ARTICLE

OBC
www.rsc.org/obc

Catalytic asymmetric addition of β-keto phosphonates to an activated imine—formation of optically active functionalized phosphonate α-amino acid derivatives

Anne Kjærsgaard and Karl Anker Jørgensen*

Danish National Research Foundation: Center for Catalysis, Department of Chemistry, Aarhus University, DK-8000, Aarhus C, Denmark. E-mail: kaj@chem.au.dk; Fax: 45 8619 6199; Tel: 45 8942 3910

Received 25th October 2004, Accepted 9th December 2004
First published as an Advance Article on the web 24th January 2005

The direct stereoselective addition of an activated imine to β-keto phosphonates in the presence of chiral Lewis acid complexes is developed. The evaluation of different activated imines shows that an *N*-tosyl-α-imino ester adds in a diastereo- and enantioselective fashion to β-keto phosphonates activated by especially chiral copper(II)-bisoxazoline complexes. An evaluation of Lewis acids, chiral ligands and reaction conditions, such as solvent, bases and other additives, shows that high yields, moderate diastereoselectivity and good enantioselectivity are obtained. The scope of the reaction is demonstrated for the reaction of β-keto phosphonates and finally, the mechanism for the catalytic stereoselective step is presented.

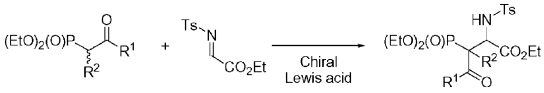
Introduction

Peptides of non-natural amino acids are attractive targets for drug discovery and, therefore, the development of new synthetic pathways to optically active amino acids containing different functionalities remains a constant need. Despite the structural and electronic differences between the phosphonate and carboxylic functionalities (in terms of size, shape, acidity and geometry) the phosphonate functionality is regarded as a bioisostere of the carboxylic group. Aminophosphonic acid derivatives can serve as haptens in catalytic enzyme antibody generation and as transition-state analogues for, *e.g.*, peptide coupling reactions and peptide hydrolysis,[1] which makes them important targets in the development of new enzyme inhibitors.[2]

The literature contains several examples of asymmetric synthesis of optically active α-amino phosphonates.[3] In 1989 Hayashi *et al.* developed a gold(I)-catalyzed reaction of diethyl(isocyanomethyl) phosphonate and different aldehydes.[4] By this procedure, chiral α-amino phosphonates were obtained in good yield and enantioselectivity when a chiral ferrocenylphosphine ligand was used. Later Shibasaki *et al.* explored the catalytic asymmetric hydrophosphonylation of imines using lanthanoid–potassium–BINOL heterobimetallic complexes as catalysts. In three successive publications hydrophosphonylations of both acyclic and cyclic imines were developed and improved.[5]

Despite the fact that β-phosphonic acid α-amino acids and derivatives thereof are biologically important molecules,[6] the asymmetric synthesis of this class of compounds has not been thoroughly studied. To our knowledge, the first truly catalytic asymmetric synthesis of β-amino phosphonates was the aminohydroxylation of α,β-unsaturated phosphonates catalyzed by potassium osmium(VI) dihydrate and the cinchona alkaloid ligand $(DHQ)_2PHAL$ developed by Sisti *et al.* in 1998,[7] followed by a similar approach by Sharpless *et al.* in 1999.[8] By these procedures, optically active β-amino-α-hydroxy phosphonates could be obtained in good yields and moderate to high enantioselectivities.

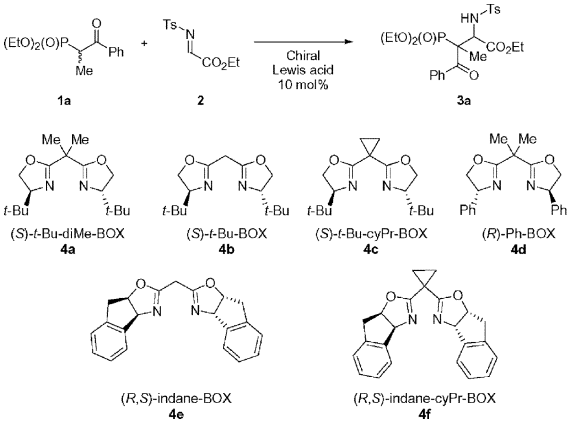
Due to the importance of optically active β-phosphonic acid α-amino acid derivatives, and the very limited number of reports on catalytic asymmetric synthesis of the title compounds, we decided to try to develop a one-step catalytic enantioselective approach for this class of compounds by the addition of β-keto phosphonates to imines using chiral Lewis acid catalysis [eqn (1)]. The present work is based on the development of catalytic enantioselective Mannich,[9] amination[10] and aldol[11] reactions where we have utilized the fact that compounds with acidic/enoliziable C–H bonds add in an enantioselective fashion (in the presence of a chiral Lewis acid catalyst) to imines, azodicarboxylates and carbonyl compounds.



(1)

Results and discussion

The investigation began by screening a series of different chiral ligands in combination with various chiral Lewis acids as catalysts for the addition of (1-methyl-2-oxo-2-phenylethyl)ethyl phosphonate (**1a**) to various *N*-protected-α-imino esters, **2** (*N*-protecting groups tested: *p*-methoxy phenyl and tosyl). We were surprised to find that the BINAP–Cu(I) complex, which has previously been found to be an effective chiral Lewis acid catalyst for the addition of a series of different substrates to **2**,[12] in the present reaction gave unsatisfactory results, both in terms of yield and selectivity, as only 20% yield and 32% ee were obtained when reacting **1a** with, *e.g.*, the *N*-tosyl-α-imino ester **2** for 4 d at room temperature. However, to our delight the combination of chiral bisoxazolines (BOX) ligands **4**,[13] and especially Cu(II) salts, turned out to be a good choice of chiral catalyst for the reaction of β-keto phosphonates **1** with **2** [eqn (2)], while α-imino esters with other *N*-protecting groups, such as *para*-methoxy phenyl did not react under the reaction conditions studied.



(2)

DOI: 10.1039/b416294c

Table 1 Screening of reaction conditions for the catalytic enantioselective addition of (1-methyl-2-oxo-2-phenylethyl)ethyl phosphonate (**1a**) to *N*-tosyl-α-imino ester **2** catalyzed by various chiral Lewis acid complexes

Entry	Catalyst	Base	Solvent	Reaction temperature/°C[a]	Yield/%[b]	Dr[c]	Ee/%[d]
1	$Cu(OTf)_2$–**4a**	—	CH_2Cl_2	Rt	32	2.0 : 1	55
2	$Cu(OTf)_2$–**4a**	Et_3N	CH_2Cl_2	Rt	>98	2.5 : 1	84
3	$Cu(OTf)_2$–**4a**	Et_3N	CH_2Cl_2	−20	25	3.0 : 1	55
4	$Cu(OTf)_2$–**4a**	Et_3N	CH_2Cl_2	Reflux	>98	2.6 : 1	72
5	$Cu(OTf)_2$–**4a**	Et_3N	$Cl(CH_2)_2Cl_2$	Rt	25	2.6 : 1	70
6	$Cu(OTf)_2$–**4a**	—	Et_2O	Rt	50	1.7 : 1	5
7	$Cu(OTf)_2$–**4a**	Et_3N	Et_2O	Rt	70	1.8 : 1	5
8	$Zn(OTf)_2$–**4a**	Et_3N	Et_2O	Rt	37	1.5 : 1	67
9	$Mg(OTf)_2$–**4a**	Et_3N	Et_2O	Rt	93	2.3 : 1	Rac.
10	$Cu(OTf)_2$–**4d**	—	CH_2Cl_2	Rt	70	1.5 : 1	50
11	$Cu(OTf)_2$–**4d**	Et_3N	CH_2Cl_2	Rt	>98	3.7 : 1	56
12	$Cu(OTf)_2$–**4b**	Et_3N	CH_2Cl_2	Rt	86	1.8 : 1	23
13	$Cu(OTf)_2$–**4c**	Et_3N	CH_2Cl_2	Rt	57	2.2 : 1	74
14	$Cu(OTf)_2$–**4e**	Et_3N	CH_2Cl_2	Rt	50	0.7 : 1	Rac.
15	$Cu(OTf)_2$–**4f**	Et_3N	CH_2Cl_2	Rt	50	1.4 : 1	9
16	$Mg(OTf)_2$–**4e**	Et_3N	CH_2Cl_2	Rt	>99	1.5 : 1	Rac.
17	$Mg(OTf)_2$–**4f**	Et_3N	Toluene	Rt	76	9.0 : 1	Rac.

[a] Rt = room temperature. [b] Isolated yield. [c] The diastereomeric ratio was measured by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [d] Ee of the major diastereomer was measured by HPLC using a chiral stationary phase.

Screening of chiral Lewis acids, solvents, bases and reaction temperature and time was carried out for the reaction of (1-methyl-2-oxo-2-phenylethyl)ethyl phosphonate (**1a**) with the *N*-tosyl-α-imino ester **2** [eqn (2)]. The initial study of the enantioselective addition of β-keto phosphonates was focused on the screening of different combinations of Lewis acids and chiral ligands **4a–f**. The results of this investigation are presented in Table 1.

The Lewis acid $Cu(OTf)_2$ in combination with *t*-Bu-DiMe-BOX ligand **4a** was the best catalytic system in terms of selectivity and, with the addition of 10% Et_3N full conversion could be reached within 4 d at room temperature with the major diastereomer formed at 84% ee (Table 1, entry 2). Lowering the reaction temperature leads to a decrease in enantioselectivity and, furthermore, the reaction proceeded at a much lower rate (entry 3). Refluxing the reaction mixture enhanced the reaction rate, but a minor decrease in enantioselectivity was observed (entry 4). Other Lewis acids such as zinc(II) and magnesium(II) also possessed the properties needed to catalyze the reaction between (1-methyl-2-oxo-2-phenylethyl)ethyl phosphonate (**1a**) and the *N*-tosyl-α-imino ester **2**. However, zinc(II) does not catalyze the reaction to the same extent as copper(II) (entry 2 *vs.* entry 8). As the indanol-derived BOX ligands **4e,f**, in combination with magnesium(II), are known to induce good selectivity in several other catalytic enantioselective reactions,[14] $Mg(OTf)_2$ was tested in the present reaction with both the indanol-derived ligands **4e,f** and ligand **4a**. A considerable enhancement of the diastereoselectivity was observed with (*R*,*S*)-indane-cyPr-BOX **4f** as the chiral ligand (entry 17), but product **3a** was obtained as a racemate in all instances. Combining the chiral ligands **4e,f** with $Cu(OTf)_2$ did not improve the selectivity.

Alteration of the bite angle of chiral ligands has been shown to have a considerable influence on the selectivity in some asymmetric reactions[15] and, therefore, we tried to modify the backbone of the ligand in an attempt to improve the stereoselectivity of the reaction. When no substituents were present in the backbone of the ligand (**4b**), a significant decrease in enantioselectivity was observed compared to the presence of two methyl groups (**4a**) (entry 12 *vs.* entry 2). Introduction of a cyclopropyl ring in the BOX ligand (**4c**) re-established the enantioselectivity, but unfortunately at the expense of the yield of **3a** (entry 13 *vs.* 2).

CH_2Cl_2 turned out to be the solvent of choice and, since addition of base was necessary to reach full conversion, a screening of different bases was carried out in this solvent at room temperature with 10 mol% $Cu(OTf)_2$-(*S*)-*t*-Bu-DiMe-BOX (**4a**) as the chiral catalyst. The results of the base screening are shown in Table 2.

Table 2 Screening of Brønsted bases for the catalytic asymmetric addition of phosphonate **1a** to *N*-tosyl-α-imino ester **2** catalysed by $Cu(OTf)_2$-(*S*)-*t*-Bu-DiMe-BOX

Entry	Base	Reaction time/h	Yield/%[a]	Dr[b]	Ee/%[c]
1	—	86	32	2.0 : 1	55
2	Et_3N	86	>98	2.5 : 1	84
3	DMA[d]	86	>98	1.9 : 1	64
4	$Et(i\text{-}Pr)_2N$	86	89	2.3 : 1	43
5	2,6-Lutidine	86	78	5.2 : 1	72

[a] Isolated yield. [b] The diastereomeric ratio was measured by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Ee of the major diastereomer was measured by HPLC using a chiral stationary phase. [d] DMA = *N*,*N*-dimethylaniline.

A base additive was clearly necessary to obtain high yields (Table 2, entry 1 *vs.* 2), however, none of the tested bases had a positive effect on either reactivity or selectivity compared to the result found for Et_3N. Similar yields were obtained with both Et_3N and the less basic DMA, but the enantioselectivity was significantly reduced by using the latter (entry 2 *vs.* 3). It was expected that a more sterically demanding base might not coordinate to the chiral Lewis acid, leading to an increase in chiral Lewis acid concentration and thereby improving the selectivities, but no improvement in selectivity was observed with, *e.g.*, Hünigs base (entry 4) and 2,6-lutidene (entry 5).

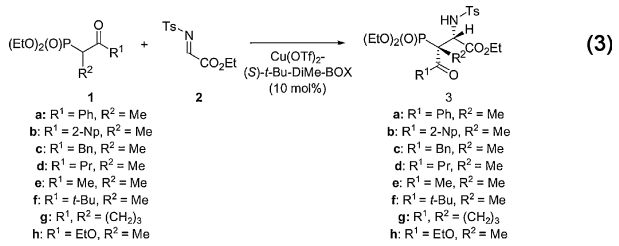
A number of studies have documented the significant impact of alcohol derivatives, *e.g.* 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), on reaction rate and selectivity in some Lewis acid catalyzed enantioselective reactions.[16] However, the addition of HFIP did not improve the yield and stereoselectivity of this reaction.

We expected that the size and the electronic properties of the keto-moiety of the β-keto phosphonate could have a pronounced effect on the reaction rate as well as on the stereoselectivity. We therefore reacted a series of ethyl β-keto phosphonates **1a–h** with *N*-tosyl-α-imino ester **2** in the presence of $Cu(OTf)_2$-(S)-*t*-Bu-DiMe-BOX (**4a**) as the chiral catalyst [eqn (3)]. The results are summarized in Table 3.

Table 3 Catalytic enantioselective addition of β-keto phosphonates **1a–h** to *N*-tosyl-α-imino ester **2** catalysed by $Cu(OTf)_2$-(*S*)-*t*-Bu-DiMe-BOX at room temperature

Entry	β-Keto phosphonate	R^1	R^2	Yield/%[a]	Dr[b]	Ee/%[c]
1	**1a**	Ph	Me	**3a**, >98[d]	2.5 : 1	84
2	**1b**	2-Np	Me	**3b**, 88	10 : 1	51
3	**1c**	$PhCH_2$	Me	**3c**, 64[d]	3.8 : 1	50
4	**1d**	Pr	Me	**3d**, 87	1.6 : 1	70
5	**1e**	Me	Me	**3e**, 61[d]	1.7 : 1	43
6	**1f**	*t*-Bu	Me	**3f**, 44[d]	6 : 1	67
7	**1g**	$-(CH_2)_3-$		**3g**, >98	1 : 1	44
8	**1h**	EtO	Me	**3h**, 72	4.6 : 1	79

[a] Isolated yield. [b] The diastereomeric ratio was measured by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Ee of the major diastereomer was measured by HPLC using a chiral stationary phase. [d] Total yield of separated diastereomers.



(3)

The catalytic enantioselective additions of β-keto phosphonates **1a–h** to *N*-tosyl-α-imino ester **2** all proceeded in moderate to excellent isolated yields (up to >98%) and diastereoselectivites (up to 10 : 1) and with up to 84% ee for **3a** (Table 3, entry 1). It appears from the results in Table 3, that both aromatic as well as alkyl groups are tolerated as functionalities at the keto-moiety. (1-Methyl-2-naphthalen-2-yl-2-oxoethyl) phosphonate **1b** gave the highest diastereoselectivity (10 : 1) and a moderate enantiomeric excess (51%) of **3b** (entry 2). When a methyl substituent is placed on the keto-functionality (**1e**) only moderate enantioselectivity (43% ee) is observed for **3e** (entry 5), while increasing the size of the alkyl substituent leads to an increase in enantioselectivity, as well as, the diastereoselectivity (entry 4, 6). Full conversion is obtained when a cyclic β-ketoester (**1g**) is used, however, only moderate enantioselectivity and no diastereoselectivity are obtained (entry 7). Replacing the keto-moiety with an ester group gives the desired product **3h** in similarly good yield and an enantioselectivity of 79% ee (entry 8). Recently, Ragnarsson *et al.*[17] demonstrated that the *N*-tosyl group can be cleaved under mild conditions, and we[9c] have shown that using this method with activated carbonyl compounds can remove the *N*-tosyl group without affecting the enantioselectivity.

The absolute configuration of the optically active β-phosphonic acid α-amino acid derivatives obtained was determined by X-ray analysis of **3e** (see the Experimental section). The data gave the stereochemistry of the chiral centers formed in the catalytic asymmetric reaction as (*R*,*R*).

We expect that the β-keto phosphonate coordinates to the copper(II) center in a bidentate fashion.[18] This coordination leads to a shielding of the *Si*-face of the β-enol phosphonate by the *tert*-butyl group of the chiral bisoxazoline ligand as outlined in Fig. 1. The *Re*-face is thus available for approach of the *N*-tosyl-α-imino ester as demonstrated in Fig. 1, in which the *N*-tosyl substituent is pointing away from the *tert*-butyl group of the chiral bisoxazoline ligand. This reaction course of the *N*-tosyl-α-imino ester accounts for both the diastereo- and enantioselective outcome of the reaction.

In summary, we have developed the first catalytic diastereo- and enantioselective addition of an activated imino ester to β-keto phosphonates. The reaction proceeds in high yields and with moderate diastereoselectivity and moderate to good enantioselectivity for various β-keto phosphonates in the presence of $Cu(OTf)_2$-(S)-*t*-Bu-DiMe-BOX as the chiral catalyst.

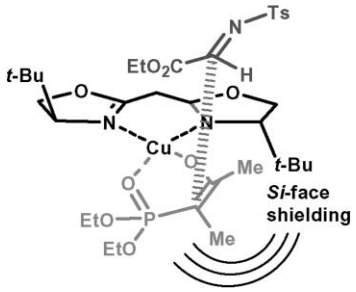


Fig. 1 Proposed intermediate and approach of the *N*-tosyl-α-imino ester.

A bidentate coordination of the β-keto phosphonate to the $Cu(OTf)_2$-(S)-*t*-Bu-DiMe-BOX chiral catalyst leads to shielding of the *Si*-face of the β-enol phosphonate and leaves the *Re*-face open for approach of the *N*-tosyl-α-imino ester in accordance with the experimental results.

Experimental

General methods

The ^{1}H NMR, ^{13}C NMR and ^{31}P NMR spectra were recorded at 400, 100 and 162 MHz, respectively. The chemical shifts are reported in ppm downfield to $CDCl_3$ ($\delta = 7.26$) for ^{1}H NMR and relative to the central $CDCl_3$ resonance ($\delta = 77.0$) for ^{13}C NMR. Coupling constants in ^{1}H NMR are in Hz. Flash chromatography (FC) was carried out using silica gel 60 (230–400 mesh). Optical rotations are reported as follows: $[\alpha]_{rt}^{D}$ (*c* in g per 100 mL solvent). The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC as indicated in the respective entries.

Materials

Commercially available compounds were used without further purification. Solvents were dried according to standard procedures. The *N*-tosyl-α-imino ester **2** was prepared from ethyl glyoxylate and *p*-toluenesulfonyl isocyanate by a literature procedure,[19] as were the ligands **4e,f**.[20]

General procedure for the catalytic asymmetric addition of phosphonates to *N*-tosyl-α-imino ester 2

$Cu(OTf)_2$ (18.1 mg, 0.05 mmol) and 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (15.5 mg, 0.05 mmol) were added to an oven or flame dried Schlenk tube equipped with a magnetic stirring bar. The mixture was stirred under vacuum for 2 h and filled with N_2. Dry CH_2Cl_2 (2 mL) was added and the solution was stirred for 0.5 h. *N*-Tosyl-α-imino ester **2** (153 mg, 0.6 mmol) was added, followed by the β-keto phosphonate (0.5 mmol) and Et_3N (6.9 μL, 0.05 mmol) and stirred for 96 h under N_2 at room temperature. The reaction mixture was filtered through a plug

of silica with EtOAc. The solvent was removed *in vacuo* and the residue was purified by FC (silica, DCM–EtOAc).

3-(Diethoxyphosphoryl)-3-methyl-4-oxo-4-phenyl-2-(toluene-4-sulfonylamino)butyric acid ethyl ester (3a)

The diastereomers were separated by FC, and the enantiomers of the major diastereomer were separated by HPLC using Daicel Chiralcel OD column (hexane–i-PrOH (97 : 3)); flow rate 1.0 mL min^{-1}; $\tau_{major} = 43.2$ min; $\tau_{minor} = 30.3$ min); $[\alpha]_{rt}^{D} = +16.4°$ ($c = 1.0$ g per 100 mL, CH_2Cl_2, 84% ee); ^1H NMR δ 7.82 (d, $J =$ 7.6 Hz, 2H, Ar*H*), 7.71 (d, $J = 8.4$ Hz, 2H, Ar*H*), 7.48–7.25 (m, 5H, Ar*H*), 6.15 (d, $J = 10.0$ Hz, 1H, N*H*), 4.75 (dd, $J = 16.6$, 10.4 Hz, 1H, NH–C*H*), 4.18–4.10 (m, 4H, POCH_2), 3.79–3.74 (m, 2H, OCH_2), 2.39 (s, 3H, PhCH_3), 1.72 (d, $J = 16.6$ Hz, 3H, C–CH_3), 1.34–1.23 (m, 6H, $POCH_2CH_3$), 0.97 (t, $J = 1.2$ Hz, 3H, OCH_2CH_3); ^{13}C NMR δ 200.5, 142.5, 137.2, 136.5, 130.6, 128.4, 127.8, 127.1, 127.0, 126.3, 62.7, 62.6, 62.5, 60.8, 59.0, 20.5, 18.2, 15.4, 15.3, 12.6; ^{31}P NMR δ 23.8; HRMS $C_{24}H_{32}NO_8PS$ $[M + Na]^+$; calculated: 548.1484, found: 548.1482.

3-(Diethoxyphosphoryl)-3-methyl-4-naphthalen-2-yl-4-oxo-2-(toluene-4-sulfonylamino)butyric acid ethyl ester (3b)

The enantiomers of the major diastereomer were separated by HPLC using a Daicel Chiralpak AD column (hexane–i-PrOH (90 : 10); flow rate 1.0 mL min^{-1}; $\tau_{major} = 18.2$ min; $\tau_{minor} = 8.3$ min); $[\alpha]_{rt}^{D} = +12.5°$ ($c = 1.0$ g per 100 mL, CH_2Cl_2, 51% ee); ^1H NMR δ 7.95 (d, $J = 7.7$ Hz, 2H, Ar*H*), 7.91–7.85 (m, 4H, Ar*H*), 7.70 (d, $J = 8.3$, 2H, Ar*H*), 7.61–7.42 (m, 2H, Ar*H*), 7.15 (d, $J =$ 8.1 Hz, 1H, Ar*H*), 6.16 (d, $J = 10.5$ Hz, N*H*), 4.90 (dd, $J = 17.0$, 10.4 Hz, 1H, NH–C*H*), 4.24–4.15 (m, 4H, POCH_2), 3.84–3.76 (m, 2H, OCH_2), 2.30 (s, 3H, PhCH_3), 1.84 (d, $J = 16.6$ Hz, 3H, C–CH_3), 1.35–1.29 (m, 6H, $POCH_2CH_3$), 0.99 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3); ^{13}C NMR δ 200.9, 143.6, 137.7, 135.2, 134.8, 132.3, 129.7, 129.6, 128.4, 128.2, 127.9, 127.5, 126.9, 125.1, 69.7, 63.8, 61.9, 60.1, 57.6, 56.2, 25.6, 21.7, 19.7, 16.7, 13.8; ^{31}P NMR δ 24.2; HRMS $C_{28}H_{34}NO_8PS$ $[M + Na]^+$; calculated: 598.1640, found: 598.1642.

3-(Diethoxyphosphoryl)-3-methyl-4-oxo-5-phenyl-2-(toluene-4-sulfonylamino)pentanoic acid ethyl ester (3c)

The diastereomers were separated by FC, and the enantiomers of the major diastereomer were separated by HPLC using a Daicel Chiralpak AS column (hexane–i-PrOH (95 : 5); flow rate 1.0 mL min^{-1}; $\tau_{major} = 29.7$ min; $\tau_{minor} = 21.3$ min); $[\alpha]_{rt}^{D} = +2.6°$ ($c = 1.0$ g per 100 mL, CH_2Cl_2, 50% ee); ^1H NMR δ 7.70 (d, $J =$ 8.3 Hz, 2H, Ar*H*), 7.31–7.10 (m, 7H, Ar*H*), 5.88 (d, $J = 10.2$ Hz, 1H, N*H*), 4.62 (dd, $J = 13.4$, 10.3 Hz, 1H, NH–C*H*), 4.2–3.83 (m, 6H, POCH_2, PhCH_2), 3.84–3.76 (m, 2H, OCH_2), 2.38 (s, 3H, ArCH_3), 1.58 (d, $J = 16.2$ Hz, 3H, C–CH_3), 1.34–1.22 (m, 6H, $POCH_2CH_3$), 1.03–0.97 (m, 3H, OCH_2CH_3); ^{13}C NMR δ 203.7, 168.9, 143.9, 137.3, 134.0, 130.2, 129.7, 128.5, 127.6, 127.1, 63.9, 63.8, 62.1, 58.8, 46.4, 25.6, 21.7, 16.6, 16.2, 13.8; ^{31}P NMR δ 24.19; HRMS $C_{25}H_{34}NO_8PS$ $[M + Na]^+$; calculated: 562.1640, found: 562.1636.

3-(Diethoxyphosphoryl)-3-methyl-4-oxo-2-(toluene-4-sulfonylamino)heptanoic acid ethyl ester (3d)

The enantiomers of the major diastereomer were separated by HPLC using Daicel Chiralpak AS column (hexane–i-PrOH (95 : 5); flow rate 1.0 mL min^{-1}; $\tau_{major} = 18.2$ min; $\tau_{minor} = 14.0$ min) $[\alpha]_{rt}^{D} = +6.7°$ ($c = 1.0$ g per 100 mL, CH_2Cl_2, 70% ee); ^1H NMR δ 7.71 (d, $J = 6.7$ Hz, 2H, Ar*H*), 7.29 (d, $J = 6.7$ Hz, 2H, Ar*H*), 5.86 (d, $J = 10.0$ Hz, 1H, N*H*), 4.56 (dd, $J = 8.4$, 10.0 Hz, 1H, NH–C*H*), 4.15–4.06 (m, 4H, POCH_2), 3.80–3.70 (m, 2H, OCH_2), 2.66–2,56 (m, 2H, COCH_2), 2.39 (s, 3H, ArCH_3), 1.60–1.25 (m, 5H, C–CH_3, CH_2CH_2), 1.25–1.15 (m, 6H, $POCH_2CH_3$), 1.06–0.86 (m, 6H, OCH_2CH_3, CH_3); ^{13}C NMR δ 159.5, 143.8, 129.7, 127.6, 115.7, 64.7, 63.6, 62.9, 62.0, 58.8, 47.5, 46.2, 45.3, 41.8, 25.6, 17.2, 16.6, 13.8, 11.3; ^{31}P NMR δ 24.7; HRMS $C_{21}H_{34}NO_8PS$ $[M + Na]^+$; calculated: 514.1640, found: 514.1643.

3-(Diethoxyphosphoryl)-3-methyl-4-oxo-2-(toluene-4-sulfonylamino)pentanoic acid ethyl ester (3e)

The diastereomers were separated by FC, and the enantiomers of the major diastereomer were separated by HPLC using a Daicel Chiralcel OJ column (hexane–i-PrOH (95 : 5); flow rate 0.8 mL min^{-1}; $\tau_{major} = 60.2$ min; $\tau_{minor} = 49.5$ min); $[\alpha]_{rt}^{D} = +2.8°$ ($c = 1.0$ g per 100 mL, CH_2Cl_2, 43% ee); ^1H NMR δ 7.71 (dd, $J =$ 1.0 Hz, $J = 6.0$ Hz, 2H, Ar*H*), 7.28 (d, $J = 6.0$ Hz, 2H, Ar*H*), 5.76 (d, $J = 10.8$ Hz, 1H, N*H*), 4.71 (dd, $J = 10.8$ Hz, $J = 4.8$ Hz, 1H, NH–C*H*), 4.21–4.02 (m, 4H, POCH_2), 3.91–3.71 (m, 2H, COCH_2), 2.43–2.41 (m, 6H, ArCH_3, CH_3), 1.48–1.26 (m, 7H, $POCH_2CH_3$, CH_3), 1.01 (m, 3H, OCH_2CH_3); ^{13}C NMR δ 143.9, 137.2, 129.7, 127.7, 63.7, 62.3, 62.1, 58.5, 58.3, 28.1, 27.9, 21.8, 16.5, 16.2, 14.7, 13.7; ^{31}P NMR δ 23.5; HRMS $C_{19}H_{30}NO_8PS$ $[M + Na]^+$; calculated: 486.1327, found: 486.1340.

3-(Diethoxyphosphoryl)-3,5,5-trimethyl-4-oxo-2-(toluene-4-sulfonylamino)hexanoic acid ethyl ester (3f)

The diastereomers were separated by FC, and the enantiomers of the major diastereomer were separated by HPLC using a Daicel Chiralpak AD column (hexane–i-PrOH (90 : 10); flow rate 1.0 mL min^{-1}; $\tau_{major} = 23.8$ min; $\tau_{minor} = 16.7$ min); $[\alpha]_{rt}^{D} = -1.1°$ ($c = 1.0$ g per 100 mL, CH_2Cl_2, 67% ee); ^1H NMR δ 7.80 (d, $J = 8.2$ Hz, 1H, Ar*H*), 7.70 (d, $J = 8.2$ Hz, 1H, Ar*H*), 7.30 (d, $J = 8.1$ Hz, 1H, Ar*H*), 7.26 (d, $J = 8.1$ Hz, 1H, Ar*H*), 5.80 (d, $J = 9.8$ Hz, 1H, N*H*), 4.85–4.78 (dd, $J = 9.8$ Hz, $J =$ 16.1 Hz, 1H, NH–C*H*), 4.22–4.04 (m, 4H, POCH_2), 3.91–3.62 (m, 2H, OCH_2), 2.40 (d, $J = 11.7$ Hz, 3H, C–CH_3), 2.05 (s, 3H, Ph–CH_3), 1.34–1.20 (m, 15H, $POCH_2CH_3$, $C(CH_3)_3$), 1.01 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3); ^{13}C NMR δ 143.5, 137.9, 129.9, 128.0, 127.5, 63.5, 63.4, 62.0, 59.5, 29.5, 29.4, 27.3, 21.9, 17.8, 16.5, 12.0; ^{31}P NMR δ 24.2; HRMS $C_{24}H_{32}NO_8PS$ $[M + Na]^+$; calculated: 548.1797 found: 548.1802.

[1-(Diethoxyphosphoryl)-2-oxo-cyclopentyl](toluene-4-sulfonylamino)acetic acid ethyl ester (3g)

The enantiomers of the major diastereomer were separated by HPLC using a Daicel Chiralpak AD column (hexane–i-PrOH (90 : 10); flow rate 1.0 mL min^{-1}; $[\alpha]_{rt}^{D} = +16.2°$ ($c = 1.0$ g per 100 mL, CH_2Cl_2, 44% ee); ^1H NMR 7.70 (dd, $J = 8.4$ Hz, $J = 12.4$ Hz, 2H, ArH), 7.27 (d, $J = 8.4$ Hz, $J = 2$ Hz, 2H, ArH), 5.89 (d, $J = 10.0$ Hz, NH), 4.48 (dd, $J = 11.2$, 10.0 Hz, 1H, NH–CH), 4.16–4.05 (m, 4H, $POCH_2$), 3.95–3.70 (m, 4H, OCH_2, $COCH_2$), 2.40 (s, 3H, Ar–CH_3), 2.60–2.16 (m, 2H, CH_2), 2.40–1.84 (m, 2H, CH_2), 1.35–1.24 (m, 6H, $POCH_2CH_3$), 1.11–1.04 (m, 3H, OCH_2CH_3); ^{13}C NMR δ 212.6, 169.2, 143.7, 137.5, 129.5, 127.6, 63.7, 62.1, 60.5, 57.6, 38.5, 28.1, 21.6, 16.5, 13.9; ^{31}P NMR δ 21.8; HRMS $C_{28}H_{34}NO_8PS$ $[M + Na]^+$; calculated: 498.1327 found: 498.1324.

2-(Diethoxyphosphoryl)-2-methyl-3-(toluene-4-sulfonylamino)succinic acid diethyl ester (3h)

The enantiomers of the major diastereomer were separated by HPLC using a Daicel Chiralpak AD column (hexane–i-PrOH (90 : 10); flow rate 1.0 mL min^{-1}; $[\alpha]_{rt}^{D} = +9.4°$ ($c = 1.0$ g per 100 mL, CH_2Cl_2, 79% ee); ^1H NMR δ 7.66 (d, $J = 8.0$ Hz, 2H, ArH), 7.20 (d, $J = 8.0$ Hz 2H, ArH), 5.78 (d, $J = 10.8$ Hz, NH), 4.46 (dd, $J = 16.4$, 10.8 Hz, 1H, NH–CH), 4.16–4.03 (m, 6H, $POCH_2$, OCH_2), 3.78–3.73 (m, 2H, OCH_2), 2.34 (s, 3H, Ar–CH_3), 1.40 (s, 3H, C–CH_3), 1.28–1.17 (m, 6H, $POCH_2CH_3$), 0.99 (t, $J = 7.6$ Hz, 3H, OCH_2CH_3); ^{13}C NMR δ 169.5, 168.8, 143.8, 137.3, 129.7, 127.6, 63.7, 63.0, 62.9, 62.4 61.6, 58.7, 21.7, 21.3, 17.2, 16.7, 14.1, 13.9; ^{31}P NMR δ 22.9; HRMS $C_{28}H_{34}NO_8PS$ $[M + Na]^+$; calculated: 516.1433 found: 516.1418.

X-Ray analysis of 3-(diethoxyphosphoryl)-3-methyl-4-oxo-2-(toluene-4-sulfonylamino)pentanoic acid ethyl ester (3e)†

$C_{19}H_{30}NO_8PS$ crystallises in the monoclinic space group $P2_1$ with unit cell: $a = 7.997(2)$ Å, $b = 12.221(2)$ Å, $c = 11.812(2)$ Å, $\beta = 100.647(4)°$, $V = 1134.4(4)$ Å^3 at 100 K. $Z = 2$, μ(MoKα) = 0.257 mm^{-1}. A total of 32788 reflections were measured, averaging to 9477 independent, $R_{int} = 0.022$; 7921 reflections with $I > 0$ were used in the refinements finishing at $R = 0.033$, $R_w = 0.048$. The absolute configuration was established by refinement according to Rogers[21] using all 7921 non-negative reflections including 3798 Bijvoet pairs.

X-ray crystallographic data for compound **3e** are deposited with Cambridge Crystallographic Data Centre. These data can be obtained free of charge *via* http://www.ccdc.ac./const/retrieving.html (or from Cambridge Crystallographic Center, 12, Union Road, Cambridge CB21EZ, UK; fax: (44)-1223-336-033; or deposit@ccdc.cam.ac.uk).

Acknowledgements

This work has been made possible by a grant of the Danish National Research Foundation. Thanks are expressed to Dr Rita G. Hazell for X-ray analysis.

References

1 V. Gouverneur and M. N. Lalloz, *Tetrahedron Lett.*, 1996, **37**, 6331.
2 (*a*) R. Hirschmann, A. B. Smidt, III, C. M. Taylor, P. A. Benkovic, S. D. Taylor, K. M. Yager, P. A. Sprengeler and S. J. Benkovic, *Science*, 1994, **265**, 234; (*b*) F. Meyer, A. Laaziri, A. M. Papini, J. Uziel and S. Jugé, *Tetrahedron*, 2004, **60**, 3593; (*c*) W. W. Smith and P. A. Bartlett, *J. Am. Chem. Soc.*, 1998, **120**, 4622.
3 (*a*) K. M. Tager, C. M. Taylor and A. B. Smith, III, *J. Am. Chem. Soc.*, 1994, **116**, 9377; (*b*) A. B. Smith, III, K. M. Tager and C. M. Taylor, *J. Am. Chem. Soc.*, 1995, **117**, 10879; (*c*) F. A. Davies, S. Lee, H. Yan and D. D. Titus, *Org. Lett.*, 2001, **3**, 1757; (*d*) F. A. Davies and K. R. Prasad, *J. Org. Chem.*, 2003, **68**, 7249; (*e*) C. De Risi, D. Perrone, A. Dondoni, G. P. Pollini and V. Bertolasi, *Eur. J. Org. Chem.*, 2003, **10**, 1904; (*f*) S. Hanessian and Y. L. Bennani, *Tetrahedron Lett.*, 1990, **31**, 6465; (*g*) C. Pousset and M. Larchevêque, *Tetrahedron Lett.*, 2002, **43**, 5257.
4 M. Sawamura, Y. Ito and T. Hayashi, *Tetrahedron Lett.*, 1989, **30**, 2247.
5 (*a*) H. Sasai, S. Arai, Y. Tahara and M. Shibasaki, *J. Org. Chem.*, 1995, **60**, 6656; (*b*) H. Gröger, Y. Saida, H. Sasai, K. Yamaguchi, J. Martens and M. Shibasaki, *J. Am. Chem. Soc.*, 1998, **120**, 3089; (*c*) I. Schlemmeinger, Y. Saida, H. Gröger, W. Maison, N. Durot, H. Sasai, M. Shibasaki and J. Martens, *J. Org. Chem.*, 2000, **65**, 4818.
6 For examples and applications of different naturally occurring β-amino phophonates/phosphonic acids see, *e.g.*: *Aminophosphonic and Aminophosphinic Acids, Chemistry and Biological Activity*, ed. V. P. Kukhar and H. R. Hudson, John Wiley & Sons, New York, 2000.
7 G. Cravotto, G. B. Giovenzana, R. Pagliarin, G. Palmisano and M. Sisti, *Tetrahedron: Asymmetry*, 1998, **9**, 745.
8 A. A. Thomas and K. B. Sharpless, *J. Org. Chem.*, 1999, **64**, 8379.
9 (*a*) M. Marigo, A. Kjærsgaard, K. Juhl, N. Gathergood and K. A. Jørgensen, *Chem. Eur. J.*, 2003, **9**, 2359; (*b*) L. Bernadi, A. S. Gothelf, R. G. Hazell and K. A. Jørgensen, *J. Org. Chem.*, 2003, **68**, 2583; (*c*) K. Juhl, N. Gathergood and K. A. Jørgensen, *Angew. Chem. Int. Ed.*, 2001, **40**, 2995.
10 (*a*) M. Marigo, K. Juhl and K. A. Jørgensen, *Angew. Chem. Int. Ed.*, 2003, **42**, 1367; (*b*) K. Juhl and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2002, **124**, 2420; (*c*) see also: D. A. Evans and S. G. Nelson, *J. Am. Chem. Soc.*, 1997, **119**, 6542; (*d*) D. A. Evans and S. G. Nelson, *Org. Lett.*, 1999, **1**, 595; (*e*) Y. Yamamoto and H. Yamamoto, *J. Am. Chem. Soc.*, 2004, **126**, 4128; (*f*) N. Moniyama and H. Yamamoto, *J. Am. Chem. Soc.*, 2003, **125**, 6038; (*g*) N. Moniyama and H. Yamamoto, *J. Am. Chem. Soc.*, 2004, **126**, 5360; (*h*) D. A. Evans and S. G. Nelson, *J. Am. Chem. Soc.*, 1997, **119**, 6452; (*i*) for a recent review see: E. Erdik, *Tetrahedron*, 2004, **60**, 8747.
11 (*a*) K. Juhl, N. Gathergood and K. A. Jørgensen, *Chem. Commun.*, 2000, 2211; (*b*) N. Gathergood, K. Juhl, T. B. Poulsen, K. Thordrup and K. A. Jørgensen, *Org. Biomol. Chem.*, 2004, **2**, 1077.
12 See, *e.g.*: S. Yao, S. Saaby, R. G. Hazell and K. A. Jørgensen, *Chem. Eur. J.*, 2000, **6**, 2435.
13 (*a*) A. K. Ghosh, P. Mathivanen and J. Cappiello, *Tetrahedron: Asymmetry*, 1998, **9**, 1; (*b*) K. A. Jørgensen, M. Johannesen, S. Yao, H. Audrain and J. Thorhauge, *Acc. Chem. Res.*, 1999, **32**, 605; (*c*) J. S. Johnson and D. A. Evans, *Acc. Chem. Res.*, 2000, **33**, 325; (*d*) H. A. McManus and P. J. Guiry, *Chem. Rev.*, 2004, **104**, 4151.
14 (*a*) Catalytic enantioselective conjugate addition of 1,3-dicarbonyl compounds to nitroalkenes: J. Ji, D. M. Barnes, J. Zhang, S. A. King, S. J. Wittenberger and H. E. Morton, *J. Am. Chem. Soc.*, 1999, **121**, 10215; D. M. Barnes, J. Ji, M. G. Fickes, M. A. Fitzgerald, S. A. King, H. E. Morton, F. A. Plagge, M. Preskill, S. H. Wagaw, S. J. Wittenberger and J. Zhang, *J. Am. Chem. Soc.*, 2002, **124**, 13097; (*b*) radical addition to α,β-unsaturated imides: M. P. Sibi, N. Prabagaran, S. G. Ghorpade and C. P. Jasperse, *J. Am. Chem. Soc.*, 2003, **125**, 11796; (*c*) conjugate additions of O-benzylhydrozylamine to unsaturated amides: M. P. Sibi, J. J. Shay, M. Liu and C. P. Jasperse, *J. Am. Chem. Soc.*, 1998, **120**, 6615.
15 (*a*) I. W. Davies, L. Gerena, L. Castonguay, C. H. Senanayake, R. D. Larsen, T. R. Vershoeven and P. J. Reider, *Chem. Commun.*, 1996, **15**, 1753; (*b*) M. P. Sibi and J. Jio, *J. Org. Chem.*, 1997, **62**, 3800.
16 See *e.g.*: (*a*) J. Zhou and Y. Tang, *J. Am Chem. Soc.*, 2002, **124**, 9030; (*b*) R. Takita, T. Ohshima and M. Shibasaki, *Tetrahedron Lett.*, 2002, **43**, 4661; (*c*) D. A. Evans, T. Rovis, M. C. Kozlowski and J. S. Tedrow, *J. Am. Chem. Soc.*, 1999, **121**, 1994; (*d*) D. A. Evans and D. S. Johnson, *Org. Lett.*, 1999, **1**, 595.
17 B. Nyasse, L. Grehn and U. Ragnarsson, *Chem. Commun.*, 1997, 1017.
18 For a discussion of the coordination of bidentate substrates to chiral copper(II) bisoxazoline complexes and structure of the chiral intermediate see *e.g.*: J. Thorhauge, M. Roberson, R. G. Hazell and K. A. Jørgensen, *Chem. Eur. J.*, 2002, **8**, 1888.
19 G. R. Heintzelman, S. M. Weinreb and M. Parvez, *J. Org. Chem.*, 1996, **61**, 4594.
20 D. M. Barnes, J. Ji, M. G. Fickes, M. A. Fitzgerald, S. A. King, H. E. Morton, F. A. Plagge, M. Preskill, S. H. Wagaw, S. J. Wittenberger and J. Zhang, *J. Am. Chem. Soc.*, 2002, **124**, 13097.
21 D. Rogers, *Acta Crystallogr., Sect. A*, 1981, **37**, 734.

† CCDC reference number 253695. See http://www.rsc.org/suppdata/ob/b4/b416294c/ for crystallographic data in .cif format.