An easy entry to optically active α-amino phosphonic acid derivatives using phase-transfer catalysis (PTC)†

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The unprecedented use of phase-transfer catalysis (PTC) in an asymmetric hydrophosphonylation reaction allows the obtainment of a range of optically active α-amino phosphonic acid derivatives directly from α-amido sulfones.

α-Amino phosphonic acids and their derivatives are key compounds in medicinal chemistry.[1] Often incorporated into peptides α-amino phosphonic acids have shown, among others, very promising and useful anticancer,[2] anti-inflammatory,[2] antirheumatic,[2a,3] antibacterial[4] and antifungal properties.[5] The striking biological activity of these α-amino acid analogues stems in several instances from the efficient inhibition of different protease or synthetase enzymes.[6]

The nucleophilic addition of phosphite esters **2** to electron deficient double bonds is certainly one of the most versatile routes for the introduction of a phosphonate moiety at a carbon atom,[7] and the hydrophosphonylation of imines giving α-amino phosphonic acid derivatives has been studied in detail. Few efficient asymmetric catalytic protocols for this transformation are currently available,[8] relying on the use of chiral Lewis acids,[9] or based on organocatalytic concepts.[10] Though these latter procedures give a satisfactory solution in terms of practicability and ready applicability, they do not appear suitable to prepare important α-amino phosphonic acids, such as phosphoalanine (Ala^P), phosphophenylalanine (Phe^P), and their substituted derivatives,[2–6] due to the instability of the corresponding linear unbranched imines.[10] We envisioned that the recently developed use of α-amido sulfones **1**[11] under phase-transfer catalysis (PTC) conditions,[12] generating *in situ* a very reactive imine, could prevent the imine–enamine tautomerism, responsible for the previously reported lack of reactivity.[10a] However, to our knowledge no asymmetric hydrophosphonylation reactions have been reported to date using PTC, despite several positive features typical of this organocatalytic method, such as the mild reaction conditions, the environmental friendliness, the experimental simplicity and the relatively easy scalability.[13]

We tentatively ascribed this lack of precedents to the tautomeric phosphonate/phosphite equilibrium (Scheme 1), wherein

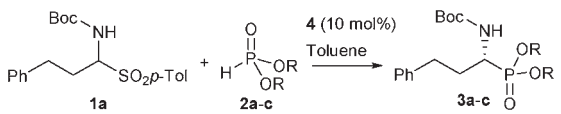
Scheme 1

the considerable nucleophilicity of both the protonated and deprotonated phosphite tautomer[14] could lead to a significant background reaction.[15] An additional matter of concern in our reaction plan was the low efficiency of deprotonated phosphites in forming an imine from α-amido sulfones **1**.[11b,16]

Nevertheless, confident in that a careful choice of reaction conditions could make possible a reliable and successful protocol for the asymmetric hydrophosphonylation of imines using PTC, we tested the behaviour of α-amido sulfone **1a** with phosphite esters (Table 1), in combination with different phase-transfer catalysts **4a–f** (Fig. 1) easily obtained from inexpensive (hydro)quinine.[17]

Initial exploratory efforts directed toward the use of diethyl phosphite **2a** gave encouraging indications about the feasibility of this transformation and confirmed our expectations of the tolerance of this system to linear, unbranched imines, as the product **3a** was obtained with very good levels of purity in

Table 1 Representative optimisation results[a]



Entry	Phosphite **2** (R)	Cat. **4**	Base (equiv.)	T/°C	Conv.[b] (%) (**3**)	ee[c] (%)
1	**2a** (Et)	**4a**	K_2CO_3 (5)	r.t.	>90 (**3a**)	13
2	**2a** (Et)	**4b**	K_2CO_3 (5)	r.t.	>90 (**3a**)	23
3	**2a** (Et)	**4b**	K_2CO_3 (1)	r.t.	45 (**3a**)	7
4	**2b** (Me)	**4b**	CsF (5)	−30	>90 (**3b**)	67
5	**2b** (Me)	**4c**	CsF (5)	−30	>90 (**3b**)	79
6	**2b** (Me)	**4d**	CsF (5)	−30	>90 (**3b**)	77
7	**2b** (Me)	**4e**	CsF (5)	−30	>90 (**3b**)	83
8	**2c** (Bn)	**4e**	Cs_2CO_3 (5)	−30	>90 (**3c**)	80
9[d]	**2b** (Me)	**4e**	KOH (3)	−78	>90 (**3b**)	87
10[d]	**2c** (Bn)	**4e**	CsOH (1.5)	−78	>90 (**3c**)	82
11[de]	**2b** (Me)	**4f**	KOH (3)	−78	>90 (**3b**)	89

[a] *Conditions*: 0.10 mmol **1a**, 0.15 mmol **2**, 0.010 mmol cat. **4**, toluene (0.05 M), base, 18–48 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC using a Daicel Chiralpak AD-H column. [d] 0.1 M reaction. [e] 5 mol% catalyst.

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† Electronic supplementary information (ESI) available: Experimental procedures, products characterisation and copies of the NMR spectra. See DOI: 10.1039/b807027j

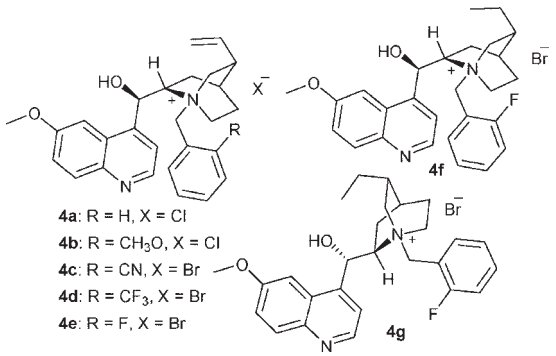


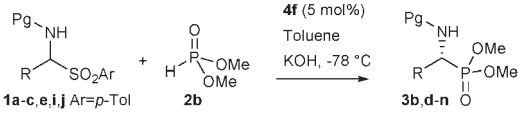
Fig. 1

the crude reaction mixture. These experiments showed also the beneficial effect exerted on the enantioselectivity by a substituent at the *ortho* position of the benzylic moiety of the catalyst[18] (Table 1, entries 1–2, 13% *vs.* 23% ee). The drop in enantioselectivity observed decreasing the amount of base (Table 1, entry 3, 7% ee), highlighted on the other hand the necessity of the efficient formation of the phosphite anion. A screening of different commercially available phosphites[19] identified dimethyl and dibenzyl phosphites **2b** and **2c** as the most promising leads.

Decreasing the reaction temperature to −30 °C was also found beneficial for the enantioselectivity, although the type of inorganic base had to be carefully optimised. Using 5 equivalents of CsF, catalysts **4b–e** (Fig. 1) all bearing an *ortho* substituent at the benzylic quinuclidinic moiety could be used at −30 °C with dimethyl phosphite **2b** (Table 1, entries 4–7), the 2-fluoro substituted **4e** giving the best asymmetric induction (Table 1, entry 7, 83% ee). Similar results were obtained using dibenzyl phosphite **2c**, although in this latter case the inorganic base had to be changed to Cs_2CO_3 (Table 1, entry 8, 80% ee). The use of hydroxides allowed to perform the reaction at lower temperature (−78 °C), giving the α-amido dimethyl phosphonate **3b** with a useful level of enantioselectivity (Table 1, entry 9, 87% ee), whereas the improvement in the case of the dibenzyl derivative **3c** was less pronounced (Table 1, entry 10, 82% ee). Pursuing the reaction with dimethyl phosphite **2b**, an additional small improvement in the enantioselectivity was observed even at a lower catalyst loading, when catalyst **4f**, derived from hydroquinine, was used in the reaction, (Table 1, entry 11, 89% ee).

We then proceeded to evaluate the scope of the reaction, using dimethyl phosphite **2b** with different α-amido sulfones **1a–l** under the optimised conditions. After demonstrating the possibility of performing the reaction with **1a** on a preparative scale with similar results (Table 2, entry 1, 94% yield, 88% ee), we investigated the tolerance of this transformation to a change in the protecting group at the nitrogen atom. Although a larger excess of phosphite **2b** (3 equiv. *vs.* 1.5 equiv.)[20] had to be used to drive the reaction to completion in a reasonable time with the N-Cbz protected α-amido sulfone **1b**, the corresponding N-Cbz α-amino phosphonic acid ester **3d** could be obtained with satisfactory results (Table 2, entry 2, 95% yield, 84% ee). Under these conditions, several α-amido sulfones derived from α- or β-branched (**1c–f**), as well as linear unbranched aldehydes (**1g–l**), gave the corresponding α-amino

Table 2 Reaction scope[a]



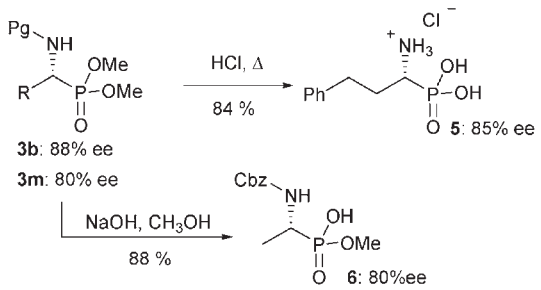
Entry	α-Amido sulfone **1**	R	Pg	Product **3**	Yield[b] (%)	ee[c] (%)
1	**1a**	$Ph(CH_2)_2$	Boc	**3b**	94[d] (88)	88[d] (34)
2	**1b**	$Ph(CH_2)_2$	Cbz	**3d**	95	84
3	**1c**	*c*-C_6H_{11}	Boc	**3e**	94	82[e]
4	**1d**	*c*-C_6H_{11}	Cbz	**3f**	93 (99)	89 (78)
5	**1e**	$(CH_3)_2CHCH_2$	Boc	**3g**	93	83[e]
6	**1f**	$(CH_3)_2CHCH_2$	Cbz	**3h**	66	86[f]
7	**1g**	$CH_3(CH_2)_5$	Boc	**3i**	84	87[e]
8	**1h**	$CH_3(CH_2)_4$	Cbz	**3j**	97 (94)	95 (84)
9	**1i**	CH_3CH_2	Boc	**3k**	78	80[e]
10	**1j**	CH_3	Boc	**3l**	84	79[e]
11	**1k**	CH_3	Cbz	**3m**	76	80[f]
12	**1l**	$PhCH_2$	Boc	**3n**	83	84

[a] *Conditions*: 0.10 mmol **1**, 0.15 mmol **2e** (Pg = Boc), 0.30 mmol **2e** (Pg = Cbz), 0.005 mmol **4f**, toluene (0.1 M), KOH (0.30 mmol), −78 °C, 60 h. Results in parenthesis refer to the opposite enantiomer, obtained using **4g** (0.010 mmol) as the catalyst. [b] Isolated yields. [c] Determined by HPLC using a Daicel Chiralpak AD-H column. [d] 1 mmol scale. [e] Determined after Boc deprotection and Cbz derivatisation (See ESI†). [f] Absolute configuration determined as R (See ESI†).

phosphonic acid dimethyl esters **3e–n** in generally good yields and useful enantioselectivities (Table 2, entries 3–12, 66–97% yield, 79–95% ee). The obtainment of the ^{P}Ala and ^{P}Phe precursors **3l–n** (Table 2, entries 10–12), which cannot be accessed from alkenyl imines employed by Joly and Jacobsen to overcome the instability of linear unbranched imines,[10a] well witnesses the complementarity of the present method to previous organocatalytic reports. α-Amido sulfones derived from aromatic aldehydes gave the corresponding products in nearly racemic form, presumably due to a base-promoted racemisation.

The absolute configuration of the products was determined to be *R* by comparison of the optical rotation of some of the adducts with literature values (Table 2, entries 6, 11).[6a,d] This configuration, matching the stereochemistry of natural L-α-amino acids, has been found to be useful in most applications of α-amino phosphonic acid derivatives especially as protease inhibitors.[3–6] The quasi-enantiomeric catalyst **4g** derived from hydroquinidine (Fig. 1) gave access to the antipode of the products, though with diminished selectivities and a rather capricious behaviour (Table 2, entries 1, 4, 8, values in parentheses, 88–99% yield, 34–84% ee).

A salient feature of this catalytic method is the possibility of obtaining products bearing easily removable, or useful in peptide couplings, protecting groups at nitrogen. Indeed, with trivial experimental procedures, these adducts can be transformed either into α-amino phosphonic acids, as exemplified by the conversion of **3b** into the optically active α-amino phosphonic acid **5**, or into N-protected phosphonic acid monomethyl esters such as **6**, a known intermediate in the assembly of phosphono-peptides inhibitors of protease enzymes[6a,b,e] (Scheme 2).



Scheme 2

In conclusion, the development of the first asymmetric hydrophosphonylation using PTC, allowed to use directly α-amido sulfones **1** in a new and straightforward protocol for the hydrophosphonylation of imines, leading to the obtainment of optically active α-amino phosphonic acid derivatives **3**. Good assets of the present method are the trivial experimental procedures, the easy availability of substrates and catalysts, and the complementary scope with respect to previously reported organocatalytic processes. Finally, the possibility of converting very easily the catalytic adducts into α-amino phosphonic acids and/or useful intermediates for the synthesis of phosphono-peptides highlights an additional advantage associated with this strategy.

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20 The competition for the quaternary ammonium salt of the lipophilic sulfinate anion (generated during the formation of the imine) with the deprotonated phosphite can be the reason for the necessity of using an excess of phosphite, and for the long reaction time (60 h).