Diastereoselective hydrophosphonylation of imines using (*R*,*R*)-TADDOL phosphite. Asymmetric synthesis of α-aminophosphonic acid derivatives†

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Efficient synthesis of α-aminophosphonic acid derivatives is achieved, the key step being a diastereoselective hydrophosphonylation of *N*-diphenylphosphinyl imines using a readily available chiral cyclic (*R*,*R*)-TADDOL-phosphite derived from inexpensive natural tartaric acid.

Introduction

α-Aminophosphonic acids[1] are structural analogous to α-amino acids, obtained by isosteric substitution of the carboxylic acid by a phosphonate moiety. As expected from this analogy the single α-aminophosphonic acid molecules or their phosphonate esters as well as phosphapeptides containing α-aminophosphonic units show an assorted biological activity[2] as happens of catalytic antibodies,[3a] peptide mimetics,[3b] enzyme inhibitors,[3c–e] and antibacterial agents.[3f] Moreover they are key compounds in agrochemistry and have found several applications as fungicides[4a] or herbicides.[4b]

The Pudovik reaction[5] is one of the most straight methods for the synthesis of α-aminophosphonic acid derivatives, which involves a variant of Strecker reaction based in the nucleophilic addition of phosphites to imines. Because the biological activity of α-aminophosphonic acid derivatives depends very often on the absolute configuration of their α carbon, a strong effort has been made in the study of stereoselective Pudovik reactions,[6] mainly focused in the catalytic hydrophosphonylation of imines.[7] However, there are only few examples of diastereoselective Pudovik reactions with acyclic imines using chiral phosphites.[6] Addition of (–)-bornyl and (–)-menthyl phosphites **I** and **II** (Fig. 1) to *N*-benzylimine derived from benzaldehyde has been reported to afford α-aminophosphonates with moderate to good diastereoselectivity.[8]

Last years we have been involved in the synthesis of α-[9] and β-aminophosphonate[10] derivatives and we even used TADDOL phosphoimidate derivatives as catalyst for the asymmetric synthesis of α-dehydroaminoester derivatives.[11] In this context, we thought[12,13] that TADDOL derived phosphite[14] **IV** (Fig. 1) would be a suitable candidate as phosphorus nucleophile for Pudovik reactions. (*R*,*R*)-TADDOL auxiliary is easily prepared in a simple two step procedure from cheap natural tartaric acid[15] and, unlike natural alcohols, only one unit of chiral auxiliary relative to phosphorus is needed for the preparation of the hydrogenphosphonate ester. Moreover, TADDOL phosphite derivative shows a C-2 symmetry, implying the presence of a non chiral phosphorus(V)

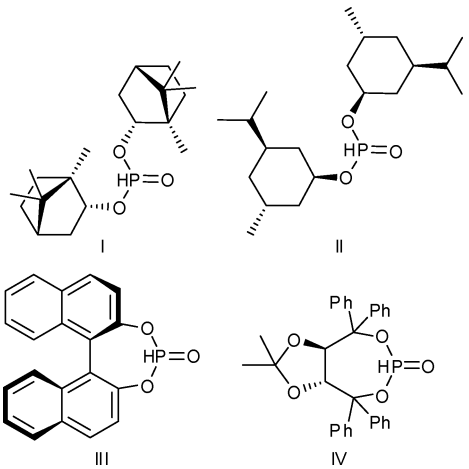
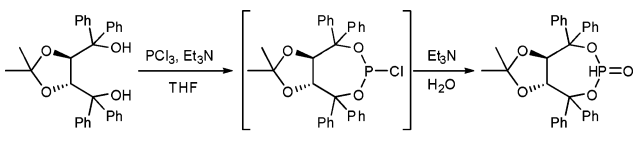


Fig. 1 (–)-Borneol **I**, (–)-Menthol **II**, (*R*)-(+)-BINOL **III** and TADDOL **IV** derived phosphites.

which avoids the presence of mixtures of diastereoisomers and their separation. Furthermore, the endocyclic P–O bonds in the 7-membered ring, now including four sp^3 carbons, would be more stable than in the case of BINOL phosphite **III** as this is a less strained structure. Now, as a continuation of our work in the field of aminophosphorus compounds we report here a diastereoselective hydrophosphonylation of imines using a TADDOL derived phosphite and applied to the stereoselective synthesis of α-aminophosphonic acids.

Results and discussion

(*R*,*R*)-TADDOL derived phosphite **3** is easily synthesized by generation of chlorophosphite **2** from (*R*,*R*)-TADDOL **1** and PCl_3 and subsequent hydrolysis '*in situ*' with triethylamine in aqueous media (Scheme 1, 95%).



Scheme 1 Synthesis of (*R*,*R*)-TADDOL phosphite **3**.

First we tested the hydrophosphonylation reaction of several aldimines derived from benzaldehyde in THF or CH_2Cl_2 (Table 1). In terms of chiral induction, it was established that the use of diphenylphosphinylimines is preferred if compared to tosyl or benzylamines. The larger size of diphenylphosphinyl substituent at the nitrogen might be the reason for this behaviour. The benefits of diphenylphosphinyl substituent on the electronic activation

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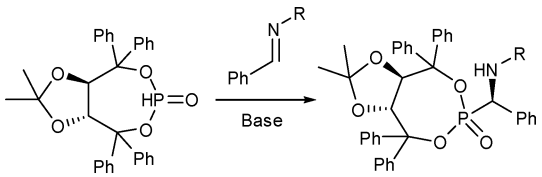
† Electronic supplementary information (ESI) available: Preparation and full characterization of compounds **3**, **4f–h** and **5** and copies of ^1H, ^{13}C of α-aminophosphonates **4**. See DOI: 10.1039/c003004j

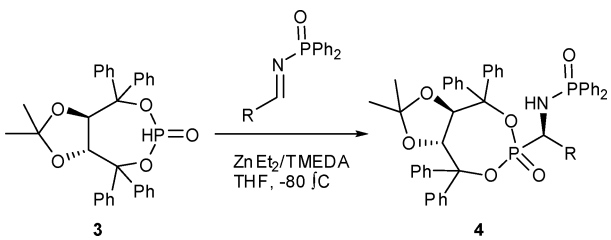
Table 1 Hydrophosphonylation of aldimines derived from benzaldehyde with (*R*,*R*)-TADDOL phosphite **3**



Entry	*R*	Base	Solvent	*T*/°C	%Conv[a]	dr[a]
1	Bz	LDA (1 eq.)	THF	–80	97	56 : 44
2	Bz	$ZnEt_2$/TMEDA (1 eq.)	THF	–80	48	65 : 35
3	Ts	LDA (1 eq.)	THF	–80	88	75 : 25
4	Ts	$ZnEt_2$/TMEDA (1 eq.)	THF	–80	79	62 : 38
5	$POPh_2$	Et_3N (1 eq.)	CH_2Cl_2	r.t.	90	45 : 55
6	$POPh_2$	No	CH_2Cl_2	r.t.	0	—
7	$POPh_2$	No	CH_2Cl_2	40	0	—
8	$POPh_2$	LDA	THF	–80	75	74 : 26
9	$POPh_2$	$ZnEt_2$ (1 eq.)	THF	–80	70	70 : 30
10	$POPh_2$	$ZnEt_2$/TMEDA (1 eq.)	THF	–80	82	92 : 8
11	$POPh_2$	$ZnEt_2$/TMEDA (1.2 eq.)	THF	–80	90	>95 : 5
12	$POPh_2$	$ZnEt_2$/TMEDA (1.5 eq.)	THF	–80	95	>95 : 5
13	$POPh_2$	$ZnEt_2$/TMEDA (1.8 eq.)	THF	–80	97	>95 : 5
14	$POPh_2$	$ZnEt_2$/TMEDA (2.1 eq.)	THF	–80	97	>95 : 5

[a] Determined by ^{31}P NMR.

Table 2 Hydrophosphonylation of *N*-diphenylphosphinyl aldimines with (*R*,*R*)-TADDOL phosphite **3**



Entry	Comp.	R	%Yield[a]	^{31}P NMR (major)	^{31}P NMR (minor)	dr[b]
1	**4a**	Ph	80	18.2, 25.0	17.1, 24.8	>95 : 5
2	**4b**	1-Naphthyl	75	18.6, 25.1	16.5, 25.0	>95 : 5
3	**4c**	2-Naphthyl	73	18.0, 25.1	16.9, 25.5	>95 : 5
4	**4d**	*p*-MeO–C_6H_4	82	18.3, 24.5	17.2, 24.5	>95 : 5
5	**4e**	*p*-CF_3–C_6H_4	75	17.2, 25.3	16.2, 25.1	>95 : 5
6	**4f**	2-Furyl	80	14.5, 25.4	14.5, 25.3	91 : 9
7	**4g**	2,4,6-$Me_3C_6H_2$	59	18.6, 24.7	20.4, 23.8	85 : 15
8	**4h**	*i*-Pr	65	19.2, 23.0	18.9, 22.7	87 : 13

[a] Isolated yield. [b] Determined by ^{31}P NMR.

of aldimines as well as its effects in stereoselective nucleophilic addition reactions is well documented.[16]

Moreover, although very good conversions were obtained in general at low temperature when the reaction was performed using one equivalent of LDA as a base (Table 1, Entries 1, 3, 8), much better diastereoselectivities with still a good yield are obtained when $ZnEt_2$ is used instead (Table 1, Entries 2, 4, 10). The presence of one equivalent of tetramethylethylenediamine (TMEDA) is crucial in order to favour the solubility of $ZnEt_2$ in THF at low temperature by a coordination effect between the Zn and N atoms, since very low yields were obtained when TMEDA was not present (Table 1, Entry 9). Switching the solvent to CH_2Cl_2 did not improve the diastereoselectivity when Et_3N was used as a base (Table 1, Entry 5) and, in the same solvent, the hydrophosphinylation reaction did not proceed in the absence of a base (Table 1, Entries 6–7). The conversions in THF at low temperature were finally improved to almost quantitative when the amount of $ZnEt_2$/TMEDA was increased (Table 1, Entries 10–14) without dropping in the diastereoselectivities.

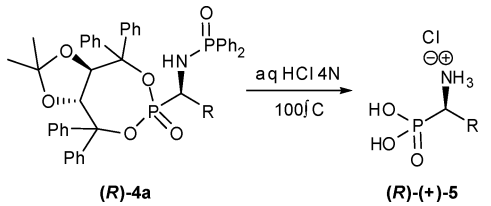
With these results in hands we extended the hydrophosphonylation reaction to several aromatic diphenylphosphinyl aldimines (Table 2). Treatment of *N*-diphenylphosphinyl aldimines in THF at –80 °C with TADDOL phosphonate **3** in the presence of 1.2 eq. of $ZnEt_2$ and TMEDA during 12 h afforded in good yields the corresponding aminophosphonates **4** with very good diastereoselectivities.

The reaction is applicable to *N*-diphenylphosphinyl aryl aldimines (R = Ph, 1-naphthyl, 2-naphthyl), bearing electron rich (R = *p*-MeO–C_6H_4, Table 2, Entry 4) and electron poor (R = *p*-CF_3–C_6H_4, Table 2, Entry 5) substituents as well as heteroaromatic groups (*R* = 2-furyl, Table 2, Entry 6) at the α position. A substantial drop in the yield and diastereoselectivity was observed when an ortho substituted arylimine was used which may be due to the steric crowding in the electrophilic imine carbon (*R* = 2,4,6-$Me_3C_6H_2$, Table 2, Entry 7). Previous reports have described the generation '*in situ*' of *N*-phosphinylimines from phosphorylated aminosulfones using $ZnEt_2$ as base.[17] In our case, an important fall in the diastereoselectivity and conversion was observed when aromatic *N*-phosphinylimines were generated '*in situ*' with $ZnEt_2$ and subsequently treated with TADDOL phosphite **3** in the presence of TMEDA (60% yield, d.r. = 65 : 45).

The diastereoselective addition of TADDOL phosphite **3** was also extended to imines derived from aliphatic aldehydes. Although required aliphatic imines are normally only available '*in situ*', isolation of *N*-phosphinylimine derived from isobutyraldehyde, from the corresponding aminosulfone, by β-elimination of sulfonic acid using $NaHCO_3$ as base, followed by filtration and evaporation is feasible. Treatment of unpurified *N*-phosphinyl isobutyraldimine in the optimized conditions afforded the target aminophosphonate **4h** in moderate yield and diastereoselectivity (Table 2, Entry 8).

It should be emphasized that pure samples of the major diastereoisomer can be obtained in all cases by simple purification of the crude mixtures by chromatography. This strategy represents an improvement not only in conversions but also in the diastereoselectivities respect to the other two reported examples of addition of chiral phosphites to imines.

The synthesis of enantiopure aminophosphonic acids **5** is achieved by simultaneous hydrolysis of (*R*,*R*)-TADDOL phosphite and diphenylphosphinyl groups of the major diastereoisomer of α-aryl and α-alkyl α-aminophosphonates **4a,h** in refluxing aqueous HCl 4 N (Scheme 2, 77–82%). The monitoring of selective deprotection of amino group in milder conditions, at room temperature and increasing the concentration of hydrochloric acid from 0.1 M to 2 M, showed mixtures of mono-deprotected phosphonate and double-deprotected phosphonic acid. Comparison of the optical rotation with literature values showed an (*R*) absolute configuration for the aminophosphonic analog of (*R*)-phenylglycine **5a** (R = Ph) and (*R*)-valine **5b** (R = *i*-Pr).



Scheme 2 Simultaneous deprotection of amino and phosphonate groups.

According to the configuration of the stereogenic center we propose a model for the addition of phosphite[18] where the seven membered ring adopts a more stable boat conformation fixed by the *trans* configuration of the five-membered ring, where the two heteroatoms adopt the most stable equatorial orientation with the two hydrogens in axial conformation (see Fig. 2). The alkoxy group

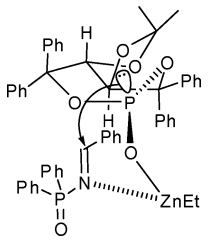


Fig. 2 Model for the hydrophosphonylation of *N*-diphenylphosphinoyl imines with (*R*,*R*)-TADDOL phosphite **3**.

in the metalated phosphite tautomer is expected to adopt an axial orientation due to the anomeric effect and the Zn counteranion ionically bonded to the oxygen would be coordinated to the lone pair of the iminic nitrogen. The diphenylphosphinoyl group pointing opposite to the Zn makes the imine approach to the phosphite lone pair with the appropriate orientation for the nucleophilic attack of the phosphorus to the *Re* face.

Conclusions

In summary we report an easy synthesis of enantiopure α-aminophosphonic acid derivatives through diastereoselective hydrophosphonylation of *N*-diphenylphosphinylimines using an efficient (*R*,*R*)-TADDOL derived phosphorus nucleophile. Easily available (*R*,*R*)-TADDOL phosphite, prepared from very cheap comercially available natural tartaric acid, affords (*R*)-α-aminophosphonic acids. This is not trivial, since it is well known that in most of the occasions (*R*) forms of α-aminophosphonic acids[2,6] are more active than their (*S*) isomers. As far as we know the results reported here represent the best conversions and/or diastereoselectivities reported so far in the addition of chiral phosphites to imines.

Experimental section

Representative example for the diastereoselective hydrophosphonylation of imines using TADDOL phosphite 3. Synthesis of 1,3-dioxolo[4,5-e][1,3,2]dioxaphosphepin, tetrahydro-2,2-dimethyl-6-[diphenylphosphinoylamino-1-phenylmethyl]-4,4,8,8 tetraphenyl-, 6-oxide, (3a*R*,8a*R*) (4a)

TADDOL phosphite **3** (1.0 g, 1.95 mmol) was dissolved in dry THF (15 mL) and the solution was cooled down to –80 °C. A 1.1 M solution of Et_2Zn in toluene (2.14 mL) and TMEDA (0.3 mL, 1.95 mmol) were injected and the mixture was stirred for 15 min at –80 °C. After that time the solution of *N*-benzylidene-*P*,*P*-diphenylphosphinic amide (0.60 g, 1.95 mmol) in dry THF (15 mL) was added dropwise. The stirring was continued for 12 h at –80 °C before quenching with sat. aq. NH_4Cl (15 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure affording crude product that was further purified by column chromatography (SiO_2, EtOAc/Hexane) affording 1.28 g (80%) of **4a** as a white solid. Mp. 165–167 °C. $[\alpha]_D^{20}$ –111.4 (*c* 1.0, CH_2Cl_2). R_f (EtOAc/Pentane 2 : 1): 0.40. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.43 (s, 3H, CH_3), 0.88 (s, 3H, CH_3), 3.75–3.80 (m, 1H, NH), 4.68–4.83 (m, 1H, CHP), 4.96 (d, $^3J_{HH}$ = 8.0 Hz, 1H, CHO), 5.54 (d,

$^{3}J_{HH}$ = 8.0 Hz, 1H, CHO), 6.96–7.90 (m, 35H, CH_{ar}).^{13}C NMR (75 MHz, $CDCl_3$): δ 26.4 (CH_3), 27.2 (CH_3), 53.4 (d, $^{1}J_{PC}$ = 161.7 Hz, CHP), 79.1 (d, $^{3}J_{PC}$ = 2.0 Hz, CHO), 80.2 (d, $^{3}J_{PC}$ = 2.0 Hz, CHO), 87.1 (d, $^{2}J_{PC}$ = 8.4 Hz, CPh_2), 91.0 (d, $^{2}J_{PC}$ = 13.4 Hz, CPh_2), 113.8 ($C(CH_3)_2$), 126.6 (2 × CH_{ar}), 127.2 (2 × CH_{ar}), 127.3 (2 × CH_{ar}), 127.4 (2 × CH_{ar}), 127.6 (CH_{ar}), 127.8 (CH_{ar}), 127.9 (CH_{ar}), 128.0 (2 × CH_{ar}), 128.1 (d, $^{3}J_{PC}$ = 5.4 Hz, 2 × CH_{ar}), 128.3 (2 × CH_{ar}), 128.4 (4 × CH_{ar}), 128.5 (CH_{ar}), 128.6 (d, $^{3}J_{PC}$ = 7.8 Hz, 2 × CH_{ar}), 128.9 (2 × CH_{ar}), 129.8 (2 × CH_{ar}), 131.2 (d, $^{1}J_{PC}$ = 102.3 Hz, 2 × Cq), 131.9 (CH_{ar}), 132.0 (CH_{ar}), 132.1 (2 × CH_{ar}), 132.2 (CH_{ar}), 132.3 (2 × CH_{ar}), 132.6 (d, $^{3}J_{PC}$ = 9.1 Hz, 2 × CHar), 136.4 (C_q), 139.4 (C_q), 139.6 (C_q), 143.7 (C_q), 144.3 (d, $^{2}J_{PC}$ = 7.6 Hz, C_q). ^{31}P NMR (120 MHz, $CDCl_3$): δ 18.2 (d, $^{3}J_{PP}$ = 39.7 Hz, $PO(OR)_2$), 25.2 (d, $^{3}J_{PP}$ = 39.7 Hz, $POPh_2$). FTIR (neat) ν_{max}/cm^{-1}: 3432 (N–H st), 1225 (P═O st). CIMS *m*/*z* (amu): 818 ([M+H], 100). HRMS (amu) Calcd for $C_{50}H_{46}NO_6P_2$ $(M+H)^+$ 818.2800; Found, 818.2772.

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