48.41: H, 6.38; N, 4.03; S, 9.23. Found: C, 48.29; H, 6.37; N, 4.01, S, 9.30%.

4.6.2. Diethyl (+)-(2*S*,3*R*)-[3-methyl-1-(*p*-toluenesulfonyl)-aziridin-2-yl)]phosphonate, 11a. Prepared according to the general procedure from enantiomerically enriched (ee 20%) aziridine (+)-(2*S*,3*R*)-**10a**. ee 20%; $[\alpha]_D^{20}$ +2.2 (*c* 0.45, CH_2Cl_2).

4.6.3. Diethyl [3-ethyl-1-(*p*-toluenesulfonyl)-aziridin-2-yl)]phosphonate, 11b. Prepared according to the general procedure from aziridine **10b** (0.194 g) to yield aziridine **11b** (0.306 g, 85% yield). Purified by flash-chromatography (SiO_2 in hexane/AcOEt). Colorless oil. ^1H NMR: δ 7.78 (d, $^3J_{HH}=8.4$ Hz, 2H, H-arom), 7.29 (d, $^3J_{HH}=8.4$ Hz, 2H, H-arom), 4.08–3.85 (m, 4H, OCH_2), 2.77 (m, $^2J_{PH}=11.8$ Hz, $^3J_{HH}=6.0$ Hz, 2H, CH-P, CH), 2.39 (s, 3H,CH_3), 1.73 (ddd, $^3J_{HH}=6.0$ Hz, $^3J_{HH}=7.3$ Hz, $^4J_{PH}=1.8$ Hz, 1H, CH) 1.24 (t, $^3J_{HH}=7.2$ Hz, 3H, CH_3), 1.17 (t, $^3J_{HH}=7.2$ Hz, 3H, CH_3), 0.82 (t, $^3J_{HH}=7.3$ Hz, 3H, CH_3) ppm; ^{13}C NMR: δ 144.9 (C-arom), 134.0 (C-arom), 130.1–128.3 (C-arom), 62.9 (CH_2O), 62.3 (CH_2O), 45.2 (CH), 36.5 (d, $^1J_{PC}=206.0$ Hz, CH-P), 21.5 (CH_3), 20.7 (CH_2) 16.2 (CH_3), 16.1 (CH_3), 14.0 (CH_3), 11.4 (CH_3) ppm; ^{31}P NMR: δ 17.1 ppm; IR (NaCl): 3070, 2936, 1611, 1397, 1165, 973 cm^{-1}; MS (EI) m/z 361 (M^+, 1). Anal calcd for $C_{15}H_{24}NO_5PS$: C, 49.85; H, 6.69; N, 3.88; S, 8.87. Found: C, 49.99; H, 6.63; N, 3.86; S, 8.94%.

4.6.4. Diethyl (+)-(2*S*,3*R*)-[3-ethyl-1-(*p*-toluenesulfonyl)-aziridin-2-yl)]phosphonate, 11b. Prepared according to the general procedure from enantiomerically enriched (ee 24%) aziridine (+)-(2*S*,3*R*)-**10b**. ee 24%; $[\alpha]_D^{20}$ +2.4 (*c* 1.00, CH_2Cl_2).

4.6.5. Diethyl [3-phenyl-1-(*p*-toluenesulfonyl)-aziridin-2-yl]phosphonate, 11c. Prepared according to the general procedure from aziridine **10c** (0.255 g) to yield aziridine **11c** (0.343 g, 84% yield). Purified by flash-chromatography (SiO_2 in hexane/AcOEt). Pale green-yellow oil. ^1H NMR: δ 7.91 (d, $^3J_{HH}=8.4$ Hz, 2H, H-arom), 7.38–7.26 (d, $^3J_{HH}=8.4$ Hz, 7H, H-arom), 4.08 (t, $^2J_{PH}=8.7$ Hz, $^3J_{HH}=8.0$ Hz 1H, CH), 3.89–3.75 (m, 3H, OCH_2), 3.54–3.45 (m, 1H, OCH_2), 2.73 (dd, $^2J_{PH}=14.5$ Hz, $^3J_{HH}=7.7$ Hz, 1H, CH-P), 2.46 (s, 3H, CH_3), 1.13 (t, $^3J_{HH}=7.6$ Hz, 3H, CH_3), 1.04 (t, $^3J_{HH}=7.0$ Hz, 3H, CH_3) ppm; ^{13}C NMR: δ 145.0 (Cipso-arom), 133.6 (Cipso-arom), 131.6 (Cipso-arom), 129.6-127.5 (C-arom), 62.3 (CH_2O), 43.9 (d, $^2J_{PC}=4.5$ Hz CH), 38.9 (d, $^1J_{PC}=206.0$ Hz, CH-P), 21.4 (CH_3), 15.8 (CH_3) ppm; ^{31}P NMR: δ 14.9 ppm; IR (NaCl): 3065, 2936, 1613, 1396, 1163, 973 cm^{-1}; MS (EI) m/z 409 (M^+, 3). Anal calcd for $C_{19}H_{24}NO_5PS$: C, 55.74; H, 5.91; N, 3.42; S, 7.83. Found: C, 55.59; H, 5.92; N, 3.44; S, 7.80%.

4.6.6. Diethyl (−)-(2*S*,3*R*)-[3-phenyl-1-(*p*-toluenesulfonyl)-aziridin-2-yl]phosphonate, 11c. Prepared according to the general procedure from enantiomerically enriched (ee 65%) aziridine (−)-(2*S*,3*R*)-**10c**. ee 65%; $[\alpha]_D^{20}$ −35.4 (*c* 0.54, CH_2Cl_2).

4.7. General procedure for the ring opening of aziridines 10 and tosyl aziridines 11

To a solution of aziridine **10**, **11** (1 mmol) in MeOH (10 mL) was added, under a N_2 atmosphere, Pd/C (20%), and then ammonium formate (10–20 mmol). The reaction mixture was kept at reflux for 1–16 h, until total consumption of the starting material (GC control). Then, NH_4OH solution (25%) was added until pH 8, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was evaporated. The crude mixture was purified by flash chromatography to yield α- and β-aminophosphonates **12**, **13**, **14** and **15**.

4.7.1. Diethyl (+)-(*R*)-[2-(*p*-toluenesulfonylamino)propyl]phosphonate, 12a. Prepared according to the general procedure from enantiomerically enriched (ee 20%) tosyl aziridine **11a** (0.348 g) to yield β-aminophosphonate **12a** (0.258 g, 74% yield). Purified by flash-chromatography (SiO_2 in AcOEt and 9:1 AcOEt/MeOH). Colorless oil. ^1H NMR: δ 7.71 (d, $^3J_{HH}=7.7$ Hz, 2H, H-arom), 7.23 (d, $^3J_{HH}=7.7$ Hz, 2H, H-arom), 5.51 (d, $^3J_{HH}=7.0$ Hz, 1H, NH), 4.07–3.83 (m, 4H, OCH_2), 3.59 (m, 1H, CH), 2.36 (s, 3H,CH_3), 1.83 (m, 2H, CH_2P), 1.18 (m, 6H, CH_3) ppm; ^{13}C NMR: δ 143.2 (C-arom), 137.9 (C-arom), 129.6 (C-arom), 127.1 (C-arom), 61.8 (CH_2O), 45.7 (d, $^2J_{PC}=4.0$ Hz, CH), 32.6 (d, $^1J_{PC}=137.5$ Hz, CH-P), 22.3 (CH_3), 21.4 (CH_3), 16.3 (CH_3) ppm; ^{31}P NMR: δ 28.1 ppm; IR (NaCl): 3170, 2983, 1589, 1162, 1025 cm^{-1}; MS (EI) m/z 349 [(M^++1), 3]. Anal calcd for $C_{14}H_{24}NO_5PS$: C, 48.13; H, 6.92; N, 4.01; S, 9.18. Found: C, 48.01; H, 6.96; N, 4.02, S; 9.27%. ee 20%; $[\alpha]_D^{20}$ +6.3 (*c* 0.24, MeOH).

4.7.2. Diethyl (+)-(*R*)-[2-(*p*-toluenesulfonylamino)-butyl]phosphonate, 12b. Prepared according to the general procedure from enantiomerically enriched (ee 24%) tosyl aziridine **11b** (0.362 g) to yield β-aminophosphonate **12b** (0.276 g, 76% yield). Purified by flash-chromatography (SiO_2 in AcOEt and 9:1 AcOEt/MeOH). Colorless oil. ^1H NMR: δ 7.70 (d, $^3J_{HH}=7.9$ Hz, 2H, H-arom), 7.22 (d, $^3J_{HH}=7.9$ Hz, 2H, H-arom), 5.61 (d, $^3J_{HH}=8.1$ Hz, 1H, NH), 4.11–3.82 (m, 4H, OCH_2), 3.39 (m, 1H, CH), 2.35 (s, 3H,CH_3), 1.92–1.70 (m, 2H, CH_2P), 1.64–1.51 (m, 2H, CH_2), 1.20 (m, 6H, CH_3), 0.75 (m, $^3J_{HH}=7.3$ Hz, 3H, CH_3) ppm; ^{13}C NMR: δ 142.9 (C-arom), 138.0 (C-arom), 129.4 (C-arom), 126.9 (C-arom), 61.5 (CH_2O), 51.1 (d, $^2J_{PC}=3.0$ Hz, CH), 29.9 (d, $^1J_{PC}=138.5$ Hz, CH-P), 28.1 (d, $^3J_{PC}=4.5$ Hz, CH_2), 21.3 (CH_3), 16.2 (CH_3), 16.1

(CH_3), 9.9 (CH_3) ppm; ^{31}P NMR: δ 28.4 ppm; IR (NaCl): 3141, 2980, 1598, 1161, 1025 cm^{-1}; MS (EI) m/z 334 [(M^+–Et), 100]. Anal calcd for $C_{15}H_{26}NO_5PS$: C, 49.57; H, 7.21; N, 3.85; S, 8.82. Found: C, 49.72; H, 7.20; N, 3.82; S, 8.89%. ee 24%; $[\alpha]_D^{20}$ +3.9 (c 0.38, MeOH).

4.7.3. Diethyl (−)-(*S*)-[1-(*p*-toluenesulfonylamino)-butyl]phosphonate, 13b. To a solution of enantiomerically enriched (ee 24%) tosyl aziridine **11b** (0.362 g, 1 mmol) in EtOH (10 mL) was added $NaBH_4$ (0.12 g, 3 mmol) and the reaction mixture was refluxed for 12 h. After this time water was added to the crude reaction and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was evaporated. The crude product containing a mixture (50:50) of β- and α-aminophosphonates **12b**, **13b** was purified by flash chromatography (SiO_2 in 1:1 hexane/AcOEt). Data for **12b**: (0.116 g, 32% yield), see spectral data in Section 4.7.2. Data for **13b**: (0.124 g, 34% yield). Pale green-yellow oil. ^1H NMR: δ 7.70 (d, $^3J_{HH}=8.1$ Hz, 2H, H-arom), 7.22 (d, $^3J_{HH}=8.1$ Hz, 2H, H-arom), 5.24 (d, $^3J_{HH}=7.8$ Hz, 1H, NH), 4.09–3.85 (m, 4H, OCH_2), 3.60 (m, 1H, CH-P), 2.35 (s, 3H, CH_3), 1.77–1.55 (m, 2H, CH_2), 1.52–1.27 (m, 2H, CH_2), 1.18 (m, 6H, CH_3), 0.73 (m, $^3J_{HH}=7.2$ Hz, 3H, CH_3) ppm; ^{13}C NMR: δ 143.2 (C-arom), 138.5 (C-arom), 129.4–126.9 (C-arom), 62.9 (CH_2O), 62.4 (CH_2O), 50.0 (d, $^1J_{PC}=157.1$ Hz, CH-P), 32.7 CH_2), 21.4 (CH_3), 18.8 (d, $^3J_{PC}=9.5$ Hz, 2H, CH_2), 16.3 (CH_3), 16.2 (CH_3), 13.6 (CH_3) ppm; ^{31}P NMR: δ 23.8 ppm; IR (NaCl): 3431, 3087, 2967, 1161, 1021 cm^{-1}; MS (EI) m/z 363 (M^+, 1). Anal calcd for $C_{15}H_{26}NO_5PS$: C, 49.57; H, 7.21; N, 3.85; S, 8.82. Found: C, 49.47; H, 7.17; N, 3.83; S, 8.77%. ee 24%; $[\alpha]_D^{20}$ −0.8 (c 0.24, MeOH).

4.7.4. Diethyl (+)-(*S*)-[2-phenyl-1-(*p*-toluenesulfonylamino)ethyl]phosphonate, 13c. Prepared according to the general procedure from enantiomerically enriched (ee 65%) tosyl aziridine **11c** (0.409 g) to yield α-aminophosphonate **13c** (0.366 g, 89% yield). Purified by flash-chromatography (SiO_2 in 1:1 hexane/AcOEt). Pale green-yellow oil. ^1H NMR: δ 7.54 (d, $^3J_{HH}=8.4$ Hz, 2H, H-arom), 7.16–7.10 (m, $^3J_{HH}=8.2$ Hz, 7H, H-arom), 5.03 (m, 1H, CH_c-P), 4.06–3.91 (m, 4H, OCH_2), 3.62 (t, $^2J_{PH}=10.8$, $^3J_{HH}=11.9$ Hz, 1H, NH), 3.12 (dt, $^2J_{PH}=14.5$ Hz, $^3J_{HaHb}=14.3$ Hz, $^3J_{HaHc}=5.7$ Hz, 1H, CH_2), 2.73 (ddd, $^2J_{PH}=12.0$ Hz, $^3J_{HaHa}=14.3$ Hz, $^3J_{HaHc}=7.3$ Hz, 1H, CH_2), 2.39 (s, 3H,CH_3), 1.23 (m, $^3J_{HH}=7.1$ Hz, 3H, CH_3), 1.15 (m, $^3J_{HH}=7.1$ Hz, 3H, CH_3) ppm; ^{13}C NMR: δ 143.1 (Cipso-arom), 138.1 (Cipso-arom), 136.2 (d,$^3J_{PC}=9.1$ Hz, Cipso-arom), 129.6–126.7 (C-arom), 63.5 (CH_2O), 62.6 (CH_2O), 51.7 (d, $^1J_{PC}=157.1$ Hz, CH-P), 36.6 (d, $^2J_{PC}=3.5$ Hz, CH_2-P), 21.4 (CH_3), 16.3 (CH_3) 16.1 (CH_3) ppm; ^{31}P NMR: δ 22.6 ppm; IR (NaCl): 3209, 3065, 2936, 1613, 1396, 1163, 973 cm^{-1}; MS (EI) m/z 411 (M^+, 1). Anal calcd for $C_{19}H_{26}NO_5PS$: C, 55.46: H, 6.37; N, 3.40; S, 7.79. Found: C, 55.58; H, 6.35; N, 3.38; S, 7.84%. ee 65%; $[\alpha]_D^{20}$ +20.0 (c 0.10, CH_2Cl_2).

4.7.5. Diethyl (+)-(*R*)-(2-aminopropyl)phosphonate, 14a. Prepared according to the general procedure from enantiomerically enriched (ee 20%) aziridine **10a** (0.193 g) to yield β-aminophosphonate **14a** (0.129 g, 66% yield). Purified by flash-chromatography (SiO_2 in AcOEt and 9:1 AcOEt/MeOH). For spectroscopic data see Ref. 36.

4.7.6. Diethyl (−)-(*R*)-(2-aminobutyl)phosphonate, 14b. Prepared according to the general procedure from enantiomerically enriched (ee 24%) aziridine **10b** (0.207 g) to yield β-aminophosphonate **14b** (0.169 g, 81% yield). Purified by flash-chromatography (SiO_2 in AcOEt and 9:1 AcOEt/MeOH). ^1H NMR: δ 4.12–3.99 (m, 4H, OCH_2), 3.10 (m, 1H, CH), 1.85 (m, 2H, CH_2-P), 1.63 (s, 2H, NH_2), 1.47 (m, 2H, CH_2), 1.31 (t, $^3J_{HH}=7.0$ Hz, 6H, CH_3), 0.95 (t, $^3J_{HH}=7.2$ Hz, 3H, CH_3) ppm; ^{13}C NMR: δ 61.5 (CH_2O), 47.8 (d, $^2J_{PC}=4.6$ Hz, CH), 32.9 (d, $^1J_{PC}=138.0$ Hz, CH_2-P), 30.9 (CH_2), 16.3 (CH_3), 10.0 (CH_3) ppm; ^{31}P NMR: δ 30.9 ppm; IR (NaCl): 3422, 2982, 1610, 1190, 1097, 985 cm^{-1}; MS (EI) m/z 209 (M^+, 19). Anal calcd for $C_8H_{20}NO_3P$: C, 45.92; H, 9.64; N, 6.69. Found: C, 45.99; H, 9.62; N, 6.70%. ee 24%; $[\alpha]_D^{20}$ −3.9 (c 0.71, CH_2Cl_2).

4.7.7. (+)-(*S*)-Diethyl [(1-amino-2-phenyl)ethyl]-phosphonate, 15c. Prepared according to the general procedure from enantiomerically enriched (ee 50%) aziridine **10c** (0.255 g) to yield α-aminophosphonate **15c** (0.185 g, 72% yield). Purified by flash-chromatography (SiO_2 in 1:1 hexane/AcOEt and 9:1 AcOEt/MeOH). ^1H NMR: δ 7.28–7.16 (m, 5H, H-arom), 4.17–4.03 (m, 3H, OCH_2), 3.19 (m, 2H, CH_2), 2.60 (dt, $^2J_{PH}=14.0$ Hz, $^3J_{HH}=8.6$ Hz, 1H, CH-P), 1.28 (m, 8H, NH_2, CH_3) ppm; ^{13}C NMR: δ 137.9 (d, $^3J_{PC}=5.6$ Hz, Cipso-arom), 129.2–126.7 (C-arom), 62.3 (CH_2O), 50.3 (d, $^1J_{PC}=154.1$ Hz, CH-P), 37.8 (CH_2), 16.5 (CH_3), 16.4 (CH_3) ppm; ^{31}P NMR: δ 28.5 ppm; IR (NaCl): 3380, 2982, 1604, 1163 cm^{-1}; MS (EI) m/z 257 (M^+, 1). Anal calcd for $C_{12}H_{20}NO_3P$: C, 56.02: H, 7.84; N, 5.44. Found: C, 55.78; H, 7.84; N, 5.43%. ee 50%; $[\alpha]_D^{20}$ +8.5 (c 0.21, CH_2Cl_2).

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