Pergamon

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Tetrahedron: *Asymmetry* 14 (2003) 2229–2238

TETRAHEDRON: *ASYMMETRY*

Efficient synthesis of β-halogeno protected L-alanines and their β-phosphonium derivatives

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Received 8 May 2003; accepted 16 June 2003

Abstract—Ring opening of oxazolines, prepared from L-serinates, with trimethylsilyl halides (TMSX) led to β-halogeno-*N*-benzoyl-α-amino esters in good to excellent yields. Quaternization of triphenylphosphine by the β-bromo or -iodo amino esters gave the corresponding β-phosphonium salts in overall yields of up to 93% and with e.e. >96%. Hydrolysis of the ester function afforded the phosphonium salt bearing an *N*-benzoyl-α-amino acid substituent, with partial racemization. However, the reaction of the TMSX with the carboxylic salt, prepared by saponification of the starting oxazoline ester, furnished the corresponding β-halogeno-*N*-benzoyl-α-amino acids in 70–95% yields. Quaternization of triphenylphosphine by the bromo or iodo derivatives led to the phosphonium salts bearing a free acid function in 95% yield, without racemization. The efficiency of this synthesis was demonstrated by the preparation of these phosphonium salts in excellent overall yields, by a one-pot procedure starting from the oxazoline.

1. Introduction

Serine is a naturally occurring amino acid available in both its enantiomeric forms and useful for the hemisynthesis of non classical derivatives by β-homologation of its side-chain.[1] Modifications of amino acid side chains can influence their steric hindrance, polarity or conformation. This is particularly important for the development of back-bone modified peptides given their structure–activity relationships and the stabilization of their bioactivity against enzymatic degradation.[2]

The principle of the hemisynthesis starting from serine, lies in its transformation into a β-cation, -anion or -radical equivalent of alanine.[1b,c] This is illustrated by protected β-bromo and β-iodo alanine which can be used as electrophilic blocks,[3] radical precursors[4] and for the preparation of organozinc reagents[5] or phosphonium salts.[6,7] In addition, I-labelled β-iodo alanine has been proposed as a localizing agent for the site of infection.[8]

In order to achieve the synthesis of phosphonium salts derived from L-alanine, which are useful for the hemisynthesis of unusual amino acids by C=C bond formation, we turned our attention to the synthesis of β-bromo or -iodo alanine precursors. It should be noted that very few examples of phosphonium salts bearing a chiral amino acid substituent have been described to date.[6,7] The stereoselective synthesis of the β-chloro amino acids derived from serine,[9,10] cystine[11] or aspartic acid,[12] is well-documented, however only a few methods lead directly to the bromo or iodo analogues.[7,13]

We previously described the synthesis of *N*,*N*-diprotected β-halogeno-α-amino esters by the reaction of the oxazolines **2** derived from L-serine **1** with chloroformates in the presence of the corresponding sodium salt,[10] and preliminary results showed the ring opening of the oxazoline **2** with trimethylsilyl halides (TMSX).[7,10] We decided to investigate further this reaction for the synthesis of β-heterosubstituted L-alanine derivatives. Herein we report an efficient stereospecific synthesis of β-halogeno (-iodo or -bromo) protected L-alanines, and their triphenyl phosphonium salt derivatives.

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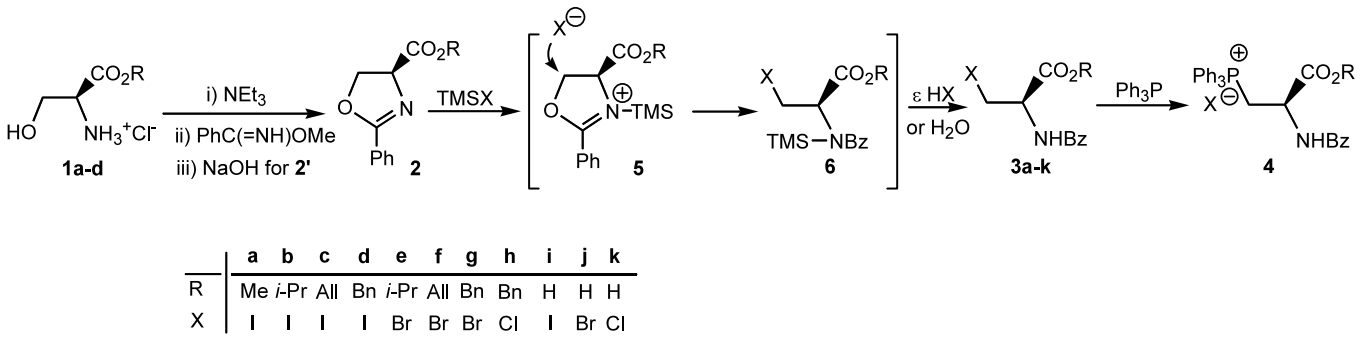
doi:10.1016/S0957-4166(03)00484-1



Scheme 1.

2. Results and discussion

The oxazolines **2a–d** were prepared in high yields according to the classical condensation of phenyl imino ether, with the appropriate L-serine ester hydrochloride **1**, using triethylamine as a base (Scheme 1). In addition, saponification of **2a** with NaOH led to the oxazoline sodium salt **2′**. Surprisingly, the pure enantiomer (*S*)-oxazoline **2a**, which is known to be a viscous product, gave crystals allowing us to establish its X-ray structure (Fig. 1).

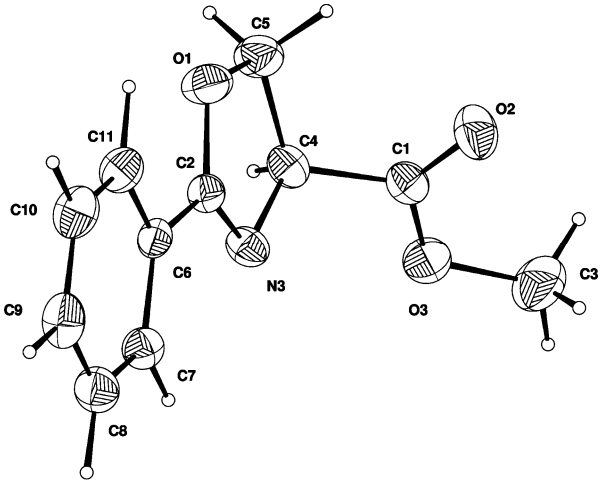


Figure 1. Crystal structure of the oxazoline **2a**. Selected bond lengths (Å) angles (°), dihedral angles (°): O(1)–C(2) 1.345(4), C(5)–O(1) 1.435(4), C(3)–O(3) 1.445(5), N(3)–C(4) 1.473(4), N(3)–C(2) 1.268(4), C(4)–C(5) 1.525(5); O(1)–C(2)–N(3) 118.5(3), C(4)–C(5)–O(1) 103.5(3), C(5)–C(4)–N(3) 105.2(3), C(1)–C(4)–N(3) 108.6(3); N(3)–C(2)–O(1)–C(5) 0.03, N(3)–C(2)–C(6)–C(7) 176.67, N(3)–C(4)–C(1)–O(2) 82.29.

The structure of compound **2a** shows the oxazoline and phenyl rings in a plane with a dihedral angle of 13°, and a C(5)–O(1) bond length close to those of the acyclic bond length C(3)–O(3) (1.435 versus 1.445 Å) (Fig. 1). It should be noted that such values cannot account for the ring opening by C(5)–O(1) bond cleavage when the oxazoline reacts with an electrophilic agent (vide infra).

Treatment of the oxazolines **2a–d** with TMSI (or TMSBr) in chloroform for 15 h at room temperature furnished the corresponding β-halogeno amino esters **3a–g**, which were obtained quantitatively as solids (Scheme 1 and Table 1, entries 1–7). Chiral HPLC analysis of these compounds by comparison with a racemic sample showed, in each case, a single enantiomer,[14] confirming the stereospecificity of the reaction. In the case of TMSCl, the oxazoline **2a** must be heated at reflux in THF to afford the chloro derivative **3h** (entry 8). The ring opening of the oxazolines **2** by TMSX can be explained by the formation of an oxazolinium salt **5**, which undergoes attack by the halide ion at the C(5) position leading to the C(5)–O(1) bond cleavage (Scheme 1). Cleavage of the TMS–nitrogen bond of the intermediate **6** using traces of acid (HX), or by hydrolysis during the work up, finally resulted in the product **3**.

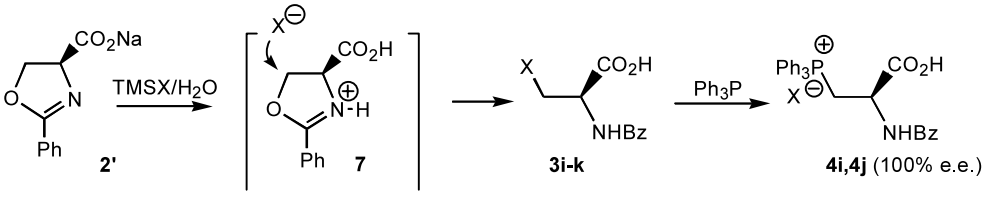
When the oxazoline sodium salt **2′** was used in place of the ester **2**, the reaction with TMSI (or TMSBr) in chloroform at room temperature took place only after the addition of water (1 equiv.) and gave the *N*-benzoyl β-halogeno α-amino acids **3i** or **3j** in high yields (Scheme 2 and Table 2, entries 1 and 2). The use of TMSCl required heating of the salt **2′** at reflux in chloroform to provide the chloro compound **3k** (entry 3). Since water is necessary for the reaction of **2′**, we assumed that this reaction resulted mainly from HX, which is generated in situ by hydrolysis of TMSX to give the oxazolinium intermediate **7**, which upon ring opening, afforded the product **3** (Scheme 2).

The β-iodo and β-bromo amino acid derivatives **3a–g** were used for the preparation of their corresponding phosphonium salts by quaternization with triphenylphosphine. This was achieved by heating **3** with PPh_3 in refluxing chloroform for 48 h, to afford the phosphonium salts **4a–g** in 68–98% isolated yields (Scheme 1 and Table 3, entries 1–7). The ^{1}H and ^{31}P NMR analysis of the phosphonium salt **4a** in the presence of the chiral hexacoordinated phosphate anion BINPHAT[15] showed the presence of only one enantiomer indicating no significant racemization for this reaction. Interestingly, the phosphonium salts **4** could also be obtained on a preparative scale according to a one-pot procedure from the oxazolines **2**. Thus, when the oxazoline **3b** was stirred with TMSI (1.5 equiv.) in chloroform at room temperature for 48 h, and the

Table 1. Preparation of *N*-benzoyl β-halogeno α-amino esters **3**

Entry	Oxazoline		TMSX		β-Halogeno α-amino ester[a]	
	R	**2**	X	equiv.	**3**	Yield[b] (%)
1	Me	**2a**	I	1.5	**3a**	96
2	*i*-Pr	**2b**	I	1.5	**3b**	99
3	All	**2c**	I	1.5	**3c**	98
4	Bn	**2d**	I	1.5	**3d**	99
5	*i*-Pr	**2b**	Br	3	**3e**	99
6	All	**2c**	Br	1.5	**3f**	98
7	Bn	**2d**	Br	1.5	**3g**	99
8	Bn	**2d**	Cl	4	**3h**	99

[a] The enantiomeric purity was checked by liquid chromatography for **3a**–**g**.
[b] Isolated yield.



Scheme 2.

Table 2. Preparation of *N*-benzoyl β-halogeno α-amino acids **3i**–**k** from oxazoline salt **2′**

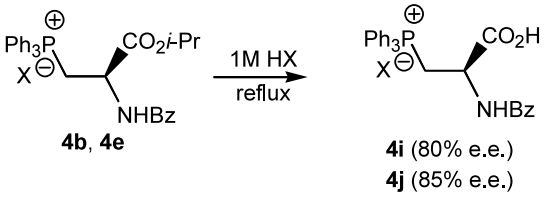
Entry	$TMSX/H_2O$		β-Halogeno α-amino acids[b]	
	X	equiv[a]	**3**	Yield[d] (%)
1	I	3	**3i**[b]	90
2	Br	3	**3j**[b]	85
3	Cl	4	**3k**[c]	75

[a] With respect to **2′**.
[b] The enantiomeric purity was checked by ^{31}P NMR of the corresponding phosphonium salt derivatives **4i**, **4j**.[7,15]
[c] The enantiomeric purity was determined after reaction with diazomethane.[16]
[d] Isolated yield.

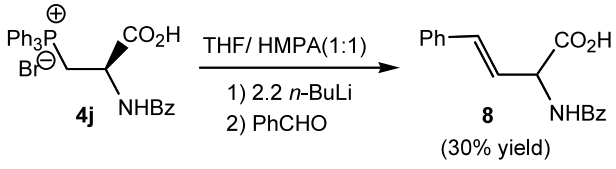
mixture refluxed with PPh_3 (2.5 equiv.) for an additional 48 h, the phosphonium salt **4b** was obtained quantitatively. Since the presence of a free carboxylic acid group on the phosphonium salt **4** is crucial in preventing elimination or racemization under the conditions required for the Wittig reaction,[6,7] we investigated the preparation of such derivatives by deprotection of the ester function. Unfortunately, deprotection of the allyl or benzyl esters **4c**, **4f** or **4d** was unsuccessful under the usual conditions, using $PhSiH_3$ or by hydrogenolysis in the presence of various transition metal catalysts. However, a partial debenzylation of **4d** was observed under the conditions described by Tsuji,[17] using a mixture of anisole and $AlCl_3$. Hydrolysis of the isopropyl derivatives **4b** or **4e** led to **4i** or **4j** after heating with a 1 M solution of HX for 24 h (Scheme 3). Unfortunately, the enantiomeric purity of **4i** or **4j** determined by ^{31}P NMR in the presence of a cinchona alkaloid revealed a partial racemization with 80 and 85% e.e., respectively.

More interestingly, the enantiomerically pure phosphonium salts **4i** and **4j** were obtained in 95% yield, by quaternization of triphenylphosphine with the bromo **3i** or iodo amino acid **3j** (Table 3, entries 8 and 9).

Unfortunately preliminary results of the Wittig reaction between the phosphonium salt **4j** and benzaldehyde led to the optically inactive α-benzamido unsaturated acid **8** in 30% yield (Scheme 4). If this moderate reactivity is comparable to those obtained with similar reagents,[6] the racemization of **8** was attributed to the excess of *n*-BuLi used to promote the Wittig reagent. Further investigations on the hemisynthesis of unsaturated amino acids via this strategy, are currently under study in our laboratory.



Scheme 3.



Scheme 4.

Table 3. Preparation of phosphonium salts **4** from the β-halogeno α-amino acid derivatives **3**

Entry	β-Halogeno α-amino acid derivatives	Phosphonium salt			
		4	R	X	Yield[a] (%)
1	**3a**	**4a**[b]	Me	I	84
2	**3b**	**4b**	*i*-Pr	I	90
3	**3c**	**4c**	Allyl	I	93
4	**3d**	**4d**	Bn	I	95
5	**3e**	**4e**	*i*-Pr	Br	98
6	**3f**	**4f**	Allyl	Br	68
7	**3g**	**4g**	Bn	Br	90
8	**3i**	**4i**[b]	H	I	95
9	**3j**	**4j**	H	Br	95

[a] Isolated yield.
[b] The enantiomeric purity was checked by NMR with chiral derivatives.[7,15]

3. Conclusion

Herein, we described an improved stereospecific synthesis of β-halogeno and β-phosphonium amino acid derivatives. The key step of this synthesis is the ring opening of an oxazoline ester derived from L-serine with trimethylsilyl halide, giving β-iodo or β-bromo L-alanine derivatives without racemization. These compounds were easily quaternized with triphenylphosphine to give the corresponding phosphonium salts in overall yields up to 85% from L-serine. In addition, even though the hydrolysis of the *i*-propyl ester gave the corresponding phosphonium salts bearing a free acid function with a partial racemization, these compounds can be obtained in high yields by the reaction of the oxazoline sodium salts (prepared by saponification of the ester) with TMSX, and subsequent quaternization of triphenylphosphine. The efficiency of this synthesis was demonstrated by the preparation of phosphonium salts in excellent overall yields, in a one-pot procedure starting from the corresponding oxazoline.

4. Experimental

4.1. General

All reactions were carried out under an argon atmosphere in dried glassware. Solvents were dried and freshly distilled under a nitrogen atmosphere. In particular, THF, diethyl ether, toluene and benzene, were distilled over sodium/benzophenone, CH_2Cl_2 over P_2O_5, hexane over calcium hydride and methanol, ethanol and isopropanol over sodium alcoholate. The reactions were carried out with chloroform stabilized with amylene. Chromatographic grade hexane and isopropanol were used without further purification for HPLC. Commercially available allyl and benzyl alcohols were distilled before use, whereas L-serine and L-serine benzyl ester hydrochloride **1d** were used without further purification. Trimethylsilyl bromide and iodide were used without purification if colorless. The phenyl imino ethyl ether hydrochloride[18] was prepared by bubbling HCl gas into a solution of benzonitrile with ethanol. The L-serine ester hydrochlorides were prepared by addition of acetyl chloride to a solution of L-serine in the corresponding alcohol for **1a**,**b**,[19b] or by bubbling HCl gas for **1c**.[18]

HPLC analyses were performed on Gilson and Shimadzu chromatographs equipped with a UV detector (flow rate 1 mL min^{-1}; $\lambda = 254$ nm). Thin-layer chromatography was performed on silica chromagel (60 F_{254}) and visualized by UV, iodine or permanganate treatment. Flash chromatography was performed on silica gel (60ACC, 6–35 microns and 35–70 microns). NMR spectra were obtained on Bruker DPX 250 and Avance 300–500 spectrometers, using TMS as the internal reference for ^1H and ^{13}C NMR and 85% phosphoric acid as the external reference for ^{31}P NMR. Melting points were measured on a Büchi 530 melting point apparatus and are uncorrected. Optical rotation values were determined at 22°C on a Perkin–Elmer 241 polarimeter. Infrared spectra were recorded on a Bruker Equinox 55 and a Vector 22. Mass spectral analyses were performed on NERMAG R10-10C, JEOL MS 700 and KRATOS Concept S, at the ENSCP (Paris), ENS (Paris) and Burgundy University (Dijon), respectively. The major peak m/z is reported with the intensity as a percentage of the base peak in brackets. Elemental analyses were measured with a precision >0.3% at the Microanalysis Laboratories of P. & M. Curie (Paris) and Burgundy Universities (Dijon). The X-ray structures were determined on a CAD4 Enraf-Nonius diffractometer at the P. & M. Curie University (Paris).

4.2. Typical procedure for oxazolines 2

A round-bottomed flask equipped with a magnetic stirrer and a reflux condenser was charged with L-serinate hydrochloride **1a**–**d** (10 mmol), chloroform (50 mL) and triethylamine (11 mmol). The mixture was stirred at room temperature until dissolution. Phenyl imino ethyl ether hydrochloride (10 mmol) was then added and the mixture refluxed for 24 h. The solvent was evaporated and triethylamine hydrochloride precipitated in ether and filtered. After removal of the solvent, the residue was purified by chromatography on silica gel with *c*-Hex/AcOEt (3:1) as the eluent. The enantiomeric

purity was checked by HPLC analysis on a Chiralcel OK Daicel column, (flow rate 1 mL min^{-1}; $\lambda = 254$ nm), by comparison with a racemic sample.

4.2.1. (*S*)-(+)-2-Phenyl-4-methoxycarbonyl-2-oxazoline 2a[18,19]. Colorless solid; 80% yield; mp <40°C; R_f: 0.35 (*c*-Hex/AcOEt 1:1); IR (KBr, cm^{-1}): 2953, 1742, 1642, 1210; ^1H NMR (250 MHz, $CDCl_3$) δ 7.99 (2H, d, $J=8$, *H* arom.), 7.43–7.33 (3H, m, *H* arom.), 4.88 (1H, dd, $J=8$, $J=11$, C*H*N), 4.65 (1H, t, $J=9$, C*H*H), 4.52 (2H, dd, $J=9$, $J=11$, CH*H*), 3.76 (3H, s, CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 171.5 (CO_2Me), 166.1 (*C*=N), 131.8, 128.5, 128.3, 127.0 (*C* arom.), 69.5 (CH_2), 68.6 (*C*HN), 52.5 (CH_3). HPLC (eluent: hexane/*i*-PrOH 9:1): (*S*)-**2a** $t_R = 57$ min; (*R*)-enantiomer $t_R = 64$ min.

Crystal data:[20] Orthorhombic; *a* (Å) = 7.409(5); *b* (Å) = 7.432(3); *c* (Å) = 19.268(1); α (°) = 90; β (°) = 90; γ (°) = 90; *V* (Å^3) = 1063 (1); $Z=4$; space group: $P2_12_12_1$; crystal shape: parallelepiped; crystal colour: colourless; linear absorption coefficient μ (cm^{-1}): 0.94; density ρ (g cm^3): 1.285; diffractometer: CAD4 Enraf-Nonius: radiation Mo Kα ($\lambda = 0.71069$ Å); scan type $\omega/2\theta$; scan range (°): 0.8+0.345 tgθ; θ limits (°) 1–30; temperature of measurement: room temperature; octants collected: 0, 10; 0, 10; 0, 27; number of data collected: 1818; number of unique data used for refinement: 934 $(F_o)^2 > 3\sigma(F_o)^2$: decay of standards reflections (%) <1; $R = \Sigma||F_o|-|F_c||/\Sigma|F_o|$ 0.0434; $Rw^* = [\Sigma w(||F_o|-|F_c||)^2/\Sigma wF_o^2]^{1/2}$ 0.0466; absorption correction: none; secondary extinction coefficient 212.58; goodness-of-fit 1.117; number of variables 137; $\Delta\rho_{min}$ (e Å^{-3}) −0.167; $\Delta\rho_{max}$ (e Å^{-3}) 0.158.

* Weighting scheme of form $w = w'\{1-[(||F_o|-|F_c||)/6\sigma(F_o)]^2\}^2$ with $w' = 1/\Sigma_r A_r T_r(X)$ with coefficients 16.9, −20.4, 17.0, −7.43 and 2.52 for the Chebyshev series for which $X = F_c/F_c(max)$.

4.2.2. (*S*)-(+)-2-Phenyl-4-isopropyloxycarbonyl-2-oxazoline 2b[21]. Colorless solid; 90% yield; mp <40°C; R_f: 0.5 (*c*-Hex/AcOEt 2:1); $[\alpha]_D^{22} = +130$ (*c* 2, $CHCl_3$); IR (KBr, cm^{-1}): 2953, 1730, 1630, 1205, 1090, 695; ^1H NMR (250 MHz, $CDCl_3$) δ 7.96 (2H, m, *H* arom.), 7.46–7.34 (3H, m, *H* arom.), 5.08 (1H, spt, $J=6$, C*H*(CH_3)$_2$), 4.86 (1H, dd, $J=8$, $J=11$, C*H*CH$_2$), 4.57 (2H, t, $J=9$, CHC*H*$_2$), 1.29 (3H, d, $J=6$, C*H*$_3$), 1.25 (3H, d, $J=6$, C*H*$_3$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 170.4 (CO_2iPr), 165.8 (*C*=N), 131.4, 128.3, 128.0, 126.7 (*C* arom.), 69.3 (CH_2), 68.9 ($CH(CH_3)_2$), 68.6 (*C*HN), 21.4 (CH_3). HPLC (eluent: hexane/*i*-PrOH 95:5): (*S*)-**2b** $t_R = 30$ min; (*R*)-enantiomer $t_R = 35$ min.

4.2.3. (*S*)-(+)-2-Phenyl-4-allyloxycarbonyl-2-oxazoline 2c. Colorless solid; 94% yield; mp <40°C; R_f: 0.4 (*c*-Hex/AcOEt 3:1); $[\alpha]_D^{20} = +124$ (*c* 1, $CHCl_3$); IR (KBr, cm^{-1}): 3140, 1733, 1652, 1635, 692; ^1H NMR (250 MHz, $CDCl_3$) δ 7.97 (2H, m, *H* arom.), 7.50–7.35 (3H, m, *H* arom.), 5.93 (1H, m, C*H*=CH$_2$), 5.33 (1H, ddd, $J=1$, $J=3$, $J=17$, CH=C*H*H), 5.23 (1H, ddd, $J=1$, $J=2$, $J=10$, CH=CH*H*), 4.99 (1H, dd, $J=9$, $J=11$, C*H*CH$_2$), 4.72 (4H, m, C*H*$_2$O, CO$_2$C*H*$_2$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 170.7 (CO_2Allyl), 166.2 (*C*=N), 131.7 (*C* arom.), 131.4 (*C*H=CH$_2$), 128.4, 128.2 (*C* arom.), 118.8 (CH=*C*H$_2$), 69.4 (*C*H$_2$O), 68.5 (*C*H), 66.1 (CO_2CH_2); Anal. calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.66; N, 6.06; found: C, 67.54; H, 5.72; N, 6.00; HRMS (DCI, CH_4) anal. calcd for $C_{13}H_{14}NO_3$ [M+H$^+$]: 232.0974; found: 232.0971. HPLC (eluent: hexane/*i*-PrOH 9:1): (*S*)-**2c** $t_R = 40$ min; (*R*)-enantiomer $t_R = 50$ min.

4.2.4. (*S*)-(+)-2-Phenyl-4-benzyloxycarbonyl-2-oxazoline 2d[22]. Colorless solid; 96% yield; mp <40°C; R_f: 0.5 (*c*-Hex/AcOEt 3:1); $[\alpha]_D^{20} = +94.7$ (*c* 1, $CHCl_3$); IR (KBr, cm^{-1}): 2923, 1723, 1639, 1194; ^1H NMR (250 MHz, $CDCl_3$) δ 8.00 (2H, d, $J=8$, *H* arom.), 7.53–7.31 (8H, m, *H* arom.), 5.28 (1H, d, $J=12$, C*H*$_2$Ph), 5.22 (1H, d, $J=12$, C*H*$_2$Ph), 4.96 (1H, dd, $J=8$, $J=11$, C*H*), 4.60 (2H, m, C*H*$_2$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 170.8 (CO_2Bn), 166.3 (*C*=N), 135.2, 131.7, 128.4, 127.3, 126.7 (*C* arom.), 69.2 (*C*H$_2$Ph), 68.2 (*C*H), 66.8 (*C*H$_2$); Anal. calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98; found: C, 72.42; H, 5.35; N, 4.99.

4.3. Preparation of the oxazoline sodium salt 2′[23]

Oxazoline **2a** (8.15 g, 39 mmol) was stirred at rt in a 2 M solution of NaOH (19.5 mL) for 3 h. Water (3 mL) was then added and the mixture poured into acetone (200 mL) to precipitate the salt. After filtration and drying, 8.3 g of the salt was recovered (yield 99%). ^1H NMR (250 MHz, D_2O) δ 7.77 (2H, d, $J=7$, *H* arom.), 7.53–7.36 (3H, m, *H* arom.), 4.57 (2H, m, C*H*$_2$), 4.37 (1H, t, $J=8$, C*H*); ^{13}C NMR (62.5 MHz, D_2O) δ 176.7 (CO_2Na), 166.1 (*C*=N), 133.6, 132.5, 129.1, 127.5 (*C* arom.), 62.4 (*C*H$_2$), 58.1 (*C*H).

4.4. Typical procedure for β-iodo or -bromo α-amino esters

Oxazoline (4.9 mmol) and TMSX (7.3 mmol) were stirred in chloroform[24] (15 mL) at room temperature for 48 h. The solvent was then evaporated and the residue recrystallized in hexane/benzene. The enantiomeric purity was checked by HPLC analysis on a Chiralcel OK Daicel column, (flow rate 1 mL min^{-1}; $\lambda = 254$ nm), by comparison with a racemic sample.

4.4.1. (*R*)-(+)-Methyl-2-benzamido-3-iodopropanoate 3a. White solid; mp = 134°C; $[\alpha]_D^{20} = +59$ (*c* 1, $CHCl_3$); IR (KBr, cm^{-1}): 3294, 1735, 1643, 1528, 698; ^1H NMR (250 MHz, $CDCl_3$) δ 7.84 (2H, dd, $J=2$, $J=7$, *H* arom.), 7.56–7.45 (3H, m, *H* arom.), 6.95 (1H, d, $J=7$, N*H*), 5.00 (1H, td, $J=4$, $J=7$, C*H*), 3.86 (3H, s, C*H*$_3$), 3.73 (2H, 2dd, $J=4$, $J=10$, C*H*$_2$I); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 169.7(*C*OPh), 167.1 (CO_2Me), 133.3, 132.6, 128.7, 127.0 (*C* arom.), 53.2 (*C*H$_3$), 52.6 (*C*H), 7.4 (*C*H$_2$I); Anal. calcd for $C_{11}H_{12}INO_3$: C, 39.66; H, 3.63; N, 4.20; found: C, 39.72; H, 3.66; N, 4.14. HPLC (eluent: hexane/*i*-PrOH 9:1): (*R*)-**3a** $t_R = 57$ min; (*S*)-enantiomer $t_R = 62$ min.

4.4.2. (*R*)-(+)-Isopropyl-2-benzamido-3-iodopropanoate 3b. White solid; mp = 110–111°C; $[\alpha]_D^{20} = +35.6$ (*c* 1, $CHCl_3$); IR (KBr, cm^{-1}): 3294, 1751, 1652, 1521, 750;

^{1}H NMR (250 MHz, $CDCl_3$) δ 7.80 (2H, m, *H* arom.), 7.52–7.37 (3H, m, *H* arom.), 7.05 (1H, d, $J=7$, N*H*), 5.09 (1H, spt, $J=6$, C*H*(CH_3)$_2$), 4.86 (1H, td, $J=3$, $J=7$, CH_2C*H*), 3.68 (2H, 2dd, $J=4$, $J=10$, CH_2I), 1.30 (3H, d, $J=7$, CH_3), 1.24 (3H, d, $J=7$, CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 168.7 (*C*OPh), 166.6 (*C*O_2*i*Pr), 133.3, 131.8, 128.4, 127.0 (*C* arom.), 70.3 (*C*H(CH_3)$_2$), 52.4 (*C*H), 21.6 (*C*H_3), 21.5 (*C*H_3), 7.7 (*C*H_2I); Anal. calcd for $C_{13}H_{16}INO_3$: C, 43.23; H, 4.46; N, 3.88; found: C, 43.35; H, 4.64; N, 3.71; HRMS (DCI, CH_4) anal. calcd for $C_{13}H_{17}INO_3$ [M+H$^+$]: 362.0253; found: 362.0255. HPLC (eluent: hexane/*i*-PrOH 95:5): (*R*)-**3b** $t_R=31$ min; (*S*)-enantiomer $t_R=35$ min.

4.4.3. (*R*)-(+)-Allyl-2-benzamido-3-iodopropanoate 3c. White solid; mp = 104°C; $[\alpha]_D^{20}=+31.9$ (*c* 1, $CHCl_3$); IR (KBr, cm^{-1}): 3338, 3230, 1733, 1652, 1539, 698; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.83 (2H, dd, $J=2$, $J=7$, *H* arom.), 7.54–7.43 (3H, m, *H* arom.), 7.00 (1H, d, $J=6$, N*H*), 5.95 (1H, m, C*H*=CH_2), 5.39 (1H, dd, $J=1$, $J=17$, CH=C*H*H), 5.30 (1H, dd, $J=1$, $J=10$, CH=CH*H*), 4.98 (1H, td, $J=4$, $J=7$, C*H*), 4.73 (2H, m, CH_2CH), 3.73 (2H, 2dd, $J=4$, $J=8$, CH_2I); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 170.7 (*C*OPh), 166.2 (*C*O_2Allyl), 133.2, 132.0 (*C* arom.), 131.0 (*C*H=CH_2), 128.6, 127.1 (*C* arom.), 119.5 (CH=*C*H_2), 66.9 (*C*H_2), 52.6 (*C*H), 7.4 (*C*H_2I); Anal. calcd for $C_{13}H_{14}INO_3$: C, 43.47; H, 3.93; N, 3.90; found: C, 43.42; H, 4.05; N, 3.73; HRMS (DCI, CH_4) anal. calcd for $C_{13}H_{15}INO_3$ [M+H$^+$]: 360.0097; found: 360.0098. HPLC (eluent: hexane/*i*-PrOH 9:1): (*R*)-**3c** $t_R=44$ min; (*S*)-enantiomer $t_R=48$ min.

4.4.4. (*R*)-(+)-Benzyl-2-benzamido-3-iodopropanoate 3d. White solid; mp = 97°C; R_f: 0.55 (*c*-Hex/AcOEt 3:1); $[\alpha]_D^{20}=+19.7$ (*c* 1, $CHCl_3$); IR (KBr, cm^{-1}): 3309, 1752, 1642, 1523, 697; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.82 (2H, dd, $J=7$, *H* arom.), 7.51–7.34 (8H, m, *H* arom.), 7.02 (1H, d, $J=7$, N*H*), 5.27 (1H, d, $J=12$, C*H*HPh), 5.22 (1H, d, $J=12$, CH*H*Ph), 5.00 (1H, td, $J=4$, $J=7$, C*H*), 3.70 (2H, 2dd, $J=4$, $J=10$, CH_2I); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 169.3 (*C*OPh), 166.7 (*C*O_2Bn), 134.6, 133.3, 131.9, 128.6, 127.1 (*C* arom.), 68.1 (*C*H_2Ph), 52.6 (*C*H), 7.3 (*C*H_2I); Anal. calcd for $C_{17}H_{16}INO_3$: C, 49.90; H, 3.94; N, 3.42; found: C, 50.07; H, 3.96; N, 3.33; HRMS (EI) anal. calcd for $C_{17}H_{16}INO_3$ [M$^+$]: 409.0174; found: 409.0177.

4.4.5. (*R*)-(+)-Isopropyl-2-benzamido-3-bromopropanoate 3e. White solid; mp = 97°C; $[\alpha]_D^{20}=+57.6$ (*c* 1, $CHCl_3$); IR (KBr, cm^{-1}): 3307, 1751, 1652, 1521, 750; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.80 (2H, m, *H* arom.), 7.48–7.36 (3H, m, *H* arom.), 7.10 (1H, d, $J=7$, N*H*), 5.10 (2H, m, C*H*(CH_3)$_2$, CH_2C*H*), 3.93 (2H, d, $J=13$, CH_2Br), 1.28 (3H, d, $J=6$, CH_3), 1.24 (3H, d, $J=6$, CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 168.0 (*C*OPh), 166.6 (*C*O_2*i*Pr), 133.0, 131.4, 128.1, 126.8 (*C* arom.), 69.8 (*C*H(CH_3)$_2$), 52.8 (CH_2*C*H) 33.3 (*C*H_2Br), 21.3 (CH(*C*H_3)$_2$); Anal. calcd for $C_{13}H_{16}BrNO_3$: C, 49.70; H, 5.13; N, 4.46; found: C, 49.61; H, 5.11; N, 4.30; HRMS (DCI, CH_4) anal. calcd for $C_{13}H_{17}BrNO_3$ [M+H$^+$]: 314.0391; found: 314.0389. HPLC (eluent: hexane/*i*-PrOH 95:5): (*R*)-**3e** $t_R=29$ min; (*S*)-enantiomer $t_R=31$ min.

4.4.6. (*R*)-(+)-Allyl-2-benzamido-3-bromopropanoate 3f. White solid; mp = 94°C; $[\alpha]_D^{20}=+50.7$ (*c* 1, $CHCl_3$); IR (KBr, cm^{-1}): 3320, 3140, 1733, 1652, 1539, 698; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.81 (2H, m, *H* arom.), 7.51–7.39 (3H, m, *H* arom.), 7.09 (1H, d, $J=7$, N*H*), 5.91 (1H, m, C*H*=CH_2), 5.36 (1H, dd, $J=1$, $J=17$, CH=C*H*H), 5.27 (1H, d, $J=10$, CH=CH*H*), 5.21 (1H, td, $J=3$, $J=7$, CH_2C*H*), 4.70 (2H, m, CH_2), 3.90 (2H, d, $J=3.5$, CH_2Br); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 168.7 (*C*OPh), 166.9 (*C*O_2Allyl), 133.3, 132.0 (*C* arom.), 131.0 (*C*H=CH_2), 128.6, 127.1 (*C* arom.), 119.3 (CH=*C*H_2), 66.8 (*C*H_2), 52.9 (*C*H), 33.6 (*C*H_2Br); Anal. calcd for $C_{13}H_{14}BrNO_3$: C, 50.02; H, 4.52; N, 4.49; found: C, 50.13; H, 4.65; N, 4.41; HRMS (DCI, CH_4) anal. calcd for $C_{13}H_{15}BrNO_3$ [M+H$^+$]: 312.0235; found: 312.0232. HPLC (eluent: hexane/*i*-PrOH 9:1): (*R*)-**3f** $t_R=40$ min; (*S*)-enantiomer $t_R=42$ min.

4.4.7. (*R*)-(+)-Benzyl-2-benzamido-3-bromopropanoate 3g. White solid; mp = 98°C; $[\alpha]_D^{20}=+34.8$ (*c* 1, $CHCl_3$); IR (KBr, cm^{-1}): 3307, 1744, 1638, 1524, 697; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.71 (2H, d, $J=7$, *H* arom.), 7.42–7.24 (8H, m, *H* arom.), 7.04 (1H, d, $J=7$, N*H*), 5.30 (1H, d, $J=12$, C*H*HPh), 5.25 (1H, d, $J=12$, CH*H*Ph), 5.25 (1H, m, C*H*), 3.93 (2H, 2dd, $J=3$, $J=11$, CH_2Br); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 168.8 (*C*OPh), 166.8 (*C*O_2Bn), 134.6, 133.2, 131.8, 128.5, 127.0 (*C* arom.), 67.9 (*C*H_2Ph), 53.0 (*C*H), 33.4 (*C*H_2Br); Anal. calcd for $C_{17}H_{16}BrNO_3$: C, 56.37; H, 4.45; N, 3.87; found: C, 56.39; H, 4.39; N, 3.81; HRMS (DCI, CH_4) anal. calcd for $C_{17}H_{17}BrNO_3$ [M+H$^+$]: 362.0391; found: 362.0381.

4.5. (*R*)-(+)-Benzyl-2-benzamido-3-chloropropanoate 3h

Under an inert atmosphere, oxazoline benzyl ester (1 mmol) and TMSCl (4 mmol) were stirred in refluxing THF (15 mL) for 15 h. The solvent was then evaporated and the residue recrystallized in hexane/benzene. White solid; mp = 108°C; $[\alpha]_D^{20}=+52.1$ (*c* 1, $CHCl_3$); IR (KBr, cm^{-1}): 3286, 1748, 1639, 1524, 693; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.83 (2H, d, $J=7$, *H* arom.), 7.58–7.38 (8H, m, *H* arom.), 7.07 (1H, d, $J=6$, N*H*), 5.29 (2H, s, CH_2Ph), 5.25 (1H, td, $J=3$, $J=7$, C*H*), 4.07 (2H, 2dd, $J=3$, $J=11$, CH_2Cl); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 168.8 (*C*OPh), 167.0 (*C*O_2Bn), 134.7, 133.3, 132.0, 128.6, 127.1 (*C* arom.), 68.0 (*C*H_2Ph), 53.5 (*C*H) 45.1 (*C*H_2Cl); Anal. calcd for $C_{17}H_{16}ClNO_3$: C, 64.26; H, 5.07; N, 4.41; found: C, 64.17; H, 5.08; N, 4.46; HRMS (EI) anal. calcd for $C_{17}H_{16}ClNO_3$ [M$^+$]: 317.0818; found: 317.0822.

4.6. Typical procedure for the β-halogeno-α-amino acid[25]

Water (510 mL, 28.2 mmol) and halogenotrimethylsilane (28.2 mmol) were added to a suspension of oxazoline sodium salt **2′** (2 g, 9.4 mmol) in $CHCl_3$ (30 mL).[23] In the case of TMSBr or TMSI, the mixture was stirred at room temperature for 48 h. For TMSCl, the mixture was heated for 20 h. The solvent was then removed under vacuum and the residue triturated with acetone. After removal of the sodium salt by filtration, acetone

was evaporated. The β-halogeno-α-amino acid was obtained as a mixture with a small quantity of sodium salt (<10%), but it was used without further purification.

4.6.1. (*R*)-2-Benzamido-3-iodopropanoic acid 3i. White solid; mp = 127°C; IR (KBr, cm^{-1}): 3366, 1714, 1631, 1198, 712; ^1H NMR (250 MHz, acetone-d_6) δ 8.00 (3H, m, N*H*, *H* arom.), 7.64–7.42 (3H, m, *H* arom.), 4.95 (1H, td, $J=5$, $J=7$, C*H*), 3.85 (2H, 2dd, $J=5$, $J=11$, CH_2I); ^{13}C NMR (62.5 MHz, acetone-d_6) δ 171.2 (*C*OPh), 168.1 (*C*O_2H), 135.4, 133.2, 130.0, 128.9 (*C* arom.), 55.6 (*C*H), 6.6 (*C*H_2I); HRMS (FAB, MB) anal. calcd for $C_{10}H_{11}INO_3$ [M+H$^+$]: 319.9783; found: 319.9771.

4.6.2. (*R*)-2-Benzamido-3-bromopropanoic acid 3j. White solid; mp = 106°C; IR (KBr, cm^{-1}): 3378, 3285, 1717, 1635, 719; ^1H NMR (250 MHz, acetone-d_6) δ 7.97 (2H, dd, $J=3$, $J=5$, *H* arom.), 7.53 (3H, m, *H* arom.), 5.11 (1H, t, $J=5$, C*H*), 4.02 (2H, d, $J=4$, CH_2Br); ^{13}C NMR (62.5 MHz, acetone-d_6) δ 171.1 (*C*OPh), 168.5 (*C*O_2H), 135.0, 133.2, 130.2, 129.0 (*C* arom.), 55.2 (*C*H), 33.8 (*C*H_2Br); HRMS (FAB, MB) anal. calcd for $C_{10}H_{11}BrNO_3$ [M+H$^+$]: 271.9922; found: 271.9916.

4.6.3. (*R*)-2-Benzamido-3-chloropropanoic acid 3k. White solid; mp = 113°C; IR (KBr, cm^{-1}): 3378, 3285, 1717, 1635, 719; ^1H NMR (250 MHz, acetone-d_6) δ 7.97 (2H, d, *H* arom.), 7.58–7.46 (3H, m, *H* arom.), 5.12 (1H, t, $J=5$, C*H*), 4.16 (2H, d, $J=5$, CH_2Cl); ^{13}C NMR (62.5 MHz, acetone-d_6) δ 171.1 (*C*OPh), 168.4 (*C*O_2H), 135.3, 133.3, 130.0, 128.9 (*C* arom.), 55.5 (*C*H), 45.8 (*C*H_2Cl); HRMS (FAB, MB) anal. calcd for $C_{10}H_{11}BrNO_3$ [M+H$^+$]: 228.0427; found: 228.0425.

The enantiomeric purity of **3k** was determined from its methyl ester derivative prepared by reaction with CH_2N_2: $[\alpha]_D^{20}=-13.5$ (*c* 1, EtOH); lit.[16a] $[\alpha]_D^{20}=-14$ (EtOH), lit.[16b] $[\alpha]_D^{20}=-12.9$ (EtOH).

4.7. Typical procedure for the preparation of amino ester phosphonium salts

Under an inert atmosphere, β-halogeno amino ester (4.26 mmol) and triphenylphosphine (10.1 mmol) were stirred in refluxing chloroform[24] (50 mL) for 48 h. The solvent was then evaporated and the residue triturated in ether (100 mL) to precipitate the phosphonium salt, which was recovered by filtration.

4.7.1. (*R*)-(−)-(2-Benzamido-2-methoxycarbonyl)ethyl triphenylphosphonium iodide 4a. White solid; mp = 178°C; $[\alpha]_D^{20}=-33.3$ (*c* 1, $CHCl_3$); IR (KBr, cm^{-1}): 3412, 1740, 1654, 1109, 724; ^1H NMR (250 MHz, $CDCl_3$) δ 8.90 (1H, d, $J=9$, N*H*), 7.90–7.34 (20H, m, *H* arom.), 5.33 (1H, ddd, $J=3$, $J=11$, $J=11$, C*H*HP), 5.07 (1H, ddd, $J=11$, $J=16$, $J=22$ CH*H*P), 3.90 (1H, ddd, $J=3$, $J=13$, $J=16$, C*H*), 3.60 (3H, s, CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 169.9 (d, $J=16$, *C*O_2Me), 166.7 (*C*OPh), 134.7, 133.4, 133.2, 131.7, 131.6, 131.5, 131.4, 131.2, 130.0, 129.8, 128.2, 128.0, 127.7, 117.5, 116.1 (*C* arom.), 53.1 (*C*H_3), 46.5 (*C*H), 24.7 (d, $J=55$, *C*H_2P); ^{31}P NMR (101 MHz, $CDCl_3$) δ +22.2; Anal. calcd for $C_{29}H_{27}INO_3P$: C, 58.50; H, 4.57; N, 2.35; found: C, 57.56; H, 4.86; N, 2.22; HRMS (FAB, MB) anal. calcd for $C_{29}H_{27}NO_3P$ [M$^+$−I]: 468.1728; found: 468.1739.

The enantiomeric purity of this phosphonium salt was checked by NMR using BINPHAT anion as the chiral reagent.[15]

4.7.2. (*R*)-(−)-(2-Benzamido-2-isopropyloxycarbonyl) ethyltriphenylphosphonium iodide 4b. White solid; mp = 160°C; $[\alpha]_D^{20}=-23.9$ (*c* 1, $CHCl_3$); IR (KBr, cm^{-1}): 3412, 1733, 1652, 1103, 724; ^1H NMR (250 MHz, $CDCl_3$) δ 8.90 (1H, d, $J=9$, N*H*), 7.89–7.32 (20H, m, *H* arom.), 5.33 (1H, dd, $J=3$, $J=10$, C*H*HP), 5.15 (1H, ddd, $J=10.5$, $J=15$, $J=20$, CH*H*P), 4.99 (1H, spt, $J=6$, C*H*(CH_3)$_2$), 3.94 (1H, ddd, $J=2$, $J=13$, $J=16$, C*H*), 1.23 (3H, d, $J=6$, CH(C*H*$_3$)$_2$), 1.15 (3H, d, $J=6$, CH(C*H*$_3$)$_2$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 169.4 (d, $J=15$, *C*O_2iPr), 167.2 (*C*OPh), 134.8, 133.8, 133.7, 131.8, 131.7, 130.2, 130.0, 127.9, 127.8, 118.3, 116.9 (*C* arom.), 70.9 (*C*H(CH_3)$_2$), 47.4 (*C*H), 25.0 (d, $J=50$, *C*H_2P), 21.5 (*C*H_3), 21.4 (*C*H_3); ^{31}P NMR (101 MHz, $CDCl_3$) δ +22.8; Anal. calcd for $C_{31}H_{31}INO_3P$: C, 59.72; H, 5.01; N, 2.25; found: C, 59.88; H, 4.83; N, 2.18; HRMS (FAB, MB) anal. calcd for $C_{31}H_{31}NO_3P$ [M$^+$−I]: 496.2041; found: 496.2054.

4.7.3. (*R*)-(−)-(2-Allyloxycarbonyl-2-benzamido)ethyl triphenylphosphonium iodide 4c. White solid; mp = 137°C; $[\alpha]_D^{20}=-26.2$ (*c* 1, $CHCl_3$); IR (KBr, cm^{-1}): 3305, 1751, 1652, 1436, 688; ^1H NMR (250 MHz, $CDCl_3$) δ 8.9 (1H, d, $J=9$, N*H*), 7.89–7.34 (20H, m, *H* arom.), 5.83 (1H, m, C*H*=CH$_2$), 5.40 (1H, dd, $J=2$, $J=11$, C*H*HP), 5.27 (1H, m, CH*H*P), 5.23 (1H, ddd, $J=1$, $J=3$, $J=17$, CH=C*H*H), 5.13 (1H, dd, $J=1$, $J=11$, CH=CH*H*), 4.60 (2H, ddd, $J=1$, $J=2$, $J=5$, CH_2), 3.96 (1H, ddd, $J=2$, $J=13$, $J=16$, C*H*); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 169.3 (d, $J=16$, *C*O_2Allyl), 167.0 (*C*OPh), 134.8, 133.3, 133.4, 131.6, 131.4, (*C* arom.), 130.8 (*C*H=CH$_2$), 130.1, 129.9, 127.9, 127.7, 117.7, 116.4 (*C* arom.), 118.5 (CH=*C*H$_2$), 66.8 (*C*H$_2$), 46.9 (*C*H), 24.7 (d, $J=54$, *C*H_2P); ^{31}P NMR (101 MHz, $CDCl_3$) δ +22.9; Anal. calcd for $C_{31}H_{29}INO_3P$: C, 59.91; H, 4.70; N, 2.25; found: C, 59.43; H, 4.79; N, 2.00; HRMS (FAB, MB) anal. calcd for $C_{31}H_{29}NO_3P$ [M$^+$−I]: 494.1885; found: 494.1880.

4.7.4. (*R*)-(−)-(2-Benzamido-2-benzyloxycarbonyl)ethyl triphenylphosphonium iodide 4d. White solid; mp = 165–167°C; $[\alpha]_D^{20}=-13$ (*c* 1, $CHCl_3$); IR (KBr, cm^{-1}): 3250, 1738, 1651, 1438, 688; ^1H NMR (250 MHz, $CDCl_3$) δ 8.94 (1H, d, $J=9$, N*H*), 7.88–7.23 (25H, m, *H* arom.), 5.42 (1H, dd, $J=3$, $J=10$, C*H*HP), 5.27 (1H, dd, $J=11$, $J=15$, CH*H*P), 5.15 (2H, s, CH_2Ph), 3.99 (1H, ddd, $J=3$, $J=13$, $J=16$, C*H*); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 169.6 (d, $J=15$, *C*O_2Bn), 167.2 (*C*OPh), 134.9, 134.8, 134.7, 133.7, 133.6, 131.9, 131.7, 131.6, 130.2, 130.0, 128.2, 128.0, 127.9, 118.0, 116.6 (*C* arom.), 68.2 (*C*H$_2$Ph), 47.3 (*C*H), 24.9 (d, $J=55$, *C*H_2P); ^{31}P NMR (101 MHz, $CDCl_3$) δ +22.6; Anal. calcd for $C_{35}H_{31}INO_3P$: C, 62.60; H, 4.66; N, 2.09; found: C, 62.69; H, 4.77; N, 2.00; HRMS (FAB, MB) anal. calcd for $C_{35}H_{31}NO_3P$ [M$^+$−I]: 544.2041; found: 544.2026.

4.7.5. (*R*)-(−)-(2-Benzamido-2-isopropyloxycarbonyl) ethyltriphenylphosphonium bromide 4e. White solid; mp = 187°C; $[\alpha]_D^{20} = -28$ (*c* 1, $CHCl_3$); IR (KBr, cm^{-1}): 3412, 1747, 1652, 1109, 724; ^1H NMR (250 MHz, $CDCl_3$) δ 9.44 (1H, d, $J = 7$, N*H*), 7.90–7.32 (20H, m, *H* arom.), 5.35 (2H, m, CH_2P), 4.98 (1H, spt, $J = 6$, CH(CH_3)$_2$), 3.88 (1H, m, C*H*), 1.24 (3H, d, $J = 6$, CH(CH_3)$_2$), 1.15 (3H, d, $J = 6$, CH(CH_3)$_2$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 169.7 (d, $J = 16$, *C*O_2iPr), 167.2 (*C*OPh), 134.8, 134.0, 133.8, 132.1, 131.6, 130.2, 130.0, 128, 127.9, 118.4, 117.0 (*C* arom.), 70.9 (*C*H(CH_3)$_2$), 47.4 (*C*H), 24.7 (d, $J = 55$, *C*H_2P), 21.6 (*C*H_3), 21.5 (*C*H_3); ^{31}P NMR (101 MHz, $CDCl_3$) δ +22.9; Anal. calcd for $C_{31}H_{31}BrNO_3P$: C, 64.59; H, 5.42; N, 2.43; found: C, 64.13; H, 5.51; N, 2.17; HRMS (FAB, MB) anal. calcd for $C_{31}H_{31}NO_3P$ [M^+−Br]: 496.2041; found: 496.2045.

4.7.6. (*R*)-(−)-(2-Allyloxycarbonyl-2-benzamido)ethyl triphenylphosphonium bromide 4f. White solid; mp = 151°C; $[\alpha]_D^{20} = -23.9$ (*c* 1, $CHCl_3$); IR (KBr, cm^{-1}): 3305, 1750, 1652, 1436, 689; ^1H NMR (250 MHz, $CDCl_3$) δ 8.53 (1H, d, $J = 9$, N*H*), 7.92–7.28 (20H, m, *H* arom.), 5.80 (1H, m, C*H*=CH_2), 5.54–5.32 (2H, m, CH_2P), 5.24 (1H, ddd, $J = 1$, $J = 3$, $J = 17$, CH=C*H*H), 5.14 (1H, ddd, $J = 1$, $J = 3$, $J = 11$, CH=CH*H*), 4.60 (2H, ddd, $J = 1$, $J = 3$, $J = 6$, CH_2), 3.88 (1H, ddd, $J = 2$, $J = 13$, $J = 15$, C*H*); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 169.8 (d, $J = 16$, *C*O_2Allyl), 167.1 (*C*OPh), 134.8, 133.8, 133.6, 131.8, 131.6 (*C* arom.), 131.0 (*C*H=CH_2), 130.2, 130.0, 127.9, 127.8, 118.0, 116.6 (*C* arom.), 118.5 (CH=*C*H_2), 66.9 (*C*H_2), 47.1 (*C*H), 24.4 (d, $J = 55$, *C*H_2P); ^{31}P NMR (101 MHz, $CDCl_3$) δ +22.8; Anal. calcd for $C_{31}H_{29}BrNO_3P$: C, 64.82; H, 5.09; N, 2.44; found: C, 64.80; H, 5.29; N, 2.34; HRMS (FAB, MB) anal. calcd for $C_{31}H_{29}NO_3P$ [M^+−Br]: 494.1885; found: 494.1874.

4.7.7. (*R*)-(−)-(2-Benzamido-2-benzyloxycarbonyl)ethyl triphenylphosphonium bromide 4g. White solid; mp = 165°C; $[\alpha]_D^{20} = -18.5$ (*c* 1, $CHCl_3$); IR (KBr, cm^{-1}): 3420, 1741, 1652, 1438, 688; ^1H NMR (250 MHz, $CDCl_3$) δ 9.48 (1H, d, $J = 8$, N*H*), 7.85–7.18 (25H, m, *H* arom.), 5.38 (2H, m, CH_2P), 5.10 (2H, s, CH_2Ph), 3.84 (1H, ddd, $J = 2$, $J = 13$, $J = 15$, C*H*); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 169.8 (d, $J = 16$, *C*O_2Bn), 167.1 (*C*OPh), 134.8, 134.2, 134.0, 133.8, 133.6, 131.8, 131.5, 130.2, 130.0, 128.7, 128.0, 127.9, 127.8, 118.0, 116.6 (*C* arom.), 68.0 (*C*H_2Ph), 47.2 (*C*H), 24.5 (d, $J = 55$, *C*H_2P); ^{31}P NMR (101 MHz, $CDCl_3$) δ +22.9; Anal. calcd for $C_{35}H_{31}BrNO_3P$: C, 67.31; H, 5.00; N, 2.24; found: C, 66.41; H, 5.02; N, 2.12; HRMS (FAB, MB) anal. calcd for $C_{35}H_{31}NO_3P$ [M^+−Br]: 544.2041; found: 544.2032.

4.8. Preparation of the amino ester phosphonium salt 4b by a one pot procedure from the oxazoline 2b

TMSI (1.5 equiv.) was added to a 0.3 M solution of oxazoline **2** in $CHCl_3$.[24] The mixture was stirred at room temperature for 48 h. A 0.3 M solution of triphenylphosphine (2.5 equiv.) in $CHCl_3$ was added and the mixture was heated under reflux for 48 h. The phosphonium salt **4b** was recovered quantitatively using a similar work-up as described in Section 4.7.

4.9. Preparation of the amino acid phosphonium salts

4.9.1. By quaternization of triphenylphosphine with a β-halogeno amino acid. Triphenylphosphine (1.05 g, 4 mmol) was added to either β-iodo (1.6 mmol) or β-bromo amino acid (1.6 mmol) in $CHCl_3$ (35 mL).[24] The mixture was heated under reflux for 48 h. with some of the phosphonium salt being recovered by filtration. The filtrate was then evaporated and the residue stirred in ether in order to precipitate the phosphonium salt and to extract the phosphine excess. The combined precipitates gave a white powder in 95% yield.

4.9.1.1. (*R*)-(−)-(2-Benzamido-2-carboxyl)ethyltriphenyl phosphonium iodide 4i. White solid; mp = 195°C; $[\alpha]_D^{20} = -42$ (*c* 1, MeOH); IR (KBr, cm^{-1}): 3413, 2925, 1741, 1624, 1439, 746; ^1H NMR (250 MHz, CD_3OD) δ 7.84–7.30 (20H, m, *H* arom.), 5.02 (1H, ddd, $J = 3$, $J = 11$, $J = 13$, C*H*), 4.22 (1H, ddd, $J = 3$, $J = 14$, $J = 17$, C*H*HP), 3.97 (1H, ddd, $J = 11$, $J = 16$, $J = 22$, CH*H*P); ^{13}C NMR (62.5 MHz, CD_3OD) δ 172.1 (d, $J = 15$, *C*O_2H), 169.7 (*C*OPh), 136.4, 136.3, 135.0, 134.9, 133.8, 133.3, 131.6, 131.4, 129.3, 128.4, 119.9, 118.5 (*C* arom.), 48.4 (CH), 25.6 (d, $J = 55$, *C*H_2P); ^{31}P NMR (101 MHz, CD_3OD) δ +22.3; Anal. calcd for $C_{28}H_{25}INO_3P$: C, 57.85; H, 4.33; N, 2.41; found: C, 57.99; H, 4.36; N, 2.29; HRMS (FAB, MB) anal. calcd for $C_{28}H_{25}NO_3P$ [M^+−I]: 454.1572; found: 454.1582.

The enantiomeric purity of this phosphonium salt was checked by NMR using cinchonidine,[7] or BINPHAT anion as the chiral reagent.[15]

4.9.1.2. (*R*)-(−)-(2-Benzamido-2-carboxyl)ethyltriphenyl phosphonium bromide 4j. White solid; mp = 135°C; $[\alpha]_D^{20} = -37.4$ (*c* 1, MeOH); IR (KBr, cm^{-1}): 3413, 2904, 1741, 1623, 747; ^1H NMR (250 MHz, CD_3OD) δ 7.93–7.42 (20H, m, *H* arom.), 5.10 (1H, ddd, $J = 3$, $J = 10$, $J = 13$, C*H*), 4.32 (1H, ddd, $J = 3$, $J = 14$, $J = 17$, C*H*HP), 4.09 (1H, ddd, $J = 11$, $J = 16$, $J = 22$, CH*H*P); ^{13}C NMR (62.5 MHz, CD_3OD) δ 172.9 (d, $J = 16$, *C*O_2H), 170.3 (*C*OPh), 137.1, 135.8, 135.7, 135.3, 134.5, 134.1, 132.4, 132.2, 130.1, 129.3, 120.7, 119.3 (*C* arom.), 48.8 (*C*H), 26.31 (d, $J = 55$, *C*H_2P); ^{31}P NMR (101 MHz, CD_3OD) δ +22.3; HRMS (FAB, MB) anal. calcd for $C_{28}H_{25}NO_3P$ [M^+−Br]: 454.1572; found: 454.1560.

The enantiomeric purity of this phosphonium salt was checked by ^{31}P NMR using cinchonine as the chiral reagent.[7]

4.9.2. By hydrolysis of the (*R*)-(−)-(2-benzamido-2-isopropyloxycarbonyl)ethyltriphenylphosphonium salts. In an aqueous solution of either HI or HBr (50 mL), phosphonium salt **4b** or **4e** (1.6 mmol) was heated under reflux for 24 h. After cooling, the phosphonium salt **4i** or **4j** was precipitated and extracted with $CHCl_3$. After drying, the solvent was evaporated and the residue stirred in ether in order to precipitate the phosphonium salt.

The enantiomeric purity of the phosphonium salts was determined by ^{31}P NMR using cinchona alkaloid as the chiral reagent:[7] **4i** and **4j** were obtained in 80 and 85% e.e., respectively.

4.10. Preparation of the amino acid phosphonium salts by a one pot procedure from the oxazoline salt 2′

Water (3 equiv.) and TMSBr (or TMSI; 3 equiv.) were added to a 0.4 M suspension of oxazoline sodium salt **2′** (1 equiv.) in $CHCl_3$.[24] The mixture was stirred at room temperature for 48 h. A 0.2 M solution of triphenylphosphine (2.5 equiv.) in $CHCl_3$ was then added and the mixture was heated under reflux for 48 h. The phosphonium salts were recovered with a yield up to 80%, using a similar work up as described in Section 4.9.1.

4.11. Preparation of 2-benzamido-4-phenyl-3-butenoic acid 8 by a Wittig reaction using the amino acid phosphonium salt 4j

Phosphonium salt **4j** (0.629 g, 1.18 mmol) was dissolved in a THF/HMPA mixture (4 mL, 1:1) and the solution was cooled to −70°C. An *n*-BuLi reagent (1.83 mL, 2.56 mmol) was added under stirring, and the mixture warmed to room temperature for 1 h. Benzaldehyde (0.14 mL, 1.42 mmol) was then added and the mixture left for 15 h while stirring. After heating at reflux for one additional hour, the mixture was then hydrolyzed with a 1 M HCl solution (15 mL), and extracted 3 times with ether. The combined extracts were washed with an HCl solution then extracted 3 times with 10% $NaHCO_3$. The aqueous phase was acidified to pH 1, and extracted 3 times with ether. The organic extracts were successively washed with water and finally dried on $MgSO_4$. The solvent was removed under vacuum and the residue triturated with chloroform to give 100 mg of the 2-benzamido-4-phenyl-3-butenoic acid **8** ($[\alpha]_D^{20}=0$ (*c* 1, 1 M NaOH); 30% yield). White solid; mp = 210°C (lit.[26] mp = 210–212°C); IR (KBr, cm^{-1}): 3284, 3057 1724, 1623, 1427; ^1H NMR (250 MHz, DMSO) δ 12.89 (1H, l, CO_2H), 9.01 (1H, d $J=7$, N*H*), 7.95 (2H, d, $J=7$, *H* arom), 7.60–7.26 (3H, m, *H* arom), 6.76 (1H, d, $J=16$, CH=C*H*Ph), 6.49 (1H, dd, $J=7$, $J=16$, C*H*=CHPh), 5.18 (1H, t, $J=4$, C*H*); ^{13}C NMR (62.5 MHz, DMSO) δ 171.8 (CO_2H), 166.1 (*C*OPh), 136.0, 133.7, 132.4, 131.0, 128.3, 126.4, 124.5 (*C*H=CHPh), 55.2(*C*H).

Acknowledgements

We thank S. Hallut and P. Herson for the X-ray crystallographic analyses. This work was supported by the French Ministry of Research, the Burgundy Country Council and the CNRS.

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