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Asymmetric Synthesis of α,β-Diaminophosphonic Acid Derivatives with a Catalytic Enantioselective Mannich Reaction

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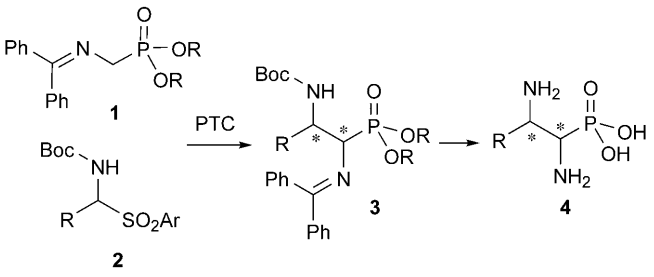
Abstract: Optically active α,β-diaminophosphonic acid derivatives were obtained from the catalytic enantioselective Mannich reaction of phosphoglycine Schiff bases with *N*-Boc-imines, generated *in situ* from α-amido sulfones.

Keywords: α-amido sulfones; asymmetric catalysis; α,β-diaminophosphonic acids; Mannich reaction; phase-transfer catalysis

α-Aminophosphonic acids are structural analogues of α-amino acids, and have been found to possess a broad range of biological activities.[1] This activity, often due to the inhibition of protease or synthetase enzymes, is usually rationalized considering the mimicking of the transition state of enzymatic peptide bond hydrolysis (or formation) by the bulky and tetrahedral phosphonic acid moiety.[2] As the absolute configuration at the α-carbon influences dramatically their biological response, several methods have been developed for the obtainment of these compounds in enantioenriched form, especially based on catalytic asymmetric methodologies.[3] In this context, a variety of strategies has been reported relying on the catalytic asymmetric hydrophosphonylation of imines,[3c,e] which is however intrinsically limited to simple α-alkyl- and α-aryl-substituted α-aminophosphonates. To overcome this restriction, we set our focus on a different approach, that is the use of the benzophenone imines **1** derived from phosphoglycine[4] as phosphoglycine anion equivalents, envisioning that this strategy could open new possibilities for the obtainment of other classes of α-aminophosphonic acids in optically active form. The potential uses of Schiff bases **1** in catalytic asymmetric transformations has been rather overlooked, as only one example, a palladium-catalyzed allylic substitution, has been reported so far.[5] However, considering their similarity with benzophenone imines derived from glycine,[6] undoubtedly one of the most successful substrates for the preparation of optically active α-amino acid derivatives,[7] we envisioned the possibility of using phase-transfer catalysis (PTC)[8] for the productive activation of phosphoglycines **1** in enantioselective reactions.

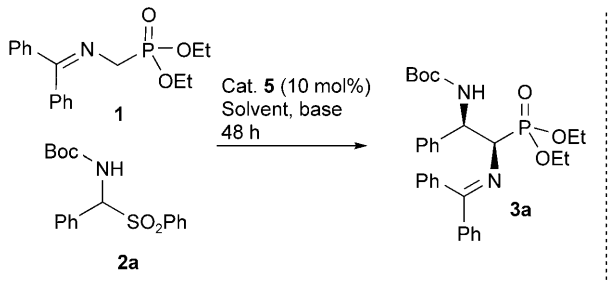
We present herein the development of a catalytic asymmetric Mannich reaction of a phosphoglycine Schiff base **1** with *N*-Boc-imines generated *in situ* from α-amido sulfones **2**,[9] giving access to precursors of enantioenriched α,β-diaminophosphonic acids **4** (Scheme 1).[10] Although these particular phosphonic acids bear considerable interest, being α,β-diamino acid analogues,[11] and their activity as efficient aminopeptidase inhibitors has been already demonstrated,[12] their enantioselective synthesis has not been thoroughly studied. To the best of our knowledge, only a handful of examples based on chiral auxiliary methodologies,[13] and a single catalytic asymmetric reaction, limited to α-methyl-α,β-diaminophosphonates,[14] have been reported so far.

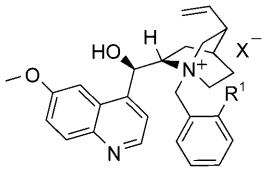
At the outset of our studies, diethyl (diphenylmethyleneamino)methanephosphonate **1**[15] was reacted with α-amido sulfone **2a** (Table 1), using commer-



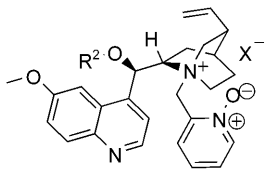
Scheme 1. Synthesis of optically active α,β-diaminophosphonic acids with a catalytic enantioselective Mannich reaction.

Table 1. Representative results from the screening of different catalysts, bases, solvents and temperatures.[a]





5a: R^1 = H, X = Cl
5b: R^1 = CN, X = Br
5c: R^1 = F, X = Br
5d: R^1 = NO_2, X = Cl
5e: R^1 = MeO, X = Cl



5f: R^2 = H, X = Cl
5g: R^2 = allyl, X = Br

Entry	Catalyst **5**	Solvent	Base	*T* [°C]	Conversion[b] [%]	*ee*[c] [%]
1	**5a**	toluene	NaOH	−30	>90	0
2	**5b**	toluene	NaOH	−30	>90	55[d]
3	**5c**	toluene	NaOH	−30	>90	12
4	**5d**	toluene	NaOH	−30	89	40
5	**5e**	toluene	NaOH	−30	>90	7
6	**5f**	toluene	NaOH	−30	>90	53
7	**5g**	toluene	NaOH	−30	>90	7
8	**5f**	toluene	$CsOH·H_2O$	−55	>90	70
9	**5f**	toluene/CH_2Cl_2 9:1	$CsOH·H_2O$	−55	<10	-
10	**5f**	toluene/*i*-Pr_2O 9:1	$CsOH·H_2O$	−55	70	45
11	**5f**	toluene/TBME 9:1	$CsOH·H_2O$	−55	>90	80

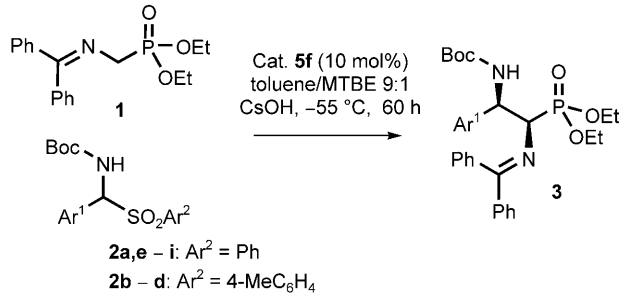
[a] Reactions were carried out with **2a** (0.10 mmol), **1** (0.12 mmol), catalyst **5** (0.010 mmol), the inorganic base (0.50 mmol) in the solvent (1 mL), at the stated temperature for 48 h. In all experiments, a single *syn* diastereoisomer was observed in the crude mixture by ^{1}H NMR spectroscopy.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Determined by chiral stationary phase HPLC.
[d] 0.20 mmol NaOH were used.

cially available catalyst **5a** derived from quinine, in toluene as the solvent. Among the different bases tested, only hydroxides such as NaOH could promote the reaction to a considerable extent at −30 °C, although no appreciable enantioselectivity was observed with catalyst **5a** (entry 1). Remarkably, in this and in the following experiments, the product **3a** was always obtained as a single *syn*-diastereoisomer.[16] This excellent *syn*-diastereoselectivity is in line with literature precedents concerning base or phase-transfer catalyzed Mannich additions of glycine and phosphoglycine Schiff bases to *N*-Boc-imines,[9d,10a] where it was explained considering an acyclic transition state model for the Mannich addition (i.e., kinetic control).[17,18]

A series of ammonium salts derived from quinine featuring an *ortho*-substituted benzyl group was then prepared and tested (entries 2–7), considering the proven efficiency of this class of catalysts both in enantioselective alkylations of benzophenone glycine imines,[19] and in asymmetric Mannich additions to *N*-Boc-imines.[20] A strong influence of the nature of this substituent on the reaction outcome could be in fact observed, with the 2-picolyl *N*-oxide catalyst **5f** giving the best results in terms of enantioinduction (entry 6). Allylation of the hydroxy group of **5f** resulted in the very inefficient catalyst **5g**, which furnished the product in nearly racemic form (entry 7). The requirement of a free alcoholic moiety in the catalyst structure is in line with the results observed in related transformations,[9b,c,20] and has been recently rationalized considering its capability in coordinating and stabilizing the anionic nucleophile through a hydrogen bond interaction.[21] Using catalyst **5f**, further experiments revealed that with CsOH as the base it was possible to decrease the reaction temperature to −55 °C, increasing the enantioselectivity of the product **3a** (entry 8).[22] Given the non-feasibility of a further decrease in the temperature, we decided to test different solvent mixtures in the reaction. The use of mixtures of toluene and a small amount of a chlorinated or ethereal co-solvent gave contrasting results (entries 9–11). In particular, only TBME showed a positive effect on the enantioselectivity observed (entry 11), allowing the obtainment of the Mannich adduct **3a** with a reasonable 80% *ee*.

Under these conditions, the generality of the reaction was inspected using different α-amido sulfones **2** derived from aromatic aldehydes (Table 2).[23] A range of α,β-diaminophosphonic derivatives **3a–i**

Table 2. Generality of the Mannich reaction.[a]



Entry	Sulfone **2**	Ar^1	Adduct **3**	Yield[b] [%]	*ee*[c] [%]
1	**2a**	Ph	**3a**	89	80[d]
2	**2b**	*o*-MeC_6H_4	**3b**	89	92
3	**2c**	*m*-MeC_6H_4	**3c**	79	78
4	**2d**	*p*-MeC_6H_4	**3d**	96	72
5	**2e**	*o*-BrC_6H_4	**3e**	60	94
6	**2f**	*p*-ClC_6H_4	**3f**	78	66
7	**2g**	*p*-$MeOC_6H_4$	**3g**	88	50
8	**2h**	2-naphthyl	**3h**	83	74
9	**2i**	1-naphthyl	**3i**	85	90

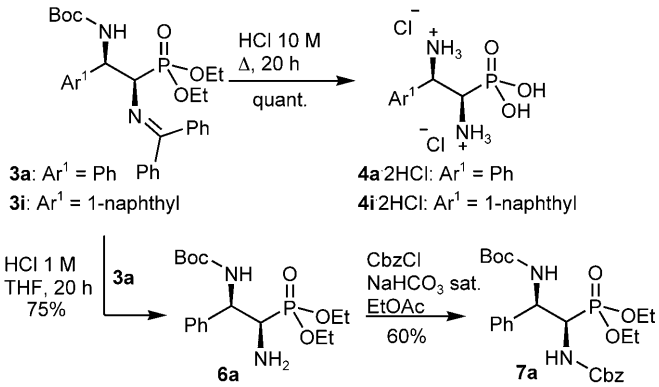
[a] Reactions were carried out with **2** (0.20 mmol), **1** (0.24 mmol), catalyst **5f** (0.020 mmol), $CsOH·H_2O$ (1.0 mmol) in a toluene/TBME mixture (2.0 mL, 9:1), at −55 °C for 60 h.

[b] Isolated yield after chromatography on silica gel. A single *syn* diastereoisomer was observed in all cases by means of ^1H,^{13}C and ^{31}P NMR spectroscopy.

[c] Determined by chiral stationary phase HPLC.[d] Absolute configuration determined by chemical derivatization (see Supporting Information).

could be obtained using this procedure in good yields (60–96%), and as single *syn* diastereoisomers in all cases.[16] The enantioselectivities observed varied with the structure of the α-amido sulfones **2** employed. In particular, substituents at the *para*-position of the aromatic ring in **2d**, **f**, **g** gave a slight decrease in the enantioselection (entries 4, 6, 7), compared to their unsubstituted counterpart **2a** (entry 1), whereas a substituent at the *meta*-position had nearly no influence (entry 3). In contrast, an electron-withdrawing or releasing *ortho*-substituent in **2b** and **2e** had a striking positive effect, as the corresponding Mannich adducts **3b** and **3e** were obtained with excellent enantioselectivities (entries 2 and 5). The beneficial influence of sterical hindrance at the *ortho*-position was further confirmed by the results obtained in the reactions with the isomeric naphthyl derivatives **2h** and **2i** (entries 8 and 9).

A good asset of the present method is the possibility of obtaining directly α,β-diaminophosphonic acid derivatives bearing a Boc protecting group and a benzophenone imine at the two nitrogen atoms, both easily removable under mild acidic conditions. As



Scheme 2. Synthetic elaborations of the Mannich adducts **3**. Cbz = benzyloxycarbonyl.

phosphonic esters are also susceptible to acidic hydrolysis, we envisioned the direct obtainment of optically active α,β-diaminophosphonic acids in a single step from the Mannich adducts. To this purpose, **3a** and **3i** were treated with 10 M HCl overnight, giving in quantitative yield the expected α,β-diaminophosphonic acid dihydrochlorides **4a**·2 HCl and **4i**·2 HCl (Scheme 2). On the other hand, due to its lability to aqueous acidic conditions, the benzophenone imine can be chemoselectively hydrolyzed with diluted aqueous acid even in the presence of the Boc protecting group, giving thus the possibility of accessing orthogonally protected α,β-diaminophosphonic acid derivatives, as exemplified for the N^1-Cbz, N^2-Boc protected **7a** (Scheme 2).

In conclusion, we have developed a catalytic asymmetric Mannich reaction using the phosphoglycine benzophenone imine **1** and α-amido sulfones **2** as imine precursors. This new transformation represents one of the very few options for the preparation of α,β-diaminophosphonic acids in optically active form with a catalytic method, and presents several attractive features such as the user-friendly operative conditions, the employment of cheap and easily obtained chiral catalysts and materials, and the straightforward conversion of the Mannich adducts to the unprotected α,β-diaminophosphonic acids. Furthermore, the demonstration of the productive activation of Schiff bases **1** using asymmetric phase-transfer catalysis might open new opportunities for the employment of these convenient phosphoglycine anion equivalents in asymmetric catalysis.[24]

Experimental Section

General Procedure

Catalyst **5f** (9.5 mg, 0.020 mmol), α-amido sulfone **2** (0.20 mmol), diethyl phosphonate **1** (78 mg, 0.24 mmol),

were weighed in a test tube, and suspended in a toluene/TBME mixture (9:1, 2.0 mL). The mixture was stirred at room temperature for 5 min, then cooled to −55 °C. Finely ground $CsOH·H_2O$ (170 mg, 1.0 mmol), weighed in an oven-dried vial, was then added in one portion. The mixture was stirred at the same temperature for 60 h, then charged directly on a silica gel column. The Mannich adduct **3** was then obtained by eluting with a *n*-hexane/EtOAc 6:4 mixture. ^1H, ^{13}C, and ^{31}P NMR spectra of the purified products showed the presence of a single diastereoisomer in all cases. The *ee* of the products **3** was determined by chiral stationary phase HPLC.

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