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N-Carbamate α-aminoalkyl-*p*-tolylsulfones—convenient substrates in the nitro-Mannich synthesis of secondary *N*-carbamate protected *syn*-2-amino-1-nitroalkanephosphonates

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ABSTRACT

An efficient one-pot synthesis of secondary *N*-carbamate protected *syn*-β-amino-α-nitroalkanephosphonates using diethyl nitromethanephosphonate and *N*-Boc or *N*-Cbz imines, generated in situ from stable *N*-Boc or *N*-Cbz α-aminoalkyl-*p*-tolylsulfones has been developed under PTC conditions. A model enantioselective version of this reaction is also described. Enantioselectivity up to 67% ee is achieved using a chiral thiourea catalyst derived from a cinchona alkaloid. Completely stereoselective conversion of the title compounds into partially *N*-carbamate protected *syn*-1,2-diaminoalkanephosphonates has also been elaborated.

1. Introduction

The aza-Henry reaction,[1–7] known also as the nitro-Mannich reaction, is usually base promoted addition of nitro compounds to *N*-protected imines, often being employed in the asymmetric synthesis of vicinal diamines and α,β-diamino acids.[1b,e,g,2,3a–c,h–j,l,4b,c,5d,6,8,9] There are however, only isolated examples of the nitro-Mannich approach to the preparation of β-amino-α-nitro- and α,β-diaminophosphonates[10–12] utilizing 1-nitroalkanephosphonates and *N*-protected imines as starting materials. In the late 1970s Petrov et al.[12] described the addition of nitromethane- and 1-nitroethanephosphonates to *N*-benzylidenebenzeneamine leading to *N*-phenyl analogues of aminonitrophosphonates. Recently, during our investigations, Johnston et al.[10] published a highly diastereo- and enantioselective addition of dialkyl 1-nitroethanephosphonates to *N*-Boc imines, catalyzed by chiral Brønsted acids, which allows obtaining *anti*-2-amino-1-nitroethanephosphonates with a quaternary center next to a phosphorus atom. Until now however, the reaction of diethyl nitromethanephosphonate with *N*-carbamate α-aminoalkyl-*p*-tolylsulfones, as convenient precursors of unstable *N*-carbamate imines, leading to the title compounds has not been described. This prompted us to present here our contribution as a new, practical synthesis of secondary 1-amino-2-nitroalkane- and 1,2-diaminoalkanephosphonates utilizing diethyl nitromethanephosphonate[13] (**1**) and *N*-carbamate α-aminoalkyl-*p*-tolylsulfones **2** as starting materials.

2. Results and discussion

It is well documented that *N*-Boc and *N*-Cbz protected α-aminoalkyl-*p*-tolylsulfones[1d,14–16] **2** can be considered as stable, crystalline, and easy to handle equivalents of *N*-Boc and *N*-Cbz imines. Not surprisingly, nucleophilic additions of deprotonated nitroalkanes to *N*-carbamate imines generated in situ from the α-amido sulfones, mentioned above by base-induced elimination, have recently been the subject of extensive studies.[4i,5a,b,d,7] In this context, easy to perform and low demanding as far as reactions conditions are concerned, phase transfer catalysis (PTC)[1f,17] approaches to the aza-Henry reaction seemed to be especially beneficial. After preliminary experimentations, standard liquid–solid PTC conditions using potassium carbonate as a base for simultaneous deprotonation and elimination, tetrabutylammonium bromide (TBAB) as catalyst and toluene as solvent were selected for the reaction of diethyl nitromethanephosphonate (**1**) with *N*-carbamate protected α-aminoalkyl-*p*-tolylsulfones **2** (Scheme 1).

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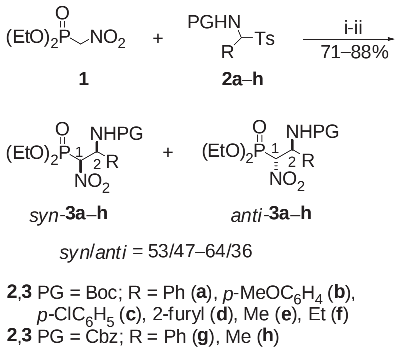


Scheme 1. Reagents and conditions: (i) K_2CO_3 solid (5 equiv), TBAB (10 mol %), toluene, rt, 26 h; (ii) aq $KHSO_4$.

As shown in Scheme 1, a vigorously stirred mixture of **1**, *N*-Boc protected α-aminoalkyl-*p*-tolylsulfones **2a**–**f** (1.03 equiv), potassium carbonate (5 equiv) and TBAB (10 mol %) in toluene afforded, after 26 h at room temperature, the mixture of *syn*- and *anti*-adducts **3a**–**f** in good yields (79–88%) after flash chromatography. The results are summarized in Table 1.

The results given in Table 1 indicate that adducts **3** are formed with low and comparable *syn*-diastereoselectivity (*syn*-**3a**–**f**/*anti*-**3a**–**f**=56/44–64/36). The reaction also works for *N*-Cbz protected α-aminoalkyl-*p*-tolylsulfones **2g**–**h** as imine surrogates, for which,

Table 1
Diethyl β-amino-α-nitrophosphonates **3a**–**h** prepared

Entry	3	R	PG	Yield[a,b] (%)	*syn/anti*[c]	*syn*-**3** Yield[d] (%)	^{31}P NMR, δ	
							syn	*anti*
1	**3a**	Ph	Boc	87	59/41	40[e]	10.36	11.02
2	**3b**	*p*-MeOC$_6$H$_4$		83	63/37	39	10.08	10.79
3	**3c**	*p*-ClC$_6$H$_4$		88	64/36	41	10.10	10.76
4	**3d**	2-Furyl		87	63/37	41	9.88	10.55
5	**3e**	Me		88	61/39	—	11.09	11.27
6	**3f**	Et		79	56/44	—	11.00	11.29
7	**3g**	Ph	Cbz	71	53/47	28[f]	10.17	10.93
8	**3h**	Me		84	57/43	—	10.67	10.81

[a] All reactions were carried out on a 2 mmol scale.
[b] Overall yield of pure *syn*- and *anti*-adducts **3a**–**h** isolated after flash chromatography.
[c] Diastereomeric ratio measured by ^{31}P NMR of the crude products.
[d] Yields of pure *syn*-**3**, after crystallization from CCl_4.
[e] Second crop of crystals was isolated in 19% yield and consisted of *anti*-**3a** mainly (*syn*/*anti*=25/75).
[f] The mixture of *syn*- and *anti*-**3g** (*syn*/*anti*=10/90) was isolated in 27% yield from the mother liquor.

the mixtures of *N*-Cbz protected *syn*- and *anti*-adducts **3g** and **3h** are isolated in much the same yields and with similar *syn*-diastereoselectivity (Table 1, entries 7–8). Facile epimerization on the carbon atom C-1, next to the nitro group, in adducts **3** and/or retro addition/re-addition occurring under the reaction conditions, seem to be responsible for the low diastereoselectivity of the above mentioned reactions.[†] We found, additionally, that stirring the mixture of **1** and **2a** or **1**, and **2g** for 10 days under the same PTC conditions, resulted, within the experimental error, in the same diastereomeric ratios of the final adducts **3a** or **3g**, respectively.

The evaluation of the scope of the reaction shows that the method is applicable to aromatic, heteroaromatic and aliphatic *N*-Boc, and *N*-Cbz protected α-aminoalkyl-*p*-tolylsulfones **2**. Pure *syn*-**3a**–**d** and *syn*-**3g** could easily be isolated in 28–41% yields from the mixture of **3a**–**d** and **3g** via simple crystallization from carbon tetrachloride (Table 1, entries 1–5 and 7, respectively). Pure aliphatic derived *syn*-adducts **3e**–**f** and **3h**, which are formed as viscous oils, could not be separated from the mixture either by crystallization or chromatography.

The mother liquors of adducts **3**, obtained after crystallizations, consisted mainly of *anti*-diastereomers **3**, and these mixtures slowly enriched themselves in *syn*-**3** after prolonged standing at room temperature.

Attempted widening of the scope of the above nitro-Mannich reaction on diethyl 1-nitroethanephosphonate,[18] a homologue of **1**, was unsuccessful. Starting 1-nitroethanephosphonate was always recovered from the reaction mixture.

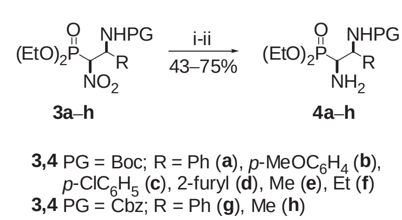
Determination of the relative *syn*/*anti* configuration of adducts **3** based on NMR analysis of diagnostic vicinal coupling constants ($^3J_{HH}$, $^3J_{HP}$, $^3J_{CP}$) failed. In almost all of the adducts diagnostic protons (H_1 and H_2) appeared as complex multiplets or the differences in the values of their vicinal coupling constants $^3J_{HH}$ were too small to be diagnostic. Therefore, the relative *syn*/*anti* configurations of **3** were established by conversion of selected compounds **3** into the appropriate imidazolidine-2-thiones **5** (vide infra). However, the phosphorus chemical shifts of **3** were consistent with the given diastereomer. In the ^{31}P NMR spectra of all of nitrophosphonates **3** the signals of the *syn*-isomers appeared 0.14–0.74 ppm upfield relative to those of the *anti*-isomers (Table 1).

Having established the synthesis of *N*-carbamate protected 2-amino-1-nitroalkanephosphonates **3**, we focused our attention on their conversion into partially protected 1,2-diaminoalkanephosphonates **4**. Several 1,2-diaminoalkanephosphonic acids act as leucine aminopeptidase inhibitors.[19] However, the number of known α,β-diaminoalkanephosphonates is limited and only a few routes to both racemic or enantioenriched compounds have been reported till now.[10,20,21]

Sodium borohydride/nickel(II) chloride[22] system in methanol was used as the reductant of choice for the nitro group. Such reductions occurred under very mild conditions, and they were shown to proceed with retention of configuration at the stereogenic center on the carbon atom next to the nitro group.[3l,4c,h,6b,d,e,23]

As shown in Scheme 2, solid $NaBH_4$ was added at −30 °C to the solution of nitrophosphonates **3** and nickel(II) chloride hexahydrate in methanol. The mixture was allowed to warm to 0 °C, and desired 1,2-diaminophosphonates **4** were isolated in moderate yields (43–75%), after quenching with aq ammonium chloride followed by flash chromatography. The approach mentioned above enables a two-step synthesis of secondary 1,2-diaminophosphonate esters (Table 2).

As shown in Table 2, *syn*-1,2-diaminophosphonates **4a**–**d** and **4g** were only obtained from the reduction of pure *syn*-adducts



Scheme 2. Reagents and conditions: (i) $NaBH_4$ (10 equiv), $NiCl_2 \times 6H_2O$ (1.05 equiv), MeOH, −30 °C, 5 min, 0 °C; (ii) aq NH_4Cl, 0 °C.

3a–**d** and **3g** (Table 2, entries 1, 3–5, and 8, respectively). In turn, the mixture of *syn*- and *anti*-adducts **3a** and **3e**–**h** afforded, after reduction, the diastereomeric mixture of *syn*- and *anti*-diaminophosphonates **4a** and **4e**–**h** in approximately the same ratio as starting nitro adducts **3** (Table 2, entries 2, 6–7, and 9–10, respectively). These results confirm that reduction of the nitro group

[†] When the solution of pure *syn*-**3a** in $CDCl_3$ was kept in the presence of pyridine for 4 h at room temperature, or when pure *syn*-**3a** was stirred in toluene in the presence of K_2CO_3/TBAB system for 48 h at room temperature, followed by standard work-up, epimerized mixture of *syn*- and *anti*-**3a** (*syn*/*anti*=58/42) was always formed. No formation of starting diethyl nitromethanephosphonate (**1**) was observed in the ^{31}P NMR spectrum of the reaction mixture, however.

Table 2
1,2-Diaminophosphonates **4a–h** prepared

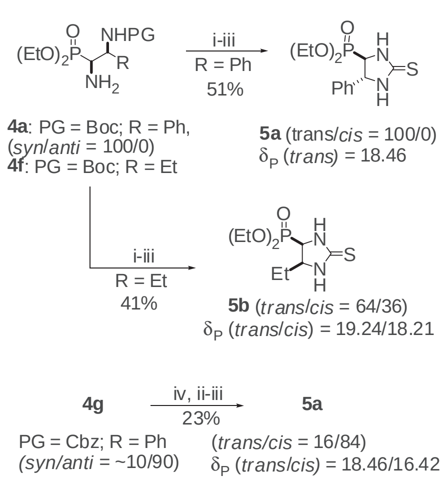
Entry	3/4	R	PG	3 *syn/anti*	4		^{31}P NMR, δ	
					Yield[a] (%)	*syn/anti*[b]	*syn*-**4**	*anti*-**4**
1	**a**	Ph	Boc	100/0	63	100/0	25.69	25.56
2	**a**	Ph		25/75[c]	54	25/75		
3	**b**	*p*-MeOC$_6$H$_4$		100/0	53	100/0	26.17	—
4	**c**	*p*-ClC$_6$H$_4$		100/0	66	100/0	25.77	—
5	**d**	2-Furyl		100/0	55	100/0	25.27	—
6	**e**	Me		61/39	43	58/42	27.16	27.08
7	**f**	Et		60/40	60	64/36[d]	27.5[d]	27.5[d]
8	**g**	Ph	Cbz	100/0	75	100/0	25.48	25.28
9	**g**	Ph		∼10/90[e]	43	16/84[d]		
10	**h**	Me		57/43	58	59/41	26.97	26.78

[a] Overall yield of pure *syn*- and *anti*-adducts **3a–h** after flash chromatography.
[b] Diastereomeric ratio measured by ^{31}P NMR of the crude products.
[c] The mixture of adducts **3a** (*syn/anti*=25/75), isolated from the mother liquor was used as substrate.
[d] As a result of overlapping of ^{31}P NMR signals, *syn/anti* ratio of diastereomeric diaminophosphonates **4** was determined by their cyclization into *trans*- and *cis*-imidazolidine-2-thiones **5** (^{31}P NMR).
[e] The mixture of nitro adducts **3g** (*syn/anti*=∼10/90), isolated from the mother liquor, was used as substrate. As a result of relatively quick epimerization of **3g** approximate ratio of diasteromer is only given.

takes place with retention of configuration on the carbon atom next to this group and simultaneously, correlate the configuration of 1,2-diaminophosphonates **4** with parent *N*-carbamate protected nitrophosphonates **3**.

Relative configuration of 1,2-diaminophosphonates **4**, in turn, was assigned by conversion of the selected adducts **4** into the appropriate imidazolidine-2-thiones **5** for which, relative configuration could easily be determined by ^{31}P NMR analysis of their chemical shifts and the ring protons vicinal coupling constant ($^3J_{HH}$) in ^{1}H NMR (Scheme 3).

As shown in Scheme 3, imidazolidine-2-thiones **5a** and **5b** were prepared in 51% and 41% overall yield via standard deprotection (TFA/CH$_2$Cl$_2$) of *N*-Boc protected *syn*-1,2-diamino-2-phenylethylphosphonate **4a** and *syn/anti*-1,2-diaminobutylphosphonates **4f**, followed by the conversion of free 1,2-diaminophosphonates thus obtained into *trans*-imidazolidine-2-thione **5a** and the mixture of *trans*- and *cis*-imidazolidine-2-thiones **5b** (trans/cis=64/36), using 1,1′-thiocarbonyldiimidazole as condensing agent in the presence of



Scheme 3. Reagents and conditions: (i) TFA, CH$_2$Cl$_2$, rt, 2 h; (ii) Et$_3$N, 1,1′-thiocarbonyldiimidazole, CH$_2$Cl$_2$, rt, 24 h; (iii) aq HCl; (iv) ammonium formate (10 equiv), 10% Pd/C (cat), MeOH, rt, 2 h, Ar.

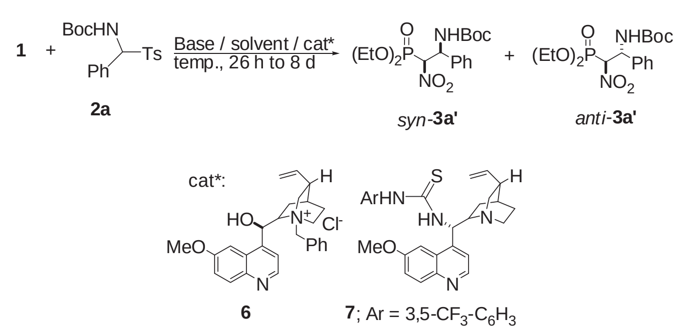
triethylamine.[24] Similarly, the mixture of *trans*- and *cis*-**4g** (cleavage of *N*-Cbz group was accomplished using ammonium formate/Pd–C system[25]) afforded the mixture of the appropriate *trans*- and *cis*-imidazolidine-2-thiones **5a** (trans/cis=16/84) in 23% yield.

The stereochemistry of the imidazolidine-2-thiones **5** was assigned by ^{1}H and ^{31}P NMR analysis. The values of the vicinal coupling constants for **5a** ($^3J_{HH(trans)}$=6.25 Hz, $^3J_{HH(cis)}$=10.0 Hz) and **5b** ($^3J_{HH(trans)}$=6.36 Hz) are consistent with the observation that *trans*-imidazolidine-2-thiones have smaller coupling constants than the corresponding *cis*-diastereomer.[26] In the ^{31}P NMR spectra of **5a** (δ_P (trans/cis)=18.46/16.42) and **5b** (δ_P (trans/cis)=19.24/18.21) the signals of the trans-isomers appeared 1.03–2.04 ppm downfield relative to those of the cis-isomers.[21k] As all steps of the above mentioned transformations occur with the retention of configurations, these results confirm the assignment of relative configuration in the parent nitro adducts **3**.

Having established the conditions of the reaction of diethyl nitromethanephosphonate (**1**) with *N*-carbamate protected α-aminoalkyl-*p*-tolylsulfones **2** we next attempted the asymmetric PTC reaction,[1f,17] using cinchona alkaloid derived quaternary ammonium salts as catalysts. Such chiral PTC catalysts were successfully employed in the highly stereoselective aza-Henry reactions of simple nitroalkanes and *N*-protected imines generated in situ from *N*-formyl or *N*-carbamate α-aminoalkyl-arylsulfones.[5a,b,d]

N-tert-Butoxycarbonylamino(phenyl)methyl-*p*-tolylsulfone (**2a**) was chosen as a model compound, and its reaction with **1** in the presence of solid K$_2$CO$_3$ or Cs$_2$CO$_3$ was investigated using quinine-derived catalyst **6** (Scheme 4).

However, irrespective of the base applied, model studies did not give significant asymmetric induction under these conditions. The major *syn*-**3a**′ was formed with low diastereoselectivity and poor enantioselectivity (Table 3, entries 1 and 2). The enantiomeric excesses were assessed from ^{31}P NMR spectra of the crude reaction mixture, taking into account diagnostic chemical shifts (δ_P) of diethyl *syn*- and *anti*-{(2-*tert*-butoxycarbonylamino)-1-[(*S*)-2-(6-methoxynaphthalen-2-yl)propionylamino]-2-phenyl-ethyl}phos-



Scheme 4. Asymmetric aza-Henry reaction of **1** with **2a**.

phonates prepared by reduction of the crude nitro adducts **3a**′ (NaBH$_4$/NiCl$_2$), followed by derivatization[27] of thus formed *syn/anti*-**4a**′ amines with (*S*)-Naproxen chloride [(*S*)-2-(6-methoxynaphthalen-2-yl)propionyl chloride].[28]

(*S*)-Naproxen chloride was proved to be a convenient chiral derivatizing agent (CDA) for the determination of enantiomeric purity as well as the absolute configuration assignments of diethyl 1-amino- and 2-aminoalkanephosphonates by NMR.[27,29] Amidation under these conditions proceeds quantitatively, and is not accompanied by racemization.[27] [‡] The diastereomeric anisochronicity in naproxen amide of **4a**′ was sufficiently large to estimate the ee of the *syn*-isomer (δ_P=21.63/22.06, Δδ=0.43). However, for the *anti*-isomer only a broad singlet (δ_P=22.38) was observed in ^{31}P NMR spectrum.

[‡] Entire derivatization (scale: 0.05 mmol) using (*S*)-Naproxen chloride as CDA, followed by determination of the ee as well as the absolute configurations assignments were performed in an NMR tube using anhydrous CDCl$_3$ as solvent and pyridine as a base.

Table 3
The asymmetric aza-Henry reaction of **1** with *N*-Boc-amino(phenyl)methyl-*p*-tolylsulfone (**2a**)

Entry	Base/solvent/time[a]	Temperature °C	cat*	Conv. (%)	**3a′** *syn*/*anti*[b]	*syn*–**3a′**/*syn*–**4a′** ee[c] (%)
1	$K_2CO_{3(s)}$/toluene/26 h	rt	**6**	99	58/42	12
2	$Cs_2CO_{3(s)}$/toluene/26 h	rt	**6**	93	59/41	10
3	$K_2CO_{3(s)}$/MeCN/3d	rt	**7**	100	55/45	10
4	$K_2CO_{3(s)}$/CH_2Cl_2/3d	rt	**7**	100	56/44	21
5	$K_2CO_{3(s)}$/THF/26h	rt	**7**	100	59/41	20
6	$K_2CO_{3(s)}$/toluene/3d[d,e,f]	rt	**7**	99	57/43	47
7	$K_2CO_{3(s)}$/toluene/3d	0	**7**	96	58/42	60
8	$K_2CO_{3(s)}$/toluene/8d	−20	**7**	94[g]	58/42	67

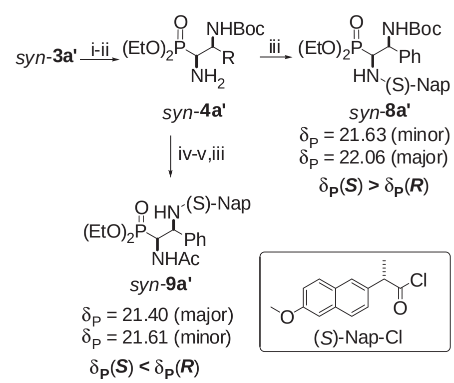
[a] Reaction conditions: scale 0.1 mmol, (c 0.1 mol/L); cat **6** (10 mol %) or cat **7** (20 mol %), base (5 equiv). Isomers **3a′**, **4a′**, and **3g′** have the same structure as their racemic counterparts.
[b] Diastereomeric ratio measured by ^{31}P NMR of the crude products.
[c] Calculated from the ^{31}P NMR spectra of (*S*)-Naproxen amides of *syn*/*anti*-**4a′** amines (δ_{syn}=21.63/22.06; δ_{anti}=22.38) obtained via reduction of **3a′** using $NaBH_4$/$NiCl_2$ system, followed by derivatization of thus formed amines **4a′** with (*S*)-Nap-Cl. Absolute configurations of the major *syn*-isomers **3a′** and **4a′**, respectively, were determined to be (*1S,2S*).
[d] For the reaction of **1** with *N*-Cbz sulfone **2g** the mixture of *syn*/*anti*-**3g′** (*syn*/*anti*=58/42) was obtained with 34% ee for *syn*-**3g′** under the same reaction conditions. In turn, only 68% conversion was obtained for the reaction conducted at 0 °C for 3 days.
[e] When the reaction of **1** with *N*-Boc sulfone **2a** was repeated at rt on 1 mmol scale, pure *syn*-nitro adduct **3a′** and *syn*-diamino adduct **4a′** (47% ee) were isolated in 27% and 61% yields, respectively.
[f] When the reaction of **1** with *N*-Boc imine, preformed independently from **2a**, was repeated at room temperature without the addition of K_2CO_3, only in the presence of catalyst **7**, 68% conversion was obtained after 24 h (*syn*/*anti*-**3a′**=56/44) and no *syn*-enantioselectivity was observed.
[g] After 24 h only 10% conversion was observed.

Much better enantioselectivities were obtained when PTC catalyst **6** was substituted for the bifunctional thiourea derived from 9-amino(9-deoxy)epiquinine[30] **7** in the model reaction. (Scheme 4, Table 3, entries 3–8). Recently, thiourea-based bifunctional organocatalysts were successfully employed in nitro-Mannich reactions of nitroalkanes with activated imines [4a,b,h,k] Thus, in the reaction of **1a** with **2a**, in the presence of **7** (20 mol %), the mixture of *syn*-**3a′** and *anti*-**3a′** was formed with low *syn*-diastereoselectivity and with moderate to good *syn*-enantioselectivity, the latter being highly solvent and temperature dependent. The use of toluene gave the highest enantioselectivity at room temperature (47% ee, Table 3, entry 6). Lower enantioselectivities were observed for other solvents (Table 3, entries 3–5). By lowering the reaction temperature to −20 °C, the ee was improved up to 67% for the major *syn*-**3a′**, however at the expense of the reaction time (Table 3, entry 8). We also found that substitution of α-amido sulfone **2a** for *N*-benzyloxycarbonylamino(phenyl)methyl-*p*-tolylsulfone (**2g**) resulted in the formation of a mixture of *syn*/*anti*-**3g′** (*syn*/*anti*=58/42) with lower *syn*-enantioselectivity (34% ee) compared with the analogous reaction in which sulfone **2a** was used as imine precursor (Table 3, footnote d). However, when the addition of diethyl nitromethanephosphonate (**1**) to *N*-Boc imine,[16c] preformed independently from *N*-Boc-amino(phenyl)methyl-*p*-tolylsulfone (**2a**), was repeated at room temperature in toluene without the addition of K_2CO_3, only in the presence of chiral catalyst **7**, the reaction was sluggish and gave a mixture of *syn*/*anti*-**3a′** (*syn*/*anti*=56/44) with no *syn*-enantioselectivity (Table 3, footnote f). This result shows that the catalyst 7 could only act as the chiral Brønsted acid in the reactions accomplished in the presence of K_2CO_3.

The results obtained for the model reaction are encouraging, however, to achieve better enantioselectivity further tuning of the catalyst structure is necessary.

Finally, the absolute configuration of two consecutive stereogenic centers in the enantioenriched *syn*-**4a′** was determined by ^{31}P NMR analysis using (*S*)-Naproxen chloride as chiral derivatizing agent[§] for amidation[29,31] of each stereogenic center separately (Scheme 5). As shown in Scheme 5, nitro adducts *syn*-**3a′** were reduced to partially protected *syn*-**4a′** amines, followed by derivatization with (*S*)-Naproxen chloride[27] to give the mixture of diasteromeric (*S*)-Naproxen amides *syn*-**8a′** (δ_P=22.06 (major) and 21.63 (minor); ratio: 74/26). According to the model proposed by us[29] for the Naproxen amides of 1-amino- and 2-aminoalkanephosphonates (Scheme 6), the upfield ^{31}P NMR chemical shift, attributed to the shielding effect of the naproxen naphthyl ring on the phosphorus atom, should be assigned to aminophosphonate with configuration (1*S*) at C-1 stereogenic center, whereas a minor, downfield chemical shift corresponds to configuration (1*R*) at the same center.

In turn, bisamides *syn*-**9a′** (δ_P=21.61 (minor), 21.40 (major); ratio: 26/74) were prepared via consecutive acylation of *syn*-**4a′** using acetic anhydride as acetylating agent, chemoselective deprotection of Boc group in thus obtained *N*-acetyl derivatives followed by derivatization

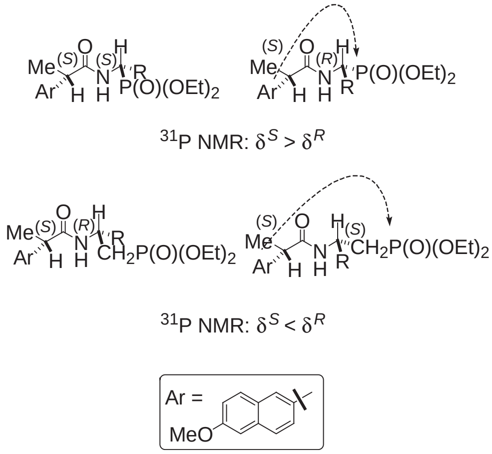


Scheme 5. The absolute configuration determination of the enantioenriched *syn*-**4a′** amines by ^{31}P NMR spectroscopy. Reagents and conditions: (i) $NaBH_4$ (10 equiv), $NiCl_2\times6H_2O$ (1.05 equiv), MeOH, −30 °C, 5 min, 0 °C; (ii) aq NH_4Cl, 0 °C; (iii) (*S*)-Nap-Cl (2.5 equiv), Pyridine/$CDCl_3$, rt, 1 h; (iv) Ac_2O (3 equiv), Et_3N (3 equiv), 4 h, rt; (v) TFA/CH_2Cl_2 (1:1 v/v), rt, 2 h.

of free amino group using (*S*)-Naproxen chloride. Employing the model mentioned above,[29] (Scheme 6) the major, upfield ^{31}P NMR chemical shift should be assigned to aminophosphonate with configuration (2*S*) at carbon C-2, whereas downfield one corresponds to configuration (2*R*) at the same center.[¶] Thus, the absolute configurations of major stereoisomers *syn*-**8a′** and *syn*-**9a′** were determined to be (1*S*) and (2*S*), respectively. This allows assigning the same configuration for parent *syn*-**4a′** and *syn*-**3a′**.

[§] Since the diaminoderivative *syn*-**4a′** is a mixture of enantiomers it is enough to use one enantiomer of Naproxen chloride for the absolute configuration assignment.

[¶] As a matter of fact, the configuration at C-2 carbon atom could also be assigned based on the absolute configuration at C-1 stereogenic center in *syn*-**8a′** and relative configuration of compounds **3** and **4**.



Scheme 6. Model for the assignment of the configuration of diethyl 1-amino- and 2-aminoalkylphosphonates from the ^{31}P NMR spectra of their (*S*)-Naproxen amides, based on the shielding effect exerted by the anisotropy cone of the naproxen naphthyl ring on the substituents in aminophosphonates [29].

3. Conclusions

In conclusion, we have shown that the reaction of diethyl nitromethanephosphonate (**1**) with *N*-Boc and *N*-Cbz protected α-aminoalkyl-*p*-tolylsulfones **2a**–**h**, as stable equivalents of *N*-carbamate imines, is a convenient and efficient method for the preparation of *N*-protected β-amino-α-nitrophosphonates **3g**–**h** and in consequence also α,β-diaminophosphonates **3a**–**h**. Additions are accomplished under PTC conditions and give the mixture of *syn*- and *anti*- nitro adducts **3g**–**h** in high yields and low *syn*-diastereoselectivity. Homologue of the nitrophosphonate **1** is unreactive under these conditions. Crystallization of the reaction mixture allows obtaining pure *syn*-**3a**–**d** and *syn*-**3g** derived from the corresponding aromatic aldehydes, which, after the reduction by $NaBH_4/NiCl_2$ system afford partially protected *syn*-1,2-diaminoalkanephosphonates **4a**–**d** and **4g** in moderate yields. A model catalytic, enantioselective version of this aza-Henry reaction was only partially successful. The moderate enantioselectivity (67%) achieved for *syn*-diastereomer **3a′**, when bifunctional thiourea derived from 9-amino(9-deoxy)epiquinine **7** is used as a catalyst in the presence of K_2CO_3. Using ^{31}P NMR spectroscopy and (*S*)-Naproxen chloride as chiral derivatizing agent the absolute configuration of the consecutive stereogenic centers in *syn*-**4a′** amine was determined.

4. Experimental

4.1. General

NMR spectra were recorded on a Bruker Avance DPX 250 instrument at 250.13 MHz for ^{1}H NMR, 62.90 MHz for ^{13}C NMR, and 101.3 MHz for ^{31}P NMR in $CDCl_3$ solution, using either tetramethylsilane as an internal and 85% H_3PO_4 as an external standard. Positive chemical shifts are downfield from external 85% H_3PO_4 for ^{31}P NMR spectra. Chemical shifts (δ) are indicated in parts per million and coupling constants (J) in hertz. For ^{13}C NMR spectra, the peak assignments were made with the assistance of CH-COSY and DEPT experiments. Partially overlapped signals are assigned by asterisks (*). The enantiomeric excesses (ee) were determined by ^{31}P NMR spectroscopy using (*S*)-Naproxen chloride as chiral derivatizing agent (CDA). Optical rotations were measured on a PolAAr 3001 (Optical Activity Ltd.) polarimeter. Elemental analyses were performed on a Perkin–Elmer PE 2400 Analyzer. IR spectra were measured on an IR Alpha Bruker (ATR) instrument and are reported in cm^{-1}. Melting points were determined in open capillaries and are uncorrected. All reagents were purchased from Fluka and were used without further purification. Diethyl nitromethanephosphonate,[13] diethyl 1-nitroethanephosphonate,[18] and *N*-Boc α-amidoalkyl-*p*-tolylsulfones[15] were prepared as described previously.

4.2. Preparation of substituted diethyl *N*-carbamate 2-amino-1-nitroalkanephosphonates 3a–h; general procedure

Solid, anhydrous K_2CO_3 (1.40 g, 10.0 mmol) was added to a solution of diethyl nitromethanephosphonate (**1**, 394 mg, 2.0 mmol), α-amido sulfone (**2**, 2.05 mmol) and tetrabutylammonium bromide (TBAB, 70 mg, 0.20 mmol) in anhydrous toluene (20 mL). The suspension was vigorously stirred for 26 h at room temperature. The mixture was carefully quenched with 10% aq $KHSO_4$ (10 mL), the organic layer separated and the aqueous phase extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were washed with brine (2×10 mL), dried over $MgSO_4$, evaporated, and subjected to flash chromatography on silica gel (AcOEt/hexanes 5:2 or 5:3 v/v) to give pure mixtures of *syn*- and *anti*-adducts **3a**–**h**. Pure *syn*-**3a**–**d** and *syn*-**3g** were obtained after crystallization from CCl_4 (Table 1).

*4.2.1. Diethyl syn-(2-tert-butoxycarbonylamino-1-nitro-2-phenylethyl) phosphonate **3a**.* Crude product was purified by flash chromatography (AcOEt/hexanes 5:2 v/v), followed by crystallization from CCl_4 to give the *title compound* **3a** (322 mg, 40%) as a colorless solid, mp 136–139 °C; [found: C, 50.73; H, 6.82; N, 6.98. $C_{17}H_{27}N_2O_7P$ requires C, 50.74; H, 6.76; N, 6.96%]; *Rf* (AcOEt/hexanes 5:2 v/v) 0.44; ν_{max} (ATR) 3315, 2974, 1711, 1560, 1520, 1256, 1161, 982, 699; δ_P (101 MHz, $CDCl_3$) 10.36; δ_H (250 MHz, $CDCl_3$) 7.38–7.29 (m, $5H_{Ar}$), 6.09–5.95 (m, 1H, N*H*Boc), 5.77–5.50 (m, 1H, C*H*NHBoc), 5.34, 5.28 (dd and br dd, respectively, 1H, $^3J_{HH}$ 7.4, 5.8 Hz, $^2J_{HP}$ 13.0, 16.0 Hz, C*H*NO_2, rotamers), 4.35–3.80 (m, 4H, $2CH_3CH_2O$), 1.42, 1.41 (2s, 9H, $(CH_3)_3C$, rotamers), 1.36–1.10 (m, 6H, $2CH_3CH_2O$); δ_C (63 MHz, $CDCl_3$) 154.4 (s, C=O), 136.8 (d, $^3J_{CP}$ 6.4 Hz, CHC_{Ar}), 128.6, 128.3, 126.8 (s, $5CH_{Ar}$), 88.4 (d, $^1J_{CP}$ 141.1 Hz, $CHNO_2$), 80.1 (s, $(CH_3)_3C$), 64.2 (d, $^2J_{CP}$ 6.1 Hz, $2CH_3CH_2O$), 53.9 (s, CHNHBoc), 28.1 (s, $(CH_3)_3C$), 16.0, 15.9 (2d, $^3J_{CP}$ 6.0, 5.8 Hz, $2CH_3CH_2O$).

*4.2.2. Diethyl syn-[2-tert-butoxycarbonylamino-2-(4-methoxyphenyl)-1-nitroethyl]phosphonate **3b**.* Crude product was purified by flash chromatography (AcOEt/hexanes 5:2 v/v), followed by crystallization from CCl_4 to give the *title compound* **3b** (337 mg, 39%) as a colorless solid, mp 145–148 °C; [found: C, 49.98; H, 6.63; N, 6.33. $C_{18}H_{29}N_2O_8P$ requires C, 50.00; H, 6.76; N, 6.48%]; R_f (AcOEt/hexanes 5:2 v/v) 0.39; ν_{max} (ATR) 3334, 2939, 1704, 1559, 1517, 1247, 1160, 1012, 841, 714; δ_P (101 MHz, $CDCl_3$) 10.08; δ_H (250 MHz, $CDCl_3$) 7.31–6.85 (m, $4H_{Ar}$), 6.17 (d, 1H, $^3J_{HH}$ 9.2 Hz, N*H*Boc), 5.55–5.42 (m, 1H, C*H*NHBoc), 5.48–5.29 (m, 1H, C*H*NO_2), 4.33–3.96 (m, 4H, $2CH_3CH_2O$), 3.78 (s, 3H, OCH_3), 1.41 (s, 9H, $(CH_3)_3C$), 1.39–1.16 (m, 6H, $2CH_3CH_2O$); δ_C (63 MHz, $CDCl_3$) 157.8 (s, C=O), 152.8 (s, CH_3OC_{Ar}), 127.1 (d, $^3J_{CP}$ 6.2 Hz, CHC_{Ar}), 112.4, 126.5, (2s, $4CH_{Ar}$), 86.8 (d, $^1J_{CP}$ 141.1 Hz, $CHNO_2$), 78.4 (s, $(CH_3)_3C$), 62.5 (d, $^2J_{CP}$ 6.4 Hz, $2CH_3CH_2O$), 53.4 (s, OCH_3), 52.1 (br s, CHNHBoc), 26.4 (s, $(CH_3)_3C$), 14.4, 14.3 (2d, $^3J_{CP}$ 5.6 Hz, $2CH_3CH_2O$).

*4.2.3. Diethyl syn-[2-tert-butoxycarbonylamino-2-(4-chlorophenyl)-1-nitroethyl]phosphonate **3c**.* Crude product was purified by flash chromatography (AcOEt/hexanes 5:3 v/v), followed by crystallization from CCl_4 to give the *title compound* **3c** (358 mg, 41%) as a colorless solid, mp 157–160 °C; [found: C, 46.52; H, 5.85; N, 6.65. $C_{17}H_{26}ClN_2O_7P$ requires C, 46.74; H, 6.00; N, 6.41%]; R_f (AcOEt/hexanes 5:2 v/v) 0.39; ν_{max} (ATR) 3332, 2974, 1709, 1560, 1514, 1246, 1159, 1011, 867; δ_P (101 MHz, $CDCl_3$) 10.10; δ_H (250 MHz, $CDCl_3$) 7.35–6.85 (m, $4H_{Ar}$), 6.09 (br d, $^3J_{HH}$ 8.1 Hz, 1H, N*H*Boc), 5.60–5.48 (m, 1H, C*H*NHBoc), 5.31 (br dd, $^3J_{HH}$ 7.8 Hz, $^2J_{HP}$ 13.0 Hz, 1H, C*H*NO_2), 4.37–3.92 (m, 4H, $2CH_3CH_2O$), 1.41 (s, 9H, $(CH_3)_3C$), 1.38–1.19 (m, 6H, $2CH_3CH_2O$); δ_C (63 MHz, $CDCl_3$) 152.8 (s, C=O), 133.8 (d, $^3J_{CP}$ 6.5 Hz, CHC_{Ar}), 132.2 (C_{Ar}), 126.7, 126.3 (CH_{Ar}), 86.4 (d, $^1J_{CP}$ 141.0 Hz, $CHNO_2$), 78.7 (s, $(CH_3)_3C$), 62.9, 63.8 (2d, $^2J_{CP}$ 6.3, 7.5 Hz, $2CH_3CH_2O$), 51.7 (br s, CHNHBoc), 26.4 (s, $(CH_3)_3C$), 14.4, 14.3 (2d, $^3J_{CP}$ 6.0 Hz, $2CH_3CH_2O$).

*4.2.4. Diethyl syn-(2-tert-butoxycarbonylamino-2-furan-2-yl-1-nitroethyl)phosphonate **3d**.* Crude product was purified by flash chromatography (AcOEt/hexanes 5:2 v/v), followed by crystallization from CCl_4 to give the *title compound* **3d** (322 mg, 41%) as a colorless solid, mp 92–95 °C; [found: C, 45.86; H, 6.42; N, 7.03. $C_{15}H_{25}N_2O_8P$ requires C, 45.92; H, 6.42; N, 7.14%]; R_f (AcOEt/hexanes 5:2 v/v) 0.44; ν_{max} (ATR) 3294, 2976, 1714, 1555, 1390, 1270, 1245, 1022, 752; δ_P (101 MHz, $CDCl_3$) 9.88; δ_H (250 MHz, $CDCl_3$) 7.38–7.36 (m, 1H, H_{Ar}), 6.37–6.32 (m, $2H_{Ar}$), 5.83–5.62 (m, 2H, CHNHBoc, NHBoc), 5.50–5.39 (m, 1H, $CHNO_2$), 4.33–3.95 (m, 4H, $2CH_3CH_2O$), 1.45, 1.44 (2s, 9H, $(CH_3)_3C$; rotamers), 1.38–1.18 (m, 6H, $2CH_3CH_2O$); δ_C (63 MHz, $CDCl_3$) 152.7 (s, C=O), 147.5 (d, $^3J_{CP}$ 7.3 Hz, CHC_{Ar}), 141.0, 108.9, 106.7 (CH_{Ar}), 84.2 (d, $^1J_{CP}$ 142.0 Hz, $CHNO_2$), 78.7 (s, $(CH_3)_3C$), 63.1, 62.6 (2d, $^2J_{CP}$ 6.5, 7.0 Hz, $2CH_3CH_2O$), 46.8 (s, CHNHBoc), 26.4 (s, $(CH_3)_3C$), 14.5, 14.2 (2d, $^3J_{CP}$ 5.7 Hz, $2CH_3CH_2O$).

*4.2.5. Diethyl syn/anti-(2-tert-butoxycarbonylamino-1-nitropropyl) phosphonates **3e**.* Crude product was purified by flash chromatography (AcOEt/hexanes 5:3 v/v) to give the *title compound* **3e** (599 mg, 88%) as a colorless viscous oil; [found: C, 42.55; H, 7.60; N, 8.08. $C_{12}H_{25}N_2O_7P$ requires C, 42.35; H, 7.40; N, 8.23]; R_f (AcOEt/hexanes 5:3 v/v) 0.37; ν_{max} (neat) 3305, 2980, 1701, 1556, 1249, 1160, 1013, 730; δ_P (101 MHz, $CDCl_3$) 11.27 (*anti*-**3e** 39%), 11.09 (*syn*-**3e** 61%); δ_H (250 MHz, $CDCl_3$) 5.34–5.00 (m, 2H, $CHNO_2$, NHBoc, *syn* and *anti*), 4.54–4.36 (m, 1H, CHNHBoc, *syn* and *anti*), 4.33–4.08 (m, 4H, $2CH_3CH_2O$, *syn* and *anti*), 1.45–1.33 (m, 18H, $2CH_3CH_2O$, CH_3CH, $(CH_3)_3C$, *syn* and *anti*); δ_C (63 MHz, $CDCl_3$) 152.9 (br s, C=O, *syn* and *anti*), 86.1, 84.8 (2d, $^1J_{CP}$ 143.3, 141.3 Hz, $CHNO_2$, *syn* and *anti*), 78.3 (br s, $(CH_3)_3C$, *syn* and *anti*), 62.9, 62.7, 62.5, 62.2 (4d, $^2J_{CP}$ 6.7, 7.0, 7.9, 6.8 Hz, $2CH_3CH_2O$, *syn* and *anti*), 45.4 (s, CHNHBoc, *syn*), 45.2 (s, CHNHBoc, *anti*), 26.4 (s, $(CH_3)_3C$, *syn* and *anti*), 16.5 (s, CH_3CH, *syn*), 15.5 (s, CH_3CH, *anti*), 14.4 (d, $^3J_{CP}$ 5.8 Hz, $2CH_3CH_2O$, *syn* and *anti*).

*4.2.6. Diethyl syn/anti-(2-tert-butoxycarbonylamino-1-nitrobutyl) phosphonates **3f**.* Crude product was purified by flash chromatography (AcOEt/hexanes 5:3 v/v) to give the *title compound* **3f** (560 mg, 79%) as a colorless viscous oil; [found: C, 44.27; H, 7.72; N, 7.71. $C_{13}H_{27}N_2O_7P$ requires C, 44.07; H, 7.68; N, 7.91%]; R_f (AcOEt/hexanes 5:3 v/v) 0.39; ν_{max} (neat) 2975, 1716, 1557, 1315, 1244, 1162, 1010, 730, 567, 464; δ_P (101 MHz, $CDCl_3$) 11.29 (*anti*-**3f** 44%), 11.0 (*syn*-**3f** 56%); δ_H (250 MHz, $CDCl_3$) 5.25–5.09 (m, 2H, $CHNO_2$, NHBoc, *syn* and *anti*), 4.36–4.16 (m, 5H, $2CH_3CH_2O$, CHNHBoc, *syn* and *anti*), 1.80–1.60 (m, 2H, CH_3CH_2CH, *syn* and *anti*), 1.44 (s, 9H, $(CH_3)_3C$, *syn* and *anti*), 1.41–1.31 (m, 6H, $2CH_3CH_2O$, *syn* and *anti*), 1.00 (br t, $^3J_{HH}$ 7.4 Hz, 3H, CH_3CH_2CH, *syn* and *anti*); δ_C (63 MHz, $CDCl_3$) 155.1, 154.9 (2s, C=O, *syn* and *anti*), 86.8 (d, $^1J_{CP}$ 142.4 Hz, $CHNO_2$, *syn*), 86.3 (d, $^1J_{CP}$ 145.6 Hz, $CHNO_2$, *anti*), 79.8 (br s, $(CH_3)_3C$, *syn* and *anti*), 64.9, 64.4, 64.3, 63.8 (4d, $^2J_{CP}$ 6.8, 5.0, 4.0, 6.9, $2CH_3CH_2O$, *syn* and *anti*), 52.9 (s, CHNHBoc, *anti*), 52.1 (s, CHNHBoc, *syn*), 28.1 (s, $(CH_3)_3C$, *syn* and *anti*), 25.3 (d, $^3J_{CP}$ 5.2 Hz, CH_3CH_2, *syn*), 24.7 (d, $^3J_{CP}$ 4.3 Hz, CH_3CH_2, *anti*), 16.1 (d, $^3J_{CP}$ 6.0 Hz, $2CH_3CH_2O$, *syn* and *anti*), 10.3 (d, $^4J_{CP}$ 2.9 Hz, CH_3CH_2).

*4.2.7. Diethyl syn-(2-benzyloxycarbonylamino-1-nitro-2-phenylethyl) phosphonate **3g**.* Crude product was purified by flash chromatography (AcOEt/hexanes 5:2 v/v), followed by crystallization from CCl_4. to give the *title compound* **3g** (244 mg, 28%) as a colorless solid, mp 100–103 °C; [found: C, 55.16; H, 5.60; N, 6.38. $C_{20}H_{25}N_2O_7P$ requires C, 55.05; H, 5.77; N, 6.42%]; R_f (AcOEt/hexanes 5:2 v/v) 0.39; ν_{max} (ATR) 3306, 2957, 1742, 1555, 1528, 1246, 1006, 813, 694; δ_P (101 MHz, $CDCl_3$) 10.93 (*anti*-**3g** 47%), 10.17 (*syn*-**3g** 53%); δ_H (250 MHz, $CDCl_3$) 7.39–7.29 (m, $10H_{Ar}$), 6.40 (br d, $^3J_{HH}$ 9.3 Hz, 1H, NH), 5.70–5.62 (m, 1H, CHPh), 5.40 (dd, $^3J_{HH}$ 6.1 Hz, $^2J_{HP}$ 16.5 Hz, 1H, $CHNO_2$), 5.17–5.03 (m, 2H, CH_2Ph), 4.15–4.01 (m, 4H, $2CH_3CH_2O$), 1.33–1.08 (m, 6H, $2CH_3CH_2O$); δ_C (63 MHz, $CDCl_3$) 155.3 (s, C=O), 136.3 (d, $^3J_{CP}$ 5.8 Hz, CHC_{Ar}), 136.0 (s, C_{Ar}), 128.7, 128.5, 128.3, 128.0, 127.2 (s, CH_{Ar}), 88.1 (d, $^1J_{CP}$ 141.0 Hz, $CHNO_2$), 67.0 (s, CH_2Ph), 64.3 (d, $^2J_{CP}$ 6.0 Hz, $2CH_3CH_2O$), 54.6 (s, CHNH), 16.0, 15.9 (2d, $^3J_{CP}$ 6.3 Hz, $2CH_3CH_2O$).

*4.2.8. Diethyl syn/anti-(2-benzyloxycarbonylamino-1-nitropropyl) phosphonates **3h**.* Crude product was purified by flash chromatography (AcOEt/hexanes 5:3 v/v) to give the *title compound* **3h** (623 mg, 84%) as a colorless viscous oil; [found: C, 48.33; H, 6.37; N, 7.21. $C_{15}H_{23}N_2O_7P$ requires C, 48.13; H, 6.19; N, 7.48%]; R_f (AcOEt/hexanes 5:2 v/v) 0.43; ν_{max} (neat) 3285, 2983, 1718, 1555, 1245, 1012, 697, 671; δ_P (101 MHz, $CDCl_3$) 10.81 (*anti*-**3h** 43%), 10.67 (*syn*-**3h** 57%); δ_H (250 MHz, $CDCl_3$) 7.36–7.29 (m, $5H_{Ar}$), 5.93 (d, 1H, $^3J_{HH}$ 8.9 Hz, NHCbz, *syn*), 5.84 (d, $^3J_{HH}$ 8.3 Hz, NHCbz, 1H, *anti*), 5.26 (dd, $^3J_{HH}$ 5.2 Hz, $^2J_{HP}$ 14.5 Hz, 1H, $CHNO_2$, *anti*), 5.16 (dd, $^3J_{HH}$ 7.2 Hz, $^2J_{HP}$ 15.2 Hz, 1H, $CHNO_2$, *syn*), 5.10, 5.05 (2s, 2H, CH_2Ph, *syn* and *anti*), 4.67–4.39 (m, 1H, CHNHCbz, *syn* and *anti*), 4.25–4.06 (m, 4H, $2CH_3CH_2O$, *syn* and *anti*), 1.42, 1.39 (2d, $^3J_{HH}$ 3.0 Hz, 3H, CH_3CH, *syn* and *anti*), 1.36–1.26 (m, 6H, $2CH_3CH_2O$, *syn* and *anti*); δ_C (63 MHz, $CDCl_3$) 153.5 (s, C=O, *syn* and *anti*), 134.4, 134.3, (2s, CH_2C_{Ar}, *syn* and *anti*), 126.7, 126.4, 126.3 (3s, CH_{Ar}, *syn* and *anti*), 86.0, 84.8 (2d, $^1J_{CP}$ 145.0, 141.9 Hz, $CHNO_2$, *syn* and *anti*), 65.1 (s, CH_2Ph, *syn* and *anti*), 63.0, 62.7, 62.6, 62.2 (4d, $^2J_{CP}$ 6.7, 6.8, 7.5, 6.8 Hz, $2CH_3CH_2O$, *syn* and *anti*), 45.9, 45.7 (2s, CHNH, *syn* and *anti*), 16.5 (s, CH_3CH, *syn*), 15.4 (s, CH_3CH, *anti*), 14.4 (d, $^3J_{CP}$ 5.7 Hz, $2CH_3CH_2O$, *syn* and *anti*).

4.3. Preparation of diethyl 2-(*N*-carbamate) protected 1,2-diaminoalkanephosphonates 4a–h; general procedure

Sodium borohydride (113 mg, 3.0 mmol) was added in two portions to a cooled to −30 °C solution of diethyl *N*-carbamate protected 2-amino-1-nitroalkanephosphonate **3** (0.3 mmol) and $NiCl_2 \times 6H_2O$ (71 mg, 0.3 mmol) in methanol (3 mL). The mixture was allowed to warm up to 0 °C for 10 min, quenched with saturated aq NH_4Cl (9 mL), and extracted with CH_2Cl_2 (3×15 mL). The combined organic phases were washed with brine (5 mL), dried over $MgSO_4$, evaporated, and subjected to flash chromatography on silica gel (AcOEt) to give pure adducts **4**.

*4.3.1. Diethyl syn-(1-amino-2-tert-butoxycarbonylamino-2-phenylethyl)phosphonate **4a**.* Crude product was purified by flash chromatography (AcOEt) to give the *title compound* **4a** (70 mg, 63%) as a colorless solid, mp 108–111 °C; [found: C, 54.63; H, 7.60; N, 7.30. $C_{17}H_{29}N_2O_5P$ requires C, 54.83; H, 7.85; N, 7.52%]; R_f (AcOEt) 0.26; ν_{max} (ATR) 3391, 3032, 1703, 1530, 1362, 1265, 1246, 1212, 1017, 966, 933, 860, 703; δ_P (101 MHz, $CDCl_3$) 25.69; δ_H (250 MHz, $CDCl_3$) 7.42–7.22 (m, $5H_{Ar}$), 6.06 (brs, 1H, NHBoc), 5.06 (ddd, $^3J_{HH}$ 3.3, 8.0 Hz, $^3J_{HP}$ 11.6 Hz, 1H, CHNHBoc), 4.22–3.99 (m, 4H, $2CH_3CH_2O$), 3.40 (dd, $^3J_{HH}$ 3.3 Hz, $^2J_{HP}$ 15.6 Hz, 1H, $CHNH_2$), 1.66 (br s, 2H, $CHNH_2$), 1.40 (s, 9H, $(CH_3)_3C$), 1.35, 1.25 (2 t, $^3J_{HH}$ 7.1 Hz, 6H, $2CH_3CH_2O$); δ_C (63 MHz, $CDCl_3$) 155.2 (s, C=O), 140.3 (d, $^3J_{CP}$ 4.7 Hz, CHC_{Ar}), 128.5, 127.4, 126.6 (C_{ar}), 79.4 (s, $(CH_3)_3C$), 62.6, 62.4 (2d, $^2J_{CP}$ 6.9 Hz, $2CH_3CH_2O$), 54.9 (br s, CHNHBoc), 53.5 (d, $^1J_{CP}$ 152.0 Hz, $CHNH_2$), 28.3 (s, $(CH_3)_3C$), 16.5, 16.3 (2d, $^3J_{CP}$ 6.7, 7.0 Hz, $2CH_3CH_2O$).

*4.3.2. Diethyl syn-[1-amino-2-tert-butoxycarbonylamino-2-(4-methoxyphenyl)-ethyl]phosphonate **4b**.* Crude product was purified by flash chromatography (AcOEt) to give the *title compound* **4b** (64 mg, 53%) as a colorless solid, mp 96–99 °C; [found: C, 53.51; H, 7.82; N, 6.92. $C_{18}H_{31}N_2O_6P$ requires C, 53.72; H, 7.76; N, 6.96%]; R_f (AcOEt) 0.20; ν_{max} (ATR) 3276, 2977, 1704, 1511, 1244, 1158, 1026, 961, 767; δ_P (101 MHz, $CDCl_3$) 25.17; δ_H (250 MHz, $CDCl_3$) 7.29–7.22 (m, $2H_{Ar}$), 6.90–6.84 (m, $2H_{Ar}$), 5.95 (br s, 1H, NHBoc), 4.95 (ddd, $^3J_{HH}$ 3.4, 8.0 Hz, $^3J_{HP}$ 13.4 Hz, 1H, C*H*NHBoc), 4.21–3.98 (m, 4H, $2CH_3CH_2O$), 3.79 (s, 3H, CH_3O), 3.36 (dd, $^3J_{HH}$ 3.4 Hz, $^2J_{HP}$ 15.0 Hz, 1H, C*H*NH_2), 1.45 (br s, 2H, NH_2), 1.39 (s, 9H, $(CH_3)_3C$), 1.34, 1.27 (2 t, $^3J_{HH}$ 7.1 Hz, 6H, $2CH_3CH_2O$), δ_C (63 MHz, $CDCl_3$) 158.8 (s, CH_3OC_{Ar}), 155.1 (s, C=O), 132.2 (br s, CHC_{Ar}), 127.6, 113.7 (CH_{Ar}), 79.2 (s, $(CH_3)_3C$), 62.4, 62.2 (2d, $^2J_{CP}$ 6.9 Hz, $2CH_3CH_2O$), 55.1 (s, CH_3O), 54.3 (br s, CHNHBoc), 53.5 (d, $^1J_{CP}$ 151.0 Hz, $CHNH_2$), 28.2 (s, $(CH_3)_3C$), 16.3, 16.2 (2d, $^3J_{CP}$ 6.6 Hz, $2CH_3CH_2O$).

4.3.3. Diethyl syn-[1-amino-2-tert-butoxycarbonylamino-2-(4-chlorophenyl)-ethyl]phosphonate ***4c***. Crude product was purified by flash chromatography (AcOEt) to give the *title compound* **4c** (81 mg, 66%) as a colorless solid, mp 111–114 °C; [found: C, 50.38; H, 7.04; N, 6.97. $C_{17}H_{28}ClN_2O_5P$ requires C, 50.19; H, 6.94; N, 6.89%]; R_f (AcOEt) 0.26; ν_{max} (ATR) 3273, 2931, 1703, 1532, 1247, 1212, 1161, 1012, 966, 738; δ_P (101 MHz, $CDCl_3$) 25.77; δ_H (250 MHz, $CDCl_3$) 7.32–7.12 (m, $4H_{Ar}$), 6.20 (br s, 1H, N*H*Boc), 4.94 (ddd, $^3J_{HH}$ 3.4, 7.7 Hz, $^3J_{HP}$ 11.6 Hz, 1H, C*H*NHBoc), 4.13–3.93 (m, 4H, $2CH_3CH_2O$), 3.26 (dd, $^3J_{HH}$ 3.4 Hz, $^2J_{HP}$ 16.1 Hz, 1H, $CHNH_2$), 1.50 (br s, 2H, NH_2), 1.32 (s, 9H, $(CH_3)_3C$), 1.34, 1.26 (2t, $^3J_{HH}$ 7.1 Hz, 6H, CH_3CH_2O); δ_C (63 MHz, $CDCl_3$) 153.4 (s, C=O), 137.2 (br d, $^3J_{CP}$ 7.0 Hz, CHC_{Ar}), 131.3 (s, ClC_{Ar}), 126.7, 126.3 (2s, $2CH_{Ar}$), 77.7 (s, $(CH_3)_3C$), 60.8, 60.6 (2d, $^2J_{CP}$ 7.0 Hz, $2CH_3CH_2O$), 52.7 (br s, CHNHBoc), 51.5 (d, $^1J_{CP}$ 152.1 Hz, $CHNH_2$), 26.5 (s, $(CH_3)_3C$), 14.6, 14.5 (2d, $^3J_{CP}$ 6.4 Hz, $2CH_3CH_2O$).

4.3.4. Diethyl syn-[(1-amino-2-tert-butoxycarbonylamino-2-furan-2-yl)ethyl]phosphonate ***4d***. Crude product was purified by flash chromatography (AcOEt) to give the *title compound* **4d** (60 mg, 55%) as a colorless solid, mp 49–52 °C; [found: C, 49.53; H, 7.59; N, 7.80. $C_{15}H_{27}N_2O_6P$ requires C, 49.72; H, 7.51; N, 7.73%]; R_f (AcOEt) 0.26; ν_{max} (ATR) 3311, 2980, 1703, 1526, 1215, 1161, 1018, 953, 759; δ_P (101 MHz, $CDCl_3$) 25.27; δ_H (250 MHz, $CDCl_3$) 7.36–7.35 (m, $1H_{Ar}$), 6.33–6.31 (m, $1H_{Ar}$), 6.27–6.25 (m, $1H_{Ar}$), 5.95 (d, $^3J_{HH}$ 8.8 Hz, 1H, N*H*Boc), 5.12 (ddd, $^3J_{HH}$ 3.7, 8.8 Hz, $^3J_{HP}$ 12.9 Hz, 1H, C*H*NHBoc), 4.23–3.93 (m, 4H, $2CH_3CH_2O$), 3.53 (dd, $^3J_{HH}$ 3.7 Hz, $^2J_{HP}$ 15.6 Hz, 1H, $CHNH_2$), 1.69 (br s, 2H, NH_2), 1.44 (s, 9H, $(CH_3)_3C$), 1.33, 1.27 (2d, $^3J_{HH}$ 7.1 Hz, 6H, $2CH_3CH_2O$); δ_C (63 MHz, $CDCl_3$) 154.9 (s, C=O), 153.0 (d, $^3J_{CP}$ 11.1 Hz, CHC_{Ar}), 141.2, 110.1, 106.9 (CH_{Ar}), 79.4 (s, $(CH_3)_3C$), 62.3, 62.1 (2d, $^2J_{CP}$ 7.0, 6.9 Hz, $2CH_3CH_2O$), 51.5 (d, $^1J_{CP}$ 153.1 Hz, $CHNH_2$), 50.1 (br s, CHNHBoc), 28.1 (s, $(CH_3)_3C$), 16.2, 16.1 (2d, $^3J_{CP}$ 4.7 Hz, $2CH_3CH_2O$).

4.3.5. Diethyl syn/anti-(1-amino-2-tert-butoxycarbonylamino-propyl)phosphonates ***4e***. Crude product was purified by flash chromatography (AcOEt) to give the *title compound* **4e** (40 mg, 43%) as a colorless oil; [found: C, 46.54; H, 8.54; N, 8.80. $C_{12}H_{27}N_2O_5P$ requires C, 46.44; H, 8.77; N, 9.03%]; R_f (AcOEt) 0.29; ν_{max} (neat) 3305, 2977, 1698, 1365, 1230, 1164, 1021, 959, 730; δ_P (101 MHz, $CDCl_3$) 27.16 (*syn*-**4e** 58%), 27.08 (*anti*-**4e** 43%); δ_H (250 MHz, $CDCl_3$) 5.24 (br s, 1H, N*H*Boc, *syn* and *anti*), 4.24–4.09 (m, 4H, $2CH_3CH_2O$, *syn* and *anti*), 4.08–3.83 (m, 1H, C*H*NHBoc, *syn* and *anti*), 3.17 (dd, $^3J_{HH}$ 3.4 Hz, $^2J_{HP}$ 15.5 Hz, 1H, $CHNH_2$, *anti*), 3.09 (dd, $^3J_{HH}$ 4.4 Hz, $^2J_{HP}$ 14.9 Hz, 1H, $CHNH_2$, *syn*), 1.77 (br s, 2H, $CHNH_2$, *syn* and *anti*), 1.44 (s, 9H, $(CH_3)_3C$, *syn* and *anti*), 1.35 (t, $^3J_{HH}$ 7.1 Hz, 6H, $2CH_3CH_2O$, *syn* and *anti*), 1.26 (d, $^3J_{HH}$ 6.8 Hz, 3H, CH_3CH, *syn*), 1.22 (d, $^3J_{HH}$ 7.0 Hz, 3H, CH_3CH, *anti*); δ_C (63 MHz, $CDCl_3$) 153.4 (s, C=O, *syn* and *anti*), 77.1(s, $(CH_3)_3C$, *syn* and *anti*), 60.5 (br s, CHNHBoc, *syn* and *anti*), 60.4, 60.2 (2d, $^2J_{CP}$ 7.1, 7.0 Hz, $2CH_3CH_2O$, *syn* and *anti*), 50.9 (d, $^1J_{CP}$ 148.3 Hz, $CHNH_2$, *syn*), 50.2 (d, $^1J_{CP}$ 144.1 Hz, $CHNH_2$, *anti*), 26.4 (s, $(CH_3)_3C$, *syn* and *anti*), 14.5 (d, $^3J_{CP}$ 5.6 Hz, $2CH_3CH_2O$, *syn* and *anti*), 14.1 (br s, CH_3CH, *syn* and *anti*).

4.3.6. Diethyl syn/anti-(1-amino-2-tert-butoxycarbonylamino-butyl)phosphonates ***4f***. Crude product was purified by flash chromatography (AcOEt) to give the *title compound* **4f** (58 mg, 60%) as a colorless oil; [found: C, 48.39; H, 9.26; N, 8.45. $C_{13}H_{29}N_2O_5P$ requires C, 48.14; H, 9.01; N, 8.64 %]; R_f (AcOEt) 0.30; ν_{max} (neat) 3300, 2975, 1706, 1507, 1238, 1164, 1021, 958, 783, 558; δ_P (101 MHz, $CDCl_3$) 27.5 (*syn*- and *anti*-**4f**); δ_H (250 MHz, $CDCl_3$) 5.23, 5.12 (2br d, $^3J_{HH}$ 8.4, 9.4 Hz, 1H, CHN*H*Boc, *syn* and *anti*), 4.23–4.08 (m, 4H, $2CH_3CH_2O$, *syn* and *anti*), 3.93–3.69 (m, 1H, CH_3CH_2CH, *syn* and *anti*), 3.17, 3.14 (2dd, $^3J_{HH}$ 3.6, 3.7 Hz $^2J_{HP}$ 15.6, 14.5 Hz, 1H, $CHNH_2$, *syn* and *anti*), 1.80–1.49 (m, 4H, NH_2, CH_3CH_2CH, *syn* and *anti*), 1.44 (s, 9H, $(CH_3)_3C$, *syn* and *anti*), 1.35, 1.34 (2t, $^3J_{HH}$ 7.1 Hz, 6H, $2CH_3CH_2O$, *syn* and *anti*), 1.00–0.90 (m, 3H, CH_3CH_2CH, *syn* and *anti*); δ_C (63 MHz, $CDCl_3$) 153.9 (s, C=O, *syn* and *anti*), 77.4 (s, $(CH_3)_3C$, *syn* and *anti*), 53.1, 52.2 (2br s, CHNHBoc, *syn* and *anti*), 60.7, 60.1 (2br d, $^2J_{CP}$ 7.9 Hz, $2CH_3CH_2O$, *syn* and *anti*), 51.0, 50.6 (2d, $^1J_{CP}$ 144.9, 148.8 Hz, $CHNH_2$, *syn* and *anti*), 27.4 (s, $(CH_3)_3C$, *syn* and *anti*), 24.4, 23 (2br s, CH_3CH_2, *syn* and *anti*), 15.5 (d, $^3J_{CP}$ 5.3 Hz, $2CH_3CH_2O$, *syn* and *anti*), 9.9, 9.8 (2s CH_3CH_2, *syn* and *anti*).

4.3.7. Diethyl syn-(1-amino-2-benzyloxycarbonylamino-2-phenylethyl)phosphonate ***4g***. Crude product was purified by flash chromatography (AcOEt) to give the *title compound* **4g** (91 mg, 75%) as a colorless solid, mp 64–66 °C; [found: C, 58.99; H, 6.66; N, 6.86. $C_{20}H_{27}N_2O_5P$ requires C, 59.11; H, 6.70; N, 6.89%]; R_f (AcOEt) 0.20; ν_{max} (ATR) 3267, 2980, 1716, 1534, 1249, 1017, 965, 790, 697, 527, 509; δ_P (101 MHz, $CDCl_3$) 25.48; δ_H (250 MHz, $CDCl_3$) 7.33–7.25 (m, $10H_{Ar}$), 6.65 (br d, $^3J_{HH}$ 8.3 Hz, 1H, N*H*Cbz), 5.15 (ddd, $^3J_{HH}$ 3.0, 8.3 Hz, $^3J_{HP}$ 11.5 Hz, 1H, C*H*NHCbz), 5.09–5.00 (m, 2H, CH_2Ph), 4.17–3.90 (m, 4H, $2CH_3CH_2O$), 3.39 (dd, $^3J_{HH}$ 3.0 Hz, $^2J_{HP}$ 16.0 Hz, 1H, $CHNH_2$), 1.65 (br s, 2H, NH_2), 1.26, 1.20 (2t, $^3J_{HH}$ 7.1 Hz, 6H, $2CH_3CH_2O$); δ_C (63 MHz, $CDCl_3$) 155.6 (s, C=O), 139.8 (d, $^3J_{CP}$ 5.0 Hz, CHC_{Ar}), 136.4 (C_{Ar}), 128.3, 128.2, 127.9, 127.8, 127.3, 126.4, (CH_{Ar}), 66.4 (s, CH_2Ph), 62.4, 62.2 (2d, $^2J_{CP}$ 9.4 Hz, $2CH_3CH_2O$), 55.1 (s, CHNHCbz), 53.3 (d, $^1J_{CP}$ 152.3 Hz, $CHNH_2$), 16.2, 16.1 (2d, $^3J_{CP}$ 5.3 Hz, $2CH_3CH_2O$).

4.3.8. Diethyl syn/anti-(1-amino-2-benzyloxycarbonylamino-propyl) phosphonates ***4h***. Crude product was purified by flash chromatography (AcOEt) to give the *title compound* **4h** (60 mg, 58%) as a colorless oil; [found: C, 52.53; H, 7.35; N, 8.16. $C_{15}H_{25}N_2O_5P$ requires C, 52.32; H, 7.32; N, 8.14%]; R_f (AcOEt) 0.14; ν_{max} (neat) 3296, 2979, 1710, 1530, 1224, 1018, 957, 696; δ_P (101 MHz, $CDCl_3$) 26.97 (*syn*-**4h** 59%), 26.78 (*anti*-**4h** 41%); δ_H (250 MHz, $CDCl_3$) 7.36–7.24 (m, $5H_{Ar}$, *syn* and *anti*), 6.00–5.87 (m, 1H, N*H*Cbz, *syn* and *anti*), 5.08 (s, 2H, CH_2Ph, *syn* and *anti*), 4.15–3.97 (m, 5H, $2CH_3CH_2O$, C*H*NHCbz, *syn* and *anti*), 3.18 (dd, $^3J_{HH}$ 3.7 Hz, $^2J_{HP}$ 16.1 Hz, 1H, $CHNH_2$, *anti*), 3.05 (dd, $^3J_{HH}$ 3.7 Hz, $^2J_{HP}$ 15.2 Hz, 1H, $CHNH_2$, *syn*), 1.89 (br s, 2H, NH_2, *syn* and *anti*), 1.41–1.15 (m, 9H, $2CH_3CH_2O$, CH_3CH, *syn* and *anti*); δ_C (63 MHz, $CDCl_3$) 154.0, 153.9 (2s, C=O, *syn* and *anti*), 134.9, 134.8 (2s, C_{Ar}, *syn* and *anti*), 126.6, 126.5, 126.1 (3s, CH_{Ar}, *syn* and *anti*), 64.6 (s, CH_2Ph, *syn* and *anti*), 60.6, 60.3 (2d, $^2J_{CP}$ 6.5, 6.1 Hz, CH_3CH_2O, *syn* and *anti*), 51.0 (d, $^1J_{CP}$ 148.5 Hz, $CHNH_2$, *syn*), 50.2 (d, $^1J_{CP}$ 144.5 Hz, $CHNH_2$, *anti*), 46.6 (s, CHNHCbz, *syn*), 46.0 (d, $^2J_{CP}$ 9.1 Hz, CHNHCbz, *anti*), 14.6 (d, $^3J_{CP}$ 5.7 Hz, $2CH_3CH_2O$, *syn* and *anti*), 14.2 (s, CH_3CH, *syn* and *anti*).

4.4. Diethyl *trans*-(5-phenyl-2-thioxoimidazolidin-4-yl) phosphonate[21k] 5a

Trifluoroacetic acid (0.9 mL, 12 mmol) was added dropwise to the solution of *syn*-**4a**, (100 mg, 0.27 mmol) in CH_2Cl_2 (1.5 mL). The mixture was stirred for 1.5 h at room temperature, and the volatile materials evaporated under reduced pressure. The oily residue was dissolved in CH_2Cl_2 (1.0 mL), triethylamine (0.19 mL, 1.35 mmol) was added to the solution and the mixture was stirred for 30 min at room temperature. Then, the solution of 1,1′-thiocarbonyldiimidazole (56 mg, 1.35 mmol) in CH_2Cl_2 (1.5 mL) was added and the mixture was stirred for 24 h at room temperature. Reaction mixture was diluted with CH_2Cl_2 (30 mL), and washed successively with 1 M aq HCl (2×3 mL), saturated $NaHCO_3$ (2×3 mL), and brine (3 mL). Organic phase was dried over $MgSO_4$, evaporated, and subjected to flash chromatography on silica gel (eluent: CH_2Cl_2/acetone 3:1 v/v) to give pure *trans*-**5a** (43 mg, 51%) as a colorless solid, mp 151–153 °C; [found: C, 49.41; H, 5.80; N, 8.69. $C_{13}H_{19}N_2O_3PS$ requires C, 49.67; H, 6.09; N, 8.91%]; R_f (CH_2Cl_2–acetone 3:1) 0.36; ν_{max} (ATR) 3144, 2904, 1532, 1472, 1232, 1024, 780; δ_P (101 MHz, $CDCl_3$) 18.46; δ_H (250 MHz, $CDCl_3$) 7.42–7.30 (m, 5H, H_{Ar}), 7.03 (br s, 2H, 2 N*H*), 5.21 (dd, $^3J_{HH}$ 6.3 Hz, $^3J_{HP}$ 20.5 Hz, 1H, C*H*C_{Ar}), 4.32–4.05 (m, 4H, CH_3CH_2O), 4.00 (d, $^3J_{HH}$ 6.3 Hz, 1H, C*H*P), 1.35, 1.31 (2t, $^3J_{HH}$ 7.1 Hz, 6H, CH_3CH_2O); δ_C (63 MHz, $CDCl_3$) 183.2 (d, $^3J_{CP}$ 4.8 Hz, *C*=S), 139.9 (d, $^3J_{CP}$ 10.1 Hz, CHC_{Ar}), 129.0, 128.8, 126.1 (s, CH_{Ar}), 63.8 (d, $^2J_{CP}$ 6.8 Hz, CH_3CH_2O), 63.3 (d, $^2J_{CP}$ 7.2 Hz, CH_3CH_2O), 61.8 (s, *C*HC_{Ar}), 61.6 (d, $^1J_{CP}$ 161.7 Hz, *C*HP), 16.5 (d, $^3J_{CP}$ 5.3 Hz, CH_3CH_2O), 16.4 (d, $^3J_{CP}$ 5.7 Hz, CH_3CH_2O).

4.5. Diethyl *trans/cis*-(5-ethyl-2-thioxoimidazolidin-4-yl) phosphonates[21k] 5b

A crude mixture of *trans*- and *cis*-**5b** was obtained in the same way as **5a**. Crude product was purified by flash chromatography (CH_2Cl_2/acetone 1:1) to give the *title trans*- and *cis*-**5b** (29 mg, 41%) as yellow solid, mp 120–123 °C; [found: C, 40.74; H, 7.38; N, 10.18. $C_9H_{19}N_2O_3PS$ requires C, 40.59; H, 7.19; N, 10.52%]; R_f (CH_2Cl_2/acetone 1:1) 0.45; ν_{max} (ATR) 3163, 2967, 1523, 1225, 1011, 965, 719, 624; δ_P (101 MHz, $CDCl_3$) 19.24 (*trans*-**5b** 64%), 18.21 (*cis*-**5b** 36%); δ_H (250 MHz, $CDCl_3$) 7.27, 7.21 (2br s, 1H, N*H*, cis), 6.83, 6.57 (2br s, 1H, N*H*, trans), 4.31–4.04 (m, 6H, $2CH_3CH_2O$, CH_3CH_2CH, trans and cis, C*H*P, cis), 3.83 (br d, $^3J_{HH}$ 6.4 Hz, 1H, C*H*P, trans), 2.03–1.77 (m, 2H, CH_3CH_2CH, cis), 1.75–1.61 (m, 2H, CH_3CH_2CH, trans), 1.36, 1.35 (2t, 6H*, $^3J_{HH}$ 7.1 Hz, $2CH_3CH_2O$, trans and cis), 1.01 (t, 3H*, $^3J_{HH}$ 7.5 Hz, CH_3CH_2, cis), 0.97 (t, 3H*, $^3J_{HH}$ 7.4 Hz, CH_3CH_2, trans); δ_C (63 MHz, $CDCl_3$) 183.3 (d, $^3J_{CP}$ 3.7 Hz, *C*=S, cis), 182.2 (d, $^3J_{CP}$ 4.3 Hz, *C*=S, trans), 63.6 (d, $^2J_{CP}$ 6.8 Hz, CH_3CH_2O, trans), 63.2 (d, $^2J_{CP}$ 6.1 Hz, CH_3CH_2O, trans), 63.1 (d, $^2J_{CP}$ 7.3, CH_3CH_2O, trans), 63.0 (d, $^2J_{CP}$ 7.4, CH_3CH_2O, cis), 61.1 (s, CH_3CH_2CH, cis), 60.0 (s, CH_3CH_2CH trans), 57.8 (d, $^1J_{CP}$ 163.2 Hz, *C*HP, trans), 56.7 (d, $^1J_{CP}$ 157.3 Hz, *C*HP, cis), 28.7 (d, $^3J_{CP}$ 10.7 Hz, CH_3CH_2CH, trans), 23.9 (d, $^3J_{CP}$ 7.0 Hz, CH_3CH_2CH, cis), 16.4, 16.3 (2br d, $^3J_{CP}$ 5.9 Hz, CH_3CH_2O, trans and cis), 11.4 (s, CH_3CH_2CH, cis), 9.0 (s, CH_3CH_2CH, trans).

4.6. Enantioselective synthesis of diethyl *syn*-(1-amino-2-*tert*-butoxycarbonylamino-2-phenylethyl)phosphonates 4a′

Solid, anhydrous K_2CO_3 (700 mg, 5.0 mmol) was added to the solution of diethyl nitromethanephosphonate (**1**, 197 mg, 1.0 mmol), α-amido sulfone **2a** (379 mg, 1.05 mmol), and chiral thiourea **7** (120 mg, 0.20 mmol) in anhydrous toluene (10 mL). The suspension was vigorously stirred for 3 d at room temperature. Then, the mixture was carefully quenched with 10% aq $KHSO_4$ (10 mL). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organic phases were washed with brine (2×10 mL), dried over $MgSO_4$, evaporated, and subjected to flash chromatography on silica gel (AcOEt/hexanes 5:2 v/v) to give 310 mg (71%) of pure *syn*- and *anti*-adducts **3a′** (*syn/anti*=57/43). Pure enantioenriched *syn*-**3a′** (109 mg) was obtained in 27% yield after crystallization from CCl_4 (Table 3). Compound *syn*-**3a′** (100 mg, 0.247 mmol) was subjected to $NaBH_4/NiCl_2$ system in methanol according to the general procedure described in Section 4.3 to give, after reduction and flash chromatography, 56 mg (61%) of *syn*-**4a′**, $[\alpha]_D^{20}$ −9.2 (*c* 0.15, $CHCl_3$, for a sample with 47% ee). The spectroscopic data of *syn*-**3a′** and *syn*-**4a′** were identical to racemic *syn*-**3a** and *syn*-**4a**.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.10.072.

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