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Synthesis of Tetrasubstituted α-Aminophosphonic Acid Derivatives from Trisubstituted α-Aminophosphonates

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An efficient method for the preparation of quaternary α-aminophosphonic acid derivatives is reported. The nucleophilic addition of organometallic reagents to α-ketiminophosphonates allows the preparation of quaternary α-aminophosphonates. The diastereoselective synthesis of a quaternary α-aminophosphonate using a chiral tartaric-acid-derived phosphonate is also described.

Introduction

Quaternary stereogenic centres are ubiquitous in natural products and pharmaceutical agents, and the efficient formation of quaternary centres is still a crucial challenge in chemical synthesis.[1] The formation of quaternary centres from ketones and ketimines was for a long time unachievable, due to the low electrophilicity of the carbonyl or ketimine groups and also to steric hindrance, both of which contributed to the lack of reactivity.[2]

Aminophosphorus derivatives are significant compounds in organic and medicinal chemistry.[3] The biological activity and natural occurrence of α-aminophosphonates was discovered half a century ago.[4] Since then, the chemistry and biology of these compounds have been widely developed.[5] They can be considered to be isosteres of α-amino acids, where the planar carboxylic acid has been substituted by a bulkier tetrahedral phosphonate moiety. As may be envisaged based on this structural analogy, simple α-aminophosphonic acid molecules or their phosphonate esters, as well as their phosphapeptide derivatives, have found numerous applications,[6] for example, as haptens of catalytic antibodies,[7a] peptide mimetics,[7b] enzyme inhibitors,[7c] and antibacterial agents,[7d] as well as agrochemical applications.[8]

The biological potential of α-aminophosphonates has resulted in considerable attention being given to the development of improved methods for their synthesis.[9] However, few methods have been described for the preparation of α-aminophosphonates containing quaternary centres in the α-position.[9] One straightforward method for the preparation of α-aminophosphonates consists of the addition of nucleophiles to α-iminophosphonates.[10] Progress in this field is complicated by the availability of the starting imines, and to date, most of the research has been limited to phosphaaldimines,[10b–10d] which may only be used for the generation of tertiary aminophosphonates.

In recent years, our group has been involved in the preparation of phosphorus-containing three-,[11] five-,[12] and six-membered[13] heterocycles, and in the preparation of simple,[14] vinylic[15] α-aminophosphonates as well as phosphadepsipeptides derived from α-aminophosphonates,[16] and we recently reported an efficient synthesis of β,γ-unsaturated α-iminophosphonates by an aza-Wittig approach.[17] These imines have been shown to have very variable reactivities, and have proved to be very useful intermediates for the synthesis of several α-aminophosphonic acid derivatives.[18] Although it is quite general, one of the drawbacks of the aza-Wittig methodology is that only *N*-aryl phosphazenes can be used for the generation of the imine bond, which means that only *N*-aryl-α-iminophosphonates can be prepared. For this reason, we recently developed an improved strategy for the synthesis of α-iminophosphonates derived from ketones by formal oxidation of the C–N single bond of the parent trisubstituted α-aminophosphonates.[10a] As part of on ongoing research into the chemistry of α-aminophosphonates and α-iminophosphonates, we report in this paper the synthesis of tetrasubstituted α-aminophosphonic acid derivatives by nucleophilic addition of Grignard reagents or sodium acetylide to α-ketiminophosphonates, which are generated by the oxidation of trisubstituted α-aminophosphonates.

Results and Discussion

The substitution of a hydrogen atom by an alkyl group (electrophilic reagent, E–X, Scheme 1) has been reported for secondary α-aminophosphonates **IV** (R^2 = H, Scheme 1).[19] However, only one example has been de-

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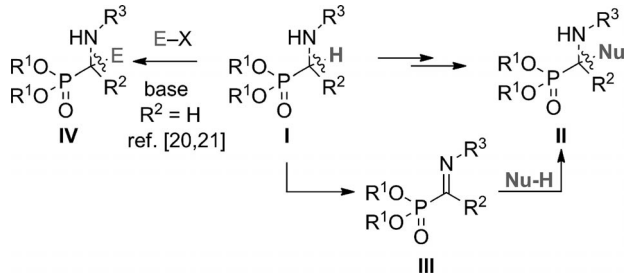
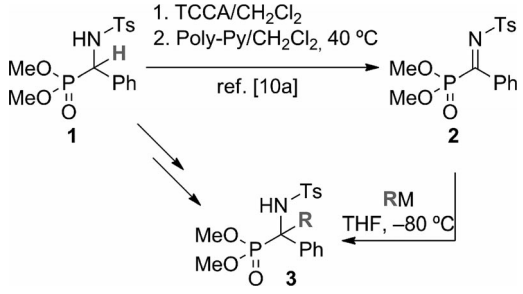
scribed for an acyclic tertiary α-aminophosphonate **IV** ($R^2 \neq H$),[20] and three examples have been reported for cyclic tertiary α-aminophosphonates **IV**.[21] The conversion of α-aminophosphonate **I** into an imine derivative would open a route for the overall substitution of a hydrogen atom by a nucleophilic reagent. This could allow the conversion of a tertiary α-aminophosphonate into a quaternary α-aminophosphonate, and may be considered to be complementary (an "umpolung reaction") to the electrophilic substitution of tertiary α-aminophosphonates. The fact that this method uses nucleophilic reagents would even allow the introduction of, for example, aryl groups, which are not easily introduced using electrophilic reagents.



Scheme 1. General strategies for the synthesis of quaternary α-aminophosphonates.

The construction of a carbon–nitrogen double bond from α-amino-phosphonate **1** may be performed by selective *N*-chlorination of tertiary *N*-tosyl α-aminophosphonate **1** with an excess of trichloroisocyanuric acid (TCCA) in CH_2Cl_2, followed by treatment with an excess of poly-(4-vinylpyridine), to give α-ketiminophosphonate **2** (Scheme 2).[10a] The presence of phosphonate and sulfonyl groups in the structure of α-ketiminophosphonates **2** gives electrophilic character to their iminic carbons and makes them suitable substrates for nucleophilic addition reactions.



Scheme 2. Synthesis of quaternary α-aminophosphonates.

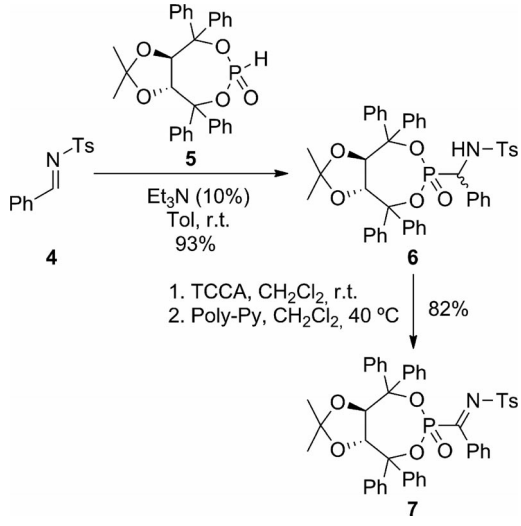
Therefore, treatment of α-ketiminophosphonate **2** with organometallic reagents at –80 °C gave quaternary α-aminophosphonates **3** in very high yields (Table 1). The reaction is quite general, since it allowed the preparation of quaternary α-aminophosphonates with the introduction of a second alkyl group (Table 1, entries 1 and 2), or of an allyl group (Table 1, entry 3) or, remarkably, of a nucleophilic aryl group (Table 1, entries 4–6) when Grignard reagents were used. But also, it allowed the incorporation of an alkynyl group (Table 1, entry 7), when sodium acetylide was used. As far as we know, these are the first examples of the formal substitution of a hydrogenatom from a tertiary α-aminophosphonate **1** by an organometallic reagent (an "umpolung reaction") to obtain a quaternary α-aminophosphonate **3** (Scheme 2; **I** and **III** in Scheme 1).

Table 1. Synthesis of quaternary α-aminophosphonates **3** from α-iminophosphonates **2**.

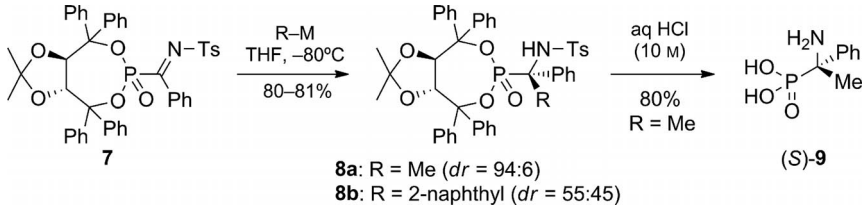
Entry		R-M	Yield [%][a]
1	**3a**	MeMgBr	80
2	**3b**	EtMgBr	81
3	**3c**	CH_2=CH–CH_2MgBr	77
4	**3d**	PhMgBr	79
5	**3e**	(2-naphthyl)MgBr	79
6	**3f**	(3,4-methylenedioxyphenyl)MgBr	78
7	**3g**	CH≡CNa	80

[a] Yield of isolated purified α-aminophosphonates **3** from α-iminophosphonates **2**.

In recent years, some syntheses of optically active quaternary α-aminophosphonic acid derivatives have been reported based on the chiral auxiliary approach. In such methods, a phosphorus reagent reacts with chiral imines[22] or amines,[23] or imidazolidine-derived phosphono esters are alkylated.[24] However, there is no precedent for the diastereoselective generation of quaternary α-aminophosphonates using a chiral phosphorus template. Therefore, TADDOL-derived (TADDOL = 2,3-*O*-isopropylidene-1,1,4,4-tetraphenylthreitol) α-ketiminophosphonate **7** was generated by oxidation of the parent α-aminophosphonate (i.e., **6**; Scheme 3). TADDOL-derived α-aminophosphonate **6** was generated by Pudovik-type hydrophosphonylation of tosylimine **4** using TADDOL phosphite **5**. α-Aminophosphonate **6** was obtained in excellent yield as a mixture of diastereoisomers (Scheme 3, 93%, *dr* = 77:23) from which a single diastereoisomer could be isolated, if needed, by crystallization from diethyl ether. Selective *N*-chlorination of *N*-tosyl α-aminophosphonate **6** with trichloroisocyanuric



Scheme 3. Synthesis of TADDOL-derived α-ketiminophosphonate **7**.



Scheme 4. Synthesis of quaternary α-aminophosphonic acid (*S*)-**9**.

acid (TCCA) in CH_2Cl_2, followed by treatment with poly(4-vinylpyridine), gave α-ketiminophosphonate **7** (Scheme 3) in good yield (82%).

Nucleophilic addition of Grignard reagents to TADDOL-derived imine **7** at low temperature in THF gave enantiomerically enriched α-aminophosphonates **8** in good yields, but with variable diastereoselectivities.

Although no significant diastereoselectivity was observed for the addition of aromatic organometallic reagents (R = 2-naphthyl; *dr* = 55:45), the addition of methylmagnesium bromide at –80 °C gave quaternary α-aminophosphonate **8a** in a highly diastereoselective fashion (*dr* = 94:6). After crystallization from Et_2O, only one of the diastereoisomers was detected by NMR spectroscopy. Simultaneous hydrolysis of the phosphonate and tosyl groups using hydrochloric acid (10 M aq.) gave enantiomerically pure quaternary α-aminophosphonic acid (*S*)-**9** in good yield (Scheme 4). Comparison of the optical rotatory power of α-aminophosphonic acid (*S*)-**9** with literature values[25] confirmed an *S*-(+) absolute configuration of the stereocentre.

Based on the configuration of the stereogenic centre, we propose a model for the addition of the nucleophilic reagent. The phosphorus-containing seven-membered ring adopts a more stable boat conformation, fixed by the *trans* configuration of the fused five-membered ring. The two heteroatoms adopt the more stable equatorial orientations, with the two hydrogen atoms in axial positions (Figure 1). In this conformation, nucleophilic attack to the *Re* face is substantially favoured, due to the presence of the axial phenyl group, which blocks the *Si* face (Figure 1).

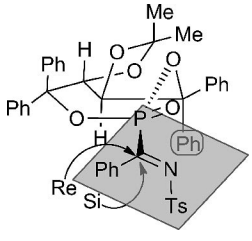


Figure 1. Model for the nucleophilic addition of organometallic reagents to α-ketiminophosphonate **7**.

Conclusions

In summary, we have described an efficient strategy for the preparation of quaternary α-aminophosphonates from tertiary α-iminophosphonates. The synthetic protocol comprises the generation of an intermediate α-iminophosphonate by oxidation of the amine C–N bond, and the subsequent nucleophilic addition of organometallic reagents. It should be noted that this method allows functionalization with nucleophilic reagents such as, for example, aryl or acetylenic groups; the introduction of such groups is less feasible when electrophilic reagents have to be used. The presence of the tosyl group on the nitrogen atom allows easy deprotection of the nitrogen, and is essential for the activation of the imine bond towards nucleophilic addition. This strategy opens a new approach for the preparation of quaternary α-aminophosphonic acid derivatives from tertiary α-aminophosphonates by formal substitution of the hydrogen atom by nucleophilic reagents, and allows the stereoselective addition of carbon nucleophiles to α-ketiminophosphonates.

Experimental Section

General Remarks: All reactions were performed under an atmosphere of dry nitrogen. ^1H (300 MHz), ^{13}C (75 MHz), and ^{31}P NMR (120 MHz) spectra were recorded in $CDCl_3$ with tetramethylsilane as an internal reference for ^1H and ^{13}C NMR spectra, and phosphoric acid as an external reference for ^{31}P NMR spectra. Chemical shifts are reported in ppm, and coupling constants are reported in Hertz. ^{13}C NMR peak assignments were supported by DEPT experiments. High-resolution mass spectra (HRMS) were obtained by positive-ion electrospray ionization (ESI). Infrared spectra (IR) were recorded as neat solids. Peaks are reported in cm^{-1}. α-Iminophosphonate **2**,[10] *N*-tosyl imine **4**,[26] and TADDOL phosphite **5**[27] were prepared following literature procedures.

Nucleophilic Addition of a Grignard Reagent or Sodium Acetylide to α-Ketiminophosphonate 2: An organometallic reagent (1.0 M solution in THF; 1.1 mL, 1.1 mmol) was added to a solution of α-ketiminophosphonate **2** (1.0 mmol) in THF (3 mL) at –80 °C. The mixture was stirred for 1 h at –80 °C, and then it was warmed to room temp. The reaction was then quenched with NH_4Cl (saturated aq.; 5 mL). The resulting mixture was diluted with CH_2Cl_2 (15 mL), washed with water (3 × 10 mL), dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography (EtOAc/hexanes, 4:1).

3a: White solid (80%), m.p. 161–162 °C (Et_2O). ^1H NMR: δ = 1.99 (d, $^3J_{P,H}$ = 16.9 Hz, 3 H, CH_3), 2.36 (s, 3 H, CH_3), 3.41 (d, $^3J_{P,H}$ = 10.6 Hz, 3 H, CH_3O), 3.82 (d, $^3J_{P,H}$ = 10.8 Hz, 3 H, CH_3O), 5.91 (d, $^3J_{P,H}$ = 7.8 Hz, 1 H, NH), 7.11 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, 2 CH_{Ar}), 7.20 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, 2 CH_{Ar}), 7.40–7.44 (m, 3 H, 3 CH_{Ar}), 7.54 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H, 2 CH_{Ar}) ppm. ^{13}C NMR: δ = 20.4 (d, $^2J_{P,C}$ = 5.2 Hz, CH_3), 21.3 (CH_3), 53.9 (d, $^2J_{P,C}$ = 7.0 Hz, CH_3O), 54.5 (d, $^2J_{P,C}$ = 7.1 Hz, CH_3O), 61.1 (d, $^1J_{P,C}$ = 152.2 Hz, $C_{quat}P$), 126.7 (2 CH_{Ar}), 128.0 (d, $^5J_{P,C}$ = 2.9 Hz, CH_{Ar}), 128.1 (d, $^4J_{P,C}$ = 2.2 Hz, 2 CH_{Ar}), 128.4 (d, $^3J_{P,C}$ = 6.0 Hz, 2 CH_{Ar}), 128.6

(2 CH_{Ar}), 133.4 (C_{quat}), 141.8 (d, $^2J_{P,C}$ = 1.7 Hz, C_{quat}), 142.3 (C_{quat}) ppm. ^{31}P NMR: δ = 26.1 ppm. IR: $\tilde{\nu}$ = 3315 (N–H st) 1332 (O=S=O st as) 1244 (P=O st), 1167 (O=S=O st sim) cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{22}NO_5PS$ $[M + H]^+$ 384.1035; found 384.1037.

3b: White solid (81%), m.p. 90–91 °C (Et_2O). ^1H NMR: δ = 1.02 (t, $^3J_{H,H}$ = 7.3 Hz, 3 H, CH_3), 2.31 (s, 3 H, CH_3), 2.37–2.66 (m, 2 H, CH_2), 3.37 (d, $^3J_{P,H}$ = 10.6 Hz, 3 H, CH_3O), 3.43 (d, $^3J_{P,H}$ = 10.5 Hz, 3 H, CH_3O), 5.63 (d, $^3J_{P,H}$ = 8.8 Hz, 1 H, NH), 7.07–7.09 (m, 5 H, 5 CH_{Ar}), 7.35 (d, $^3J_{H,H}$ = 7.0 Hz, 2 H, 2 CH_{Ar}), 7.47 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H, 2 CH_{Ar}) ppm. ^{13}C NMR: δ = 9.6 (CH_3), 21.7 (CH_3), 27.6 (CH_2), 53.9 (d, $^2J_{P,C}$ = 7.6 Hz, CH_3O), 54.5 (d, $^2J_{P,C}$ = 7.5 Hz, CH_3O), 65.9 (d, $^1J_{P,C}$ = 148.1 Hz, C_{quat}), 127.2 (CH_{Ar}), 127.3 (2 CH_{Ar}), 128.1 (d, $^3J_{P,C}$ = 2.5 Hz, 2 CH_{Ar}), 128.5 (d, $^4J_{P,C}$ = 5.2 Hz, 2 CH_{Ar}), 129.4 (2 CH_{Ar}), 136.5 (d, $^2J_{P,C}$ = 4.5 Hz, C_{quat}), 139.9 (d, $^4J_{P,C}$ = 1.4 Hz, C_{quat}), 143.2 (C_{quat}) ppm. ^{31}P NMR: δ = 25.6 ppm. IR: $\tilde{\nu}$ = 3307 (NH st), 1322 (O=S=O st as), 1230 (P=O st), 1160 (O=S=O st sim) cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{24}NO_5PS$ $[M + H]^+$ 398.1186; found 398.1193.

3c: White solid (77%), m.p. 141–142 °C (Et_2O). ^1H NMR: δ = 2.40 (s, 3 H, CH_3), 2.65 (m, 1 H, CH_2), 2.92 (m, 1 H, CH_2), 4.95–5.33 (m, 2 H, CH_2=), 5.57 (d, $^3J_{P,H}$ = 9.6 Hz, 1 H, NH), 3.49 (d, $^3J_{P,H}$ = 10.6 Hz, 3 H, CH_3O), 7.09–7.42 (m, 7 H, 7 CH_{Ar}), 7.50 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H, 2 CH_{Ar}) ppm. ^{13}C NMR: δ = 21.7 (CH_3), 39.3 (d, $^2J_{P,C}$ = 1.5 Hz, CH_2), 54.0 (d, $^2J_{P,C}$ = 7.6 Hz, CH_3O), 54.5 (d, $^2J_{P,C}$ = 7.8 Hz, CH_3O), 64.7 (d, $^1J_{P,C}$ = 148.7 Hz, CHP), 119.8 (d, $^4J_{P,C}$ = 13.6 Hz, CH_2=), 127.1 (d, $^5J_{P,C}$ = 3.7 Hz, CH_{Ar}), 127.3 (2 CH_{Ar}), 128.1 (2 CH_{Ar}), 128.6 (d, $^3J_{P,C}$ = 5.0 Hz, 2 CH_{Ar}), 129.3 (d, $^4J_{P,C}$ = 3.3 Hz, 2 CH_{Ar}), 132.9 (d, $^2J_{P,C}$ = 2.9 Hz, C_{quat}), 133.2 (d, $^3J_{P,C}$ = 11.6 Hz, CH=), 139.8 (C_{quat}), 143.3 (C_{quat}) ppm. ^{31}P NMR: δ = 24.6 ppm. IR: $\tilde{\nu}$ = 3312 (NH st), 1329 (O=S=O st as), 1240 (P=O st), 1170 (O=S=O st sim). HRMS (ESI): calcd. for $C_{19}H_{25}NO_5PS$ $[M + H]^+$ 410.1191; found 410.1188.

3d: White solid (79%), m.p. 176–177 °C (Et_2O). ^1H NMR: δ = 2.34 (s, 3 H, CH_3), 3.50 (d, $^3J_{P,H}$ = 10.5 Hz, 6 H, 2 CH_3O), 5.91 (d, $^3J_{P,H}$ = 10.0 Hz, 1 H, NH), 6.96 (d, $^3J_{H,H}$ = 8.2 Hz, 4 H, 2 CH_{Ar}), 7.06 (d, $^3J_{H,H}$ = 8.2 Hz, 4 H, 2 CH_{Ar}), 7.17–7.25 (m, 6 H, 6 CH_{Ar}), 7.79 (m, 4 H, 4 CH_{Ar}) ppm. ^{13}C NMR: δ = 21.4 (CH_3), 54.5 (d, $^2J_{P,C}$ = 7.8 Hz, 2 CH_3O), 69.2 (d, $^1J_{P,C}$ = 149.4 Hz, C_{quat}P), 126.4 (2 CH_{Ar}), 127.5 (d, $^4J_{P,C}$ = 1.5 Hz, 4 CH_{Ar}), 128.0 (d, $^5J_{P,C}$ = 2.1 Hz, 2 CH_{Ar}), 128.8 (2 CH_{Ar}), 130.3 (d, $^3J_{P,C}$ = 6.0 Hz, 4 CH_{Ar}), 135.6 (d, $^2J_{P,C}$ = 4.2 Hz, 2 C_{quat}), 139.0 (C_{quat}), 142.2 (C_{quat}) ppm. ^{31}P NMR: δ = 23.8 ppm. IR: $\tilde{\nu}$ = 3314 (NH st), 1365 (O=S=O st as), 1222 (P=O st), 1166 (O=S=O st sim). HRMS (ESI): calcd. for $C_{22}H_{25}NO_5PS$ $[M + H]^+$ 446.1191; found 446.1188.

3e: White solid (79%), m.p. 211–212 °C (Et_2O). ^1H NMR: δ = 2.09 (s, 3 H, CH_3), 3.40 (d, $^3J_{P,H}$ = 10.5 Hz, 3 H, CH_3O), 3.48 (d, $^3J_{P,H}$ = 10.6 Hz, 3 H, CH_3O), 6.00 (d, $^3J_{P,H}$ = 10.6 Hz, 1 H, NH), 6.60 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, 2 CH_{Ar}), 6.88 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H, 2 CH_{Ar}), 7.19–7.68 (m, 11 H, 11 CH_{Ar}), 7.98 (s, 1 H, 1 CH_{Ar}) ppm. ^{13}C NMR: δ = 21.2 (CH_3), 54.5 (d, $^2J_{P,C}$ = 7.7 Hz, CH_3O), 54.7 (d, $^2J_{P,C}$ = 7.9 Hz, CH_3O), 69.3 (d, $^1J_{P,C}$ = 148.2 Hz, C_{quat}), 125.8–130.2 (m, 16 CH_{Ar}), 132.3 (d, $^5J_{P,C}$ = 1.5 Hz, C_{quat}), 132.6 (d, $^2J_{P,C}$ = 4.8 Hz, C_{quat}), 132.7 (d, $^4J_{P,C}$ = 1.1 Hz, C_{quat}), 135.6 (d, $^2J_{P,C}$ = 5.5 Hz, C_{quat}), 138.6 (C_{quat}), 142.2 (C_{quat}) ppm. ^{31}P NMR: δ = 23.9 ppm. IR: $\tilde{\nu}$ = 3357 (NH st), 1325 (O=S=O st as), 1236 (P=O st), 1157 (O=S=O st sim). HRMS (ESI): calcd. for $C_{26}H_{26}NO_5PS$ $[M + H]^+$ 496.1342; found 496.1344.

3f: White solid (78%), m.p. 167–168 °C (Et_2O). ^1H NMR: δ = 2.34 (s, 3 H, CH_3), 3.41 (d, $^3J_{P,H}$ = 10.5 Hz, 3 H, CH_3O), 3.60 (d, $^3J_{P,H}$ = 10.6 Hz, 3 H, CH_3O), 5.85 (d, $^2J_{H,H}$ = 1.4 Hz, 1 H, CH_2O), 5.85 (d, $^3J_{P,H}$ = 10.9 Hz, 1 H, NH), 5.91 (d, $^2J_{H,H}$ = 1.4 Hz, 1 H, CH_2O), 6.54 (d, $^3J_{H,H}$ = 9.3 Hz, 1 H, CH_{Ar}), 6.93 (m, 2 CH_{Ar}), 6.99 (d, $^3J_{H,H}$ = 7.4 Hz, 2 H, 2 CH_{Ar}), 7.11 (dd, $^3J_{H,H}$ = 8.2, $^4J_{P,H}$ = 1.5 Hz, 2 H, 2 CH_{Ar}), 7.25–7.27 (m, 3 H, 3 CH_{Ar}), 7.62 (m, 2 H, 2 CH_{Ar}) ppm. ^{13}C NMR: δ = 21.2 (CH_3), 54.1 (d, $^2J_{P,C}$ = 7.9 Hz, CH_3O), 54.6 (d, $^2J_{P,C}$ = 7.7 Hz, CH_3O), 68.6 (d, $^1J_{P,C}$ = 149.3 Hz, C_{quat}), 101.0 (CH_2O), 106.8 (CH_{Ar}), 111.0 (d, $^3J_{P,C}$ = 6.0 Hz, CH_{Ar}), 124.8 (d, $^3J_{P,C}$ = 7.5 Hz, CH_{Ar}), 126.3 (2 CH_{Ar}), 127.3 (d, $^3J_{P,C}$ = 2.3 Hz, 2 CH_{Ar}), 128.0 (d, $^5J_{P,C}$ = 2.3 Hz, CH_{Ar}), 128.5 (2 CH_{Ar}), 128.9 (d, $^2J_{P,C}$ = 4.8 Hz, C_{quat}), 130.0 (d, $^4J_{P,C}$ = 5.4 Hz, 2 CH_{Ar}), 135.7 (d, $^2J_{P,C}$ = 5.3 Hz, C_{quat}), 139.0 (C_{quat}), 142.1 (C_{quat}), 146.6 (d, $^5J_{P,C}$ = 1.5 Hz, C_{quat}), 147.1 (d, $^4J_{P,C}$ = 1.8 Hz, C_{quat}) ppm. ^{31}P NMR: δ = 23.8 ppm. IR: $\tilde{\nu}$ = 3244 (NH st), 1335 (O=S=O st as), 1232 (P=O st) 1161 (O=S=O st sim). HRMS (ESI): calcd. for $C_{26}H_{26}NO_5PS$ $[M + H]^+$ 490.1084; found 490.1112.

3g: White solid (77%), m.p. 181–182 °C (Et_2O). ^1H NMR: δ = 2.31 (s, 3 H, CH_3), 2.67 (d, $^4J_{H,H}$ = 6.0 Hz, ≡CH), 3.39 (d, $^3J_{P,H}$ = 10.6 Hz, 3 H, CH_3O), 3.73 (d, $^3J_{P,H}$ = 10.7 Hz, 3 H, CH_3O), 5.81 (d, $^3J_{P,H}$ = 5.8 Hz, 1 H, NH), 7.08 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H, 2 CH_{Ar}), 7.20–7.22 (m, 3 H, 3 CH_{Ar}), 7.53 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H, 2 CH_{Ar}), 7.59 (m, 2 H, 2 CH_{Ar}) ppm. ^{13}C NMR: δ = 21.5 (CH_3), 55.8 (d, $^2J_{P,C}$ = 7.4 Hz, CH_3O), 55.9 (d, $^2J_{P,C}$ = 7.4 Hz, CH_3O), 58.5 (d, $^1J_{P,C}$ = 160.0 Hz, C_{quat}), 77.0 (d, $^3J_{P,C}$ = 23.1 Hz, ≡CH), 79.0 (d, $^2J_{P,C}$ = 8.8 Hz, ≡CH), 127.7 (d, $^3J_{P,C}$ = 4.7 Hz, 2 CH_{Ar}), 128.1 (d, $^4J_{P,C}$ = 2.6 Hz, 2 CH_{Ar}), 128.5 (d, $^5J_{P,C}$ = 2.9 Hz, CH_{Ar}), 129.0 (2 CH_{Ar}), 133.7 (d, $^2J_{P,C}$ = 6.2 Hz, C_{quat}), 138.2 (C_{quat}), 143.4 (C_{quat}) ppm. ^{31}P NMR: δ = 18.3 ppm. IR: $\tilde{\nu}$ = 3310 (NH st), 3257 (≡C–H st), 2109 (C≡C), 1325 (O=S=O st as), 1249 (P=O st) 1157 (O=S=O st sim). HRMS (ESI): calcd. for $C_{18}H_{20}NO_5PS$ $[M + H]^+$ 394.0873; found 394.0879.

Synthesis of TADDOL α-Aminophosphonate 6: Triethylamine (0.35 mL, 2.5 mmol) was added to a suspension of *N*-tosylimine **4** (6.48 g, 25 mmol) and TADDOL phosphite **5** (12.8 g, 25 mmol) in toluene (50 mL), and the reaction mixture was heated at reflux in toluene for 24 h. The solvent was evaporated under vacuum, and the resulting solid was purified by crystallization from diethyl ether to give **6** (17.95 g, 93%) as a mixture of diastereoisomers (*dr* = 77:23, determined by ^{31}P NMR spectroscopy). A second crystallization from diethyl ether gave a single diastereoisomer of **6** (13.7 g, 71%) as a white solid (*dr* > 95:5, determined by ^{31}P NMR spectroscopy), m.p. 235–236 °C (Et_2O). ^1H NMR: δ = 0.49 (s, 3 H, CH_3), 0.79 (s, 3 H, CH_3), 2.29 (s, 3 H, CH_3), 4.85 (dd, $^3J_{H,H}$ = 7.1, $^2J_{P,H}$ = 24.6 Hz, 1 H, CHP), 5.05 (d, $^3J_{H,H}$ = 7.9 Hz, 1 H, CHO), 5.36 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H, NH), 5.42 (d, $^3J_{H,H}$ = 7.9 Hz, 1 H, CHO), 6.91–7.51 (m, 29 H, 29 CH_{Ar}) ppm. ^{13}C NMR: δ = 21.3 (CH_3), 26.2 (CH_3), 26.8 (CH_3), 58.2 (d, $^1J_{P,C}$ = 165.1 Hz, CHP), 79.4 (CHO), 80.0 (CHO), 88.0 (d, $^2J_{P,C}$ = 8.5 Hz, C_{quat}O), 91.5 (d, $^2J_{P,C}$ = 14.0 Hz, C_{quat}O), 114.1 ($OC_{quat}O$), 126.4–129.7 (m, 29 CH_{Ar}), 133.8 (C_{quat}), 133.9 (d, $^2J_{P,C}$ = 5.4 Hz C_{quat}), 138.0 (C_{quat}), 139.4 (C_{quat}), 139.5 (C_{quat}), 143.0 (d, $^3J_{P,C}$ = 8.1 Hz, C_{quat}), 143.6 (d, $^3J_{P,C}$ = 7.1 Hz, C_{quat}) ppm. ^{31}P NMR: δ = 14.3 ppm. IR: $\tilde{\nu}$ = 3329 (NH st), 1333 (O=S=O st as), 1251 (P=O st), 1163 (O=S=O st sim). HRMS (ESI): calcd. for $C_{45}H_{42}NO_7PS$ $[M + H]^+$ 772.2498; found 772.2500.

Synthesis of TADDOL α-Iminophosphonate 7: Trichloroisocyanuric acid (3.49 g, 15 mmol) was added to a solution of α-aminophosphonate **6** (7.72 g, 10 mmol) in CH_2Cl_2 (30 mL) at room temp. The resulting suspension was stirred overnight until the disappearance of starting α-aminophosphonate **6** was observed, as monitored by ^{31}P NMR spectroscopy. Then the solid residue was removed by filtration to give a clear solution of the *N*-chloro-α-aminophosphonate intermediate (^{31}P NMR: δ = 10.2 ppm). Poly(4-vinylpyridine) (3 g), which had been dried at 100 °C overnight, was added.

The resulting suspension was stirred under reflux overnight, then it was filtered, and the filtrate was concentrated under vacuum. The crude residue was purified by crystallization from Et_2O to give **7** (6.31 g, 82%) as a white solid, m.p. 138–139 °C (Et_2O). ^{1}H NMR: δ = 0.57 (s, 3 H, CH_3), 0.70 (s, 3 H, CH_3), 2.46 (s, 3 H, CH_3), 5.17 (d, $^3J_{H,H}$ = 7.9 Hz, 1 H, CHO), 5.48 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H, CHO), 7.02–7.56 (m, 27 H, 27 CH_{Ar}), 7.73 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H, 2 CH_{Ar}) ppm. ^{13}C NMR: δ = 21.5 (CH_3), 26.5 (CH_3), 26.6 (CH_3), 79.4 (d, $^3J_{P,C}$ = 2.1 Hz, CHO), 79.9 (d, $^3J_{P,C}$ = 1.8 Hz, CHO), 88.6 (d, $^2J_{P,C}$ = 8.5 Hz, $C_{quat}O$), 92.2 (d, $^2J_{P,C}$ = 13.0 Hz, $C_{quat}O$), 114.4 ($OC_{quat}O$), 126.6 (2 CH_{Ar}), 127.0 (2 CH_{Ar}), 127.1 (2 CH_{Ar}), 127.2 (2 CH_{Ar}), 127.6 (CH_{Ar}), 127.7 (2 CH_{Ar}), 127.9 (2 CH_{Ar}), 128.1 (2 CH_{Ar}), 128.2–128.5 (m, 7 CH_{Ar}), 128.6 (CH_{Ar}), 128.6 (CH_{Ar}), 129.4 (d, $^3J_{P,C}$ = 2.6 Hz, 2 CH_{Ar}), 129.5 (2 CH_{Ar}), 131.4 (d, $^5J_{P,C}$ = 1.0 Hz, CH_{Ar}), 133.5 (d, $^2J_{P,C}$ = 27.3 Hz, C_{quat}), 137.1 (d, $^4J_{P,C}$ = 2.5 Hz, C_{quat}), 139.0 (d, $^3J_{P,C}$ = 13.6 Hz, C_{quat}), 139.1 (C_{quat}), 142.7 (C_{quat}), 143.3 (d, $^3J_{P,C}$ = 4.8 Hz, C_{quat}), 144.0 (C_{quat}), 176.6 (d, $^1J_{P,C}$ = 217.0 Hz, C=N) ppm. ^{31}P NMR: δ = –5.6 ppm. IR: $\tilde{\nu}$ = 1617 (C=N st), 1336 (O=S=O st as), 1262 (P=O st), 1166 (O=S=O st sim). MS (EI): *m*/*z* (%) = 769 (12) $[M]^+$, 614 (3), 258 (100). HRMS (ESI): calcd. for $C_{45}H_{40}NO_7PS$ $[M + H]^+$ 770.2341; found 770.2343.

Nucleophilic Addition of a Grignard Reagent to TADDOL α-Iminophosphonate 7: The organometallic reagent (1.0 M solution in THF; 0.6 mL, 0.6 mmol) was added to a solution of α-ketiminophosphonate **7** (385 mg, 0.5 mmol) in THF (1 mL) at –80 °C. The mixture was stirred for 1 h at –80 °C, and then it was warmed to room temp. The reaction was then quenched with NH_4Cl (saturated aq.; 2 mL). The resulting mixture was diluted with CH_2Cl_2 (5 mL), washed with water (3× 5 mL), dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography (EtOAc/hexanes, 4:1).

8a: *dr* = 94:6 (> 95:5 after chromatography). White solid (81%), m.p. 116–117 °C (Et_2O). ^{1}H NMR: δ = 0.49 (s, 3 H, CH_3), 0.81 (s, 3 H, CH_3), 2.00 (d, $^3J_{P,H}$ = 18.0 Hz, 3 H, CH_3), 2.39 (s, 3 H, CH_3), 5.04 (d, $^3J_{H,H}$ = 5.5 Hz, 1 H, CH), 5.42 (d, $^3J_{H,H}$ = 5.5 Hz, 1 H, CH), 7.05–7.59 (m, 29 H, 29 CH_{Ar}) ppm. ^{13}C NMR: δ = 20.5 (d, $^2J_{P,C}$ = 6.0 Hz, CH_3), 21.3 (CH_3), 26.2 (CH_3), 26.8 (CH_3), 60.4 (d, $^1J_{P,C}$ = 160.6 Hz, CHP), 78.6 (CHO), 79.2 (CHO), 86.9 (d, $^2J_{P,C}$ = 8.3 Hz, $C_{quat}O$), 91.5 (d, $^2J_{P,C}$ = 14.2 Hz, $C_{quat}O$), 113.8 ($OC_{quat}O$), 126.1–129.6 (m, 29 CH_{Ar}), 137.4 (d, $^3J_{P,C}$ = 3.4 Hz C_{quat}), 138.9 (d, $^2J_{P,C}$ = 9.9 Hz, C_{quat}), 139.0 (C_{quat}), 139.6 (C_{quat}), 142.8 (C_{quat}), 142.9 (d, $^3J_{P,C}$ = 8.2 Hz, C_{quat}), 143.6 (d, $^3J_{P,C}$ = 7.1 Hz, C_{quat}) ppm. ^{31}P NMR: δ = 18.4 ppm. IR: $\tilde{\nu}$ = 3328 (NH st), 1333 (O=S=O st as), 1251 (P=O st), 1163 (O=S=O st sim). MS (EI): *m*/*z* (%) = 785 (60) $[M]^+$, 631 (11), 353 (100). HRMS (ESI): calcd. for $C_{46}H_{44}NO_7PS$ $[M + H]^+$ 786.2654; found 786.2649.

8b: *dr* = 55:45 (63:37 after chromatography). White solid (80%), m.p. 139–140 °C (Et_2O). ^{1}H NMR: δ = 0.37 and 0.40 (s, 3 H, CH_3 major and minor), 0.68 and 0.72 (s, 3 H, CH_3 major and minor), 2.24 and 2.42 (s, 3 H, CH_3 major and minor), 4.63 and 4.73 (d, $^3J_{H,H}$ = 7.9 Hz and d, $^3J_{H,H}$ = 7.8, 1 H, CHO major and minor), 5.36 and 5.40 (d, $^3J_{H,H}$ = 7.8 Hz, and d, $^3J_{H,H}$ = 7.5 Hz, 1 H, CHO major and minor), 5.94 (d, $^3J_{P,H}$ = 7.7 Hz, 1 H, NH major and minor), 6.71–7.92 (m, 36 H, 36 CH_{Ar} major and minor). ^{13}C NMR: δ = 21.3 and 22.3 (CH_3, major and minor), 21.6 and 22.6 (CH_3, major and minor), 26.8 and 26.9 (CH_3, major and minor), 69.0 and 69.3 (d, $^1J_{P,C}$ = 156.9 Hz and d, $^1J_{P,C}$ = 157.1 Hz, CHP, minor and major), 78.5 and 78.7 (d, $^3J_{P,C}$ = 1.2 Hz and d, $^3J_{P,C}$ = 1.1 Hz, CHO, major and minor), 78.8 and 78.9 (d, $^3J_{P,C}$ = 2.3 Hz and d, $^3J_{P,C}$ = 1.9 Hz, CHO, minor and major), 87.5 and 87.6 (d, $^2J_{P,C}$ = 8.0 Hz and d, $^2J_{P,C}$ = 8.1 Hz, $C_{quat}O$, major and minor), 87.5 and 87.6 (d, $^2J_{P,C}$ = 8.0 Hz and d, $^2J_{P,C}$ = 8.1 Hz, $C_{quat}O$, major and minor), 92.8 and 93.0 (d, $^2J_{P,C}$ = 13.0 Hz and d, $^2J_{P,C}$ = 14.4 Hz, $C_{quat}O$, minor and major), 114.0 and 114.1 ($OC_{quat}O$, major and minor), 125.3–130.8 (m, 36 CH_{Ar} major and minor), 131.9–143.9 (m, 10 C_{quat} major and minor). ^{31}P NMR: δ = 17.6 (major), 17.9 (minor) ppm. IR: $\tilde{\nu}$ = 3310 (NH st), 1334 (O=S=O st as), 1259 (P=O st) 1160 (O=S=O st sim). MS (EI): *m*/*z* (%) = 785 (60) $[M]^+$, 631 (11), 353 (100). HRMS (ESI): calcd. for $C_{55}H_{48}NO_7PS$ $[M + H]^+$ 898.2967; found 898.2975.

Hydrolysis of TADDOL-Derived α-Aminophosphonate 8a: A suspension of α-aminophosphonate **9a** (393 mg, 0.5 mmol) in HCl (10 M aq.; 2 mL) was heated at reflux overnight. The resulting solution was concentrated under vacuum, the residue was dissolved in hot EtOH (2 mL), and an excess of propylene oxide was added to this solution. The mixture was stirred for 3 h at room temp., and the resulting white solid was collected by filtration to give (*S*)-**9** (80 mg, 80%). $[\alpha]_D^{20}$ = –52.6 (*c* = 0.80, 1 M NaOH). Data agree with literature values.[28]

Supporting Information (see footnote on the first page of this article): 1) ^{1}H and ^{13}C NMR spectra of quaternary *N*-tosyl α-aminophosphonates **3a–3g**, *N*-tosyl α-aminophosphonate **6**, *N*-tosyl α-iminophosphonate **7**, and quaternary *N*-tosyl α-iminophosphonates **8a** and **8b**.

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