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Catalytic enantioselective Michael addition in the synthesis of α-aminophosphonates

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Abstract—Enantioenriched (*S*)-phosphoglutaminic acid derivatives with up to 72% ee were obtained in the catalytic enantioselective Michael reaction of the achiral phosphoglycine synthon. The scope and limitation of the process in terms of the catalyst (diverse (*R*,*R*)-TADDOL derivatives) and the base (solid alkali metal *tert*-butoxides) were examined. The nature of the transition complex was also investigated.

1. Introduction

α-Aminophosphonic acids, the phosphonic analogues of amino acids have potential biological importance as the tetrahedral structure of the phosphonic moiety mimics the tetrahedral transition state of the peptide hydrolysis. Therefore they can function as enzyme inhibitors, antibiotics, and pharmacological agents.[1] It has been shown that the biological activity of α-aminophosphonic acids is influenced by the absolute configuration of the α-carbon.[2] In recent years, several synthetic methods providing α-aminophosphonates in moderate to excellent enantiomeric purity have been developed.

In most of the strategies, covalently bound chiral auxiliaries have been used, for example, in the diastereoselective addition of diethyl phosphite[3] or the lithium complex of diethyl phosphite to a chiral imine,[4] in the alkylation/Michael addition of a chiral phosphonate imine[5a–d] and in the electrophilic amination of chiral α-alkyl phosphonamides.[6] Another approach is the catalytic asymmetric hydrophosphorylation of achiral imines using lanthanoid–potassium–BINOL heterobimetallic complexes.[7] We present here our results on a two phase catalytic asymmetric Michael addition of the achiral phosphoglycine synthon, the Schiff base of the aminomethylphosphonic acid ethyl ester **1** aiming at the asymmetric synthesis of phosphoglutaminic acid derivatives, the phosphonic analogues of glutaminic acid **2**. To the best of our knowledge, catalyzed C–C bond forming reaction on the α-carbon of **1** has not been written in the literature, yet.

As the catalyst a series of (*R*,*R*)-TADDOLs (α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanols) chiral chelating diols **3a–e** was used. This family of compounds have been synthesized first by Seebach's group[8] and used successfully as catalyst in various stereoselective syntheses,[9a] such as enantioselective Grignard reactions,[9b] addition of Et_2Zn to aldehydes,[9c] Diels–Alder reaction,[9d] and deracemization.[9e,f]

Recently, it was also shown that sodium TADDOLate can also be used in the enantioselective alkylation of the Schiff's bases derived from esters of racemic alanine,[10a] and in enantioselective Michael addition of a glycine Schiff base synthon,[10b] though the latter proceeds with moderate enantioselectivity.

2. Results and discussion

The initial Michael addition reactions of **1a** were carried out using ethyl acrylate **4** (W = COOEt) as a typical

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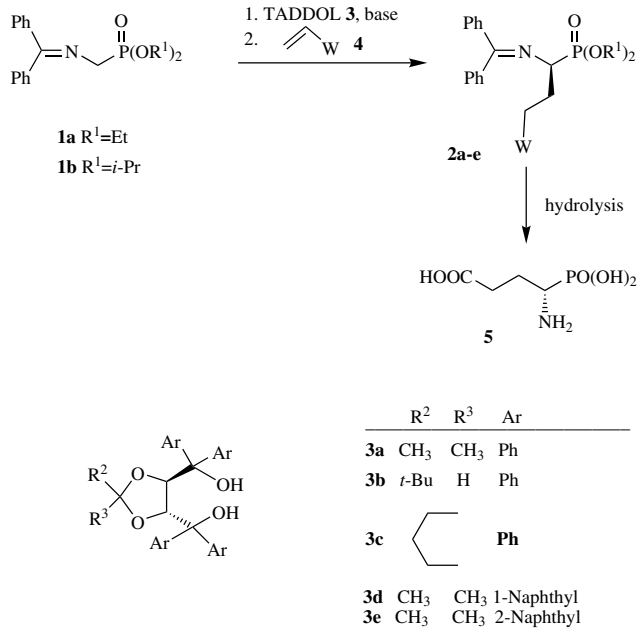

Scheme 1.

Michael acceptor and TADDOL **3a** as chiral ligand and solid potassium, sodium, and lithium *tert*-butylate as base, respectively (Scheme 1). The reaction was conducted in dry toluene at low temperature under argon atmosphere and quenched with ammonium chloride after 15 min. In the first experiments 1 equiv of catalyst **3a** and 2 equiv of base were used. It turned out that the alkali metal cation of the base was crucial in the catalytic process, as only the sodium *tert*-butylate was suitable both in terms of the conversion and the enantiomeric excess, though the ee was modest in these circumstances (Table 1, entries 1–3). Using a smaller excess of solid sodium *tert*-butylate (1.2 equiv) a slight improvement (from 32 to 37) could be observed in the ee (Table 1, entry 4).

Using the more bulky *tert*-butyl acrylate instead of the ethyl acrylate the ee almost doubled (72%, Table 1, entry 6). Surprisingly, when the amount of the catalyst was decreased to 0.1 equiv the ee dropped to 15%, but the opposite (*R*)-enantiomer was obtained in excess (Table 1, entry 5).[11] Modification of catalyst **3a** by replacing either the phenyl groups with 1- and 2-naphthyl groups **3d** and **3e**, or the dimethyl substituents of the dioxolane ring to the bulkier *tert*-butyl **3b** and tetramethylene **3c** group did not improve the stereoselectivities (Table 1, entries 7–10). Modifying the ester moiety of the Michael acceptor to a cyano group (Table 1, entry 11) and the diethyl phosphonyl group (Table 1, entry 12), respectively, reduced the enantiomeric excess dramatically to 5%.

Interestingly, when using diisopropyl phosphonate **1b**, a more bulky substrate, a decrease in the ee was obtained (Table 1, entry 13).

The effect of the solvent was also tested. We found that using a toluene–hexane 1:1 mixture both the conversion and the ee dropped dramatically, as the application of toluene–ether 1:1 mixture did not influence the outcome of the reaction.

To explain the magnitude of the ee values in our Michael addition we had to postulate that a side reaction also occurs concerning **2** as a racemic mixture. Indeed, we observed that conducting the Michael addition starting from **1a** in the absence of a chiral catalyst racemic **2** was formed quantitatively in a fast reaction (entry 14). It can be assumed from these facts that the ion pair derived from the phosphonate carbanion (anion of **1a)** formed on the solid NaO*t*Bu surface is lipophilic enough to be transferred into the toluene solution and to react with the acrylate. This supposition seems to be confirmed by the lower enantioselectivity observed in the reaction when using **1b** as substrate instead of **1a**, which is even more lipophilic, making the ion pair more capable of transferring to the solution and therefore makes the

Table 1. Asymmetric Michael addition of substrate **1** varying the catalysts **3a**–**e**, the base and the Michael acceptors[a]

Entry	R^1	Catalyst (equiv)	Base (equiv)	W	Product	Conversion[b] (%)	ee[c] (%)	Config.[d]
1	Et	**3a** (1.0)	KO*t*Bu (2.0)	COOEt	**2a**	33	5	(*S*)
2	Et	**3a** (1.0)	NaO*t*Bu (2.0)	COOEt	**2a**	100	32	(*S*)
3	Et	**3a** (1.0)	LiO*t*Bu (2.0)	COOEt	**2a**	0	—	(*S*)
4	Et	**3a** (1.0)	NaO*t*Bu (1.2)	COOEt	**2a**	94	37	(*S*)
5	Et	**3a** (0.1)	NaO*t*Bu (2.0)	COOEt	**2a**	46	15	(*R*)
6	Et	**3a** (1.0)	NaO*t*Bu (1.2)	COO*t*Bu	**2b**	95	72	(*S*)
7	Et	**3b** (1.0)	NaO*t*Bu (2.0)	COO*t*Bu	**2b**	100	61	(*S*)
8	Et	**3c** (1.0)	NaO*t*Bu (2.0)	COO*t*Bu	**2b**	100	42	(*S*)
9	Et	**3d** (1.0)	NaO*t*Bu (2.0)	COOEt	**2a**	100	30	(*S*)
10	Et	**3e** (1.0)	NaO*t*Bu (2.0)	COOEt	**2a**	100	59	(*S*)
11	Et	**3a** (1.0)	NaO*t*Bu (1.2)	CN	**2c**	29	5	(*S*)
12	Et	**3a** (1.0)	NaO*t*Bu (1.2)	$P(O)(OEt)_2$	**2d**[e]	100	5	(*S*)
13	*i*-Pr	**3a** (1.0)	NaO*t*Bu (1.2)	COO*t*Bu	**2e**	60	50	(*S*)
14	Et	—	NaO*t*Bu (2.0)	COO*t*Bu	**2b**	100	—	—

[a] The reactions carried out at −72 °C and for 15 min unless otherwise stated.
[b] Measured by ^{31}P NMR after 15 min reaction time.
[c] Determined by HPLC analysis using Chiralpak AD column and hexane–*i*-propanol 95:5 as eluent.
[d] Determined after deprotection of **2** from the specific rotation of the free 4-amino-4-phosphonobutyric acid.[12]
[e] Three days reaction time at room temperature.

Table 2. The dependence of the enantiomeric excess of the product (*S*)-**2b** of the Michael addition reaction on the enantiomeric purity of catalyst (*R*,*R*)-**3a**

Entry	ee of (*S*)-**2b**	ee of (*R*,*R*)-**3a**
1	30	20
2	45	40
3	55	60
4	66	80
5	72	100

achiral route more competitive. Another proof for the achiral route is that the enantioselectivity of the reaction can be improved by lowering the excess of base (from 2 to 1.2 equiv).

To have better insight into the catalytic process we used preprepared sodium TADDOLate as catalyst, but there was no reaction. The same result was obtained when TADDOL–NaO*t*Bu 1:1 mixture was used. To explain these results, we had to suppose that because of the low CH acidity of substrate **1** ($pK_a \sim 23$, DMSO)[13] it is not the sodium TADDOLate, but the sodium *tert*-butoxide that is responsible for its deprotonation, and TADDOL takes part in the process as a chelating agent.

To reveal the ratio of the substrate anion (anion of **1a**) and the ligand in the transition complex(es) the correlation of the ee of the TADDOL **3a** and that of the product was determined (Table 2). A positive nonlinear effect was observed indicating that not only a transition complex of 1:1 ratio might be present, but some associations also occurs.[14]

A quite different ligand–substrate ratio must be present in the case when only 10 mol % catalyst was used (Table 1, entry 4) resulting in the inversion of the stereochemistry in the reaction.

In order to establish the absolute configuration of the Michael adducts **2a**,**b**, and **2e** by comparison of the signs of specific rotation with literature values[12] these adducts were hydrolyzed in 6 M HCl to 4-phosphoglutaminic acid **5**. The values of the specific rotation were in accord with the literature data showing that partial racemization did not occur during the hydrolysis.

3. Conclusion

A catalytic asymmetric Michael addition of protected phosphoglycine synthon **1** a very weak CH acid was successfully applied for the first time as a new approach in the synthesis of phosphoglutaminic acid and phosphoproline derivatives. We have demonstrated that the nature of the base is crucial for both the chemical and stereochemical outcome of the reaction. We have also shown that rather than the chiral alkoxide, the neutral chiral diol takes part in the transition chelate formation.

4. Experimental

4.1. Typical procedure for the Michael addition

Under an argon atmosphere, the stirred mixture of the TADDOL **3** (1.5 mmol) and NaO*t*Bu (quantity specified in Table 1) in abs. toluene (5 cm^3) was cooled to −78 °C. Schiff base **1** (1.5 mmol) was added, and this was left stirring for 10 min after which the toluene solution (3 cm^3) of the acrylic compound **4** (1.8 mmol) was introduced. After stirring for 15 min at −78 °C the reaction was quenched with saturated NH_4Cl and extracted with toluene. The combined organic extracts were dried, and the toluene evaporated. Product **2** was isolated by column chromatography on Silica gel using ethyl acetate–hexane 7:3 as eluent in 75–88% chemical yield. TADDOL **3** was also recovered by the column chromatography.

4.2. Typical procedure for the hydrolysis of the Michael adduct

Michael adduct **2** (0.1 mmol) was refluxed in 6 N HCl (2 cm^3) for 30 min. The mixture was concentrated at reduced pressure, and the residue was dissolved in a mixture of abs. ethanol (1 cm^3) and propylene oxide (0.1 cm^3) and was allowed to stand for 2 days while it crystallized. The product was filtered yielding **5** as known compound.

Compound **2a**: mp 30–33 °C. $[\alpha]_D^{20} = 5.6$ (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 1.18 (3H, t, $J_{HH} = 7.2$ Hz), 1.31 (3H, t, $J_{HH} = 7.1$ Hz), 1.36 (3H, t, $J_{HH} = 7.1$ Hz), 2.16–2.37 (4H, m), 3.90–3.95 (1H, m), 4.05 (2H, q, $J_{HH} = 7.2$ Hz), 4.11–4.34 (4H, m), 7.30–7.53 (10H, m). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.1, 16.4, 16.5, 26.3 (d, $J_{PC} = 4.2$ Hz), 31.2 (d, $J_{PC} = 15.1$ Hz), 60.3, 60.6 (d, $J_{PC} = 158.6$ Hz), 62.4 (d, $J_{PC} = 7.1$ Hz), 62.7 (d, $J_{PC} = 7.1$ Hz), 127.95, 128.2, 128.4, 128.6, 128.8, 130.3, 133.8, 135.7, 139.2, 170.0, 172.8. ^{31}P NMR: (121.5 MHz, $CDCl_3$): δ 23.7. FAB-MS *m*/*z* 432.4 $[M+1]^+$ (calcd 431.46).

Compound **2b**: oil, $[\alpha]_D^{20} = -16.1$ (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 1.29 (3H, t, $J_{HH} = 7.1$ Hz), 1.34 (3H, t, $J_{HH} = 7.1$ Hz), 1.37, (9H, s), 2.15–2.26 (4H, m), 3.85–3.89 (1H, m), 4.09–4.19 (4H, m), 7.19–7.58 (10H, m). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 16.5, 16.6, 26.6 (d, $J_{PC} = 4.3$ Hz), 28.1, 32.5, 60.8 (d, $J_{PC} = 158.3$ Hz), 62.6 (d, $J_{PC} = 7.1$ Hz), 80.3, 128.0, 128.5, 130.3, 132.4, 135.7, 137.6 139.4, 171.1, 172.5. ^{31}P NMR: (121.5 MHz, $CDCl_3$): δ 23.9. FAB-MS *m*/*z* 460.5 $[M+1]^+$ (calcd 459.52).

Compound **2c**: oil, ^1H NMR (300 MHz, $CDCl_3$): δ 1.29 (3H, t, $J_{HH} = 7.1$ Hz), 1.35 (3H, t, $J_{HH} = 7.1$ Hz), 2.25–2.45 (4H, m), 3.86–3.95 (1H, m), 4.09–4.20 (4H, m), 7.27–7.82 (10H, m). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 15.9, 16.5, 16.7, 26.2 (d, $J_{PC} = 4.2$ Hz), 60.1 (d, $J_{PC} = 155.9$ Hz), 62.4 (d, $J_{PC} = 7.1$ Hz), 117.3, 128.4, 128.9, 130.7 131.1, 139.8, 142.9, 170.5. ^{31}P NMR: (121.5 MHz, $CDCl_3$): δ 22.6.

Compound **2d**: oil, ^1H NMR (300 MHz, $CDCl_3$): δ 1.27–1.37 (12H, m), 1.44–1.59 (1H, m), 1.74–1.84

(1H, m), 2.08–2.30 (2H, m), 3.82–3.90 (1H, m), 4.01–4.24 (8H, m), 7.25–7.65 (10H, m). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 16.3, 16.4, 16.5, 16.6, 21.7 (dd, $J_{PC} = 53.4$ Hz, $J_{PC} = 14.2$ Hz,), 23.6 (dd, $J_{PC} = 53.2$ Hz, $J_{PC} = 13.4$ Hz), 48.9 (dd, $J_{PC} = 148.3$ Hz, $J_{PC} = 15.9$ Hz,), 61.6 (d, $J_{PC} = 6.7$ Hz), 62.7 (d, $J_{PC} = 6.9$ Hz), 128.1, 128.3, 128.6, 128.8, 130.0, 132.4, 137.6, 139.2, 171.6. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 23.5 (1P, d, $J_{PP} = 7.9$ Hz), 31.5 (1P, d, $J_{PP} = 7.9$ Hz).

Compound **2e**: oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21–1.44 (12H, m), 1.36 (1H, s), 2.08–2.31 (4H, m), 3.75–3.83 (1H, m) 4.65–4.78 (2H, m) 7.18–7.46 (10H, m). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 24.1, 24.2, 24.3, 24.5, 26.9 (d, $J_{PC} = 4.9$ Hz), 28.3, 32.9 (d, $J_{PC} = 15.2$ Hz), 61.4 (d, $J_{PC} = 160.3$ Hz), 71.1 (d, $J_{PC} = 29.5$ Hz), 71.2 (d, $J_{PC} = 29.5$ Hz) 80.4, 128.2, 128.5, 128.7, 130.3, 132.6, 136.1, 139.8, 171.2, 172.4. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 22.1.

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