# Stereoselective Synthesis of Unsaturated and Functionalized L-NHBoc Amino Acids, Using Wittig Reaction under Mild Phase-Transfer Conditions

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S *Supporting Information*

ABSTRACT: The stereoselective synthesis of a new amino acid phosphonium salt was described by quaternization of melting triphenylphosphine with the γ-iodo NHBoc-amino ester, derived from L-aspartic acid. The deprotection of the carboxylic acid function to afford the phosphonium salt with a free carboxylic acid group was achieved by a palladium-catalyzed desallylation reaction. This phosphonium salt was used in the Wittig reaction with aromatic or aliphatic aldehydes and trifluoroacetophenone, under solid−liquid phase-transfer conditions in chlorobenzene and in the presence of K_3PO_4 as weak base, to afford the corresponding unsaturated amino acids without racemization. Thus, the reaction with substituted aldehydes allows to graft various functionalized groups on the lateral chain of the amino acid, such as trifluoromethyl, cyano, nitro, ferrocenyl, boronato, or azido. In addition, the reaction of the amino acid Wittig reagent with α,β-unsaturated aldehydes leads to amino acids bearing a diene on the lateral chain. Finally, this amino acid phosphonium salt appears to be a new powerful tool for the preparation of unsaturated and non-proteinogenic α-amino acids, directly usable for the synthesis of customized peptides.
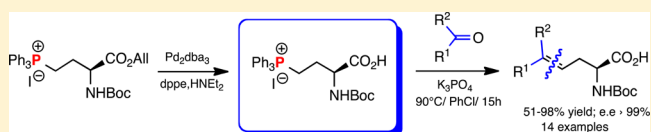
INTRODUCTION

The synthetic peptide market emerged in the recent past, and today several dozen of these compounds are used for their therapeutic applications.[1] One of the reasons for this success is that the pharmaceutical companies focus more and more on biomolecules and customized peptide drugs with specific properties, a field in full growth, on which intellectual property is still widely available.[1b] On the other hand, numerous challenging research subjects that are related to the current vaccines, antibiotics, neurohormones, or biomarkers topics involve also modified peptides.[2,3] Therefore, the demand for efficient sources of unusual amino acids useful for the high-throughput synthesis of customized peptides is of crucial interest to date.[2] In this field, unsaturated amino acids[3] are very interesting and useful non-proteinogenic analogues that can be functionalized by various chemical processes such as Diels−Alder reactions,[4] cycloadditions,[5] and catalytic transformations including hydroformylation,[6] metathesis,[7] Heck,[8] or Suzuki−Miyaura cross-coupling reactions.[9] Furthermore, these compounds are often used in peptide chemistry to confer a "β-turn" secondary structure to induce new properties.[10] Finally, several unsaturated amino acids were used as enzyme inhibitors,[11] antibiotics,[12] markers,[13] and intermediates in the total synthesis of products of biological interest.[14] Unusual amino acids bearing a C=C bond are mainly prepared using cationic,[15] anionic,[16] or radical[17] equivalent of amino acids as well as by metathesis[7] or rearrangement.[18]

Another method is to synthesize the unsaturated amino acids by C=C bond formation on the lateral chain, using a Wittig−Horner−Wadsworth−Emmons α-amino acid reagent (Figure 1). In a pioneering work, Itaya et al. described the use of the phosphonium salt **1a** derived from L-serine, for the synthesis of unusual amino acids by reaction with an aldehyde.[19] Likewise, an alternative route was reported by Sibi et al., using the phosphonium salt **2** derived from alaninol.[20] Another approach is based on the reaction of a phosphonium ylide with an aldehyde prepared from L-glutamic acid. However, in this case the method involves preparing a new Wittig reagent for each unsaturated amino acid synthesized.[21] On the other hand, the preparation of enone derived amino acids can be achieved in good yields using a Horner−Wadsworth−Emmons reaction between the β-ketophosphonate esters **3** and aldehydes.[22]

Anyway, the Wittig reaction involving an amino acid moiety is rarely described in the literature, probably due to the difficulty to prepare α-amino acid phosphonium salts, which are demanding of strategies, and also the uncertainties on the chemo- and enantioselectivity. As an example of constraint, the phosphonium salt **1a** was obtained by hydrogenolysis of the benzyl ester only in the case of the chloride, which must be prepared by counterion exchange.[19] In a previous work, we have reported an efficient preparation of phosphonium salt **1b** bearing a free carboxylic acid function by ring opening of oxazolidine derived from L-serine.[23] Unfortunately, its use in a Wittig reaction with an aldehyde gave poor reactivity, and the unsaturated amino acid was obtained as a racemic mixture.[23] Therefore, we envisaged to synthesize a new class of α-amino acid Wittig reagents, derived from L-aspartic acid **5**,[24] having
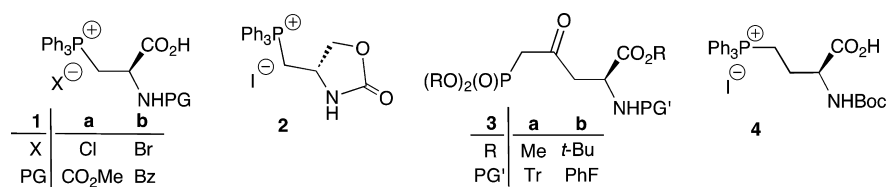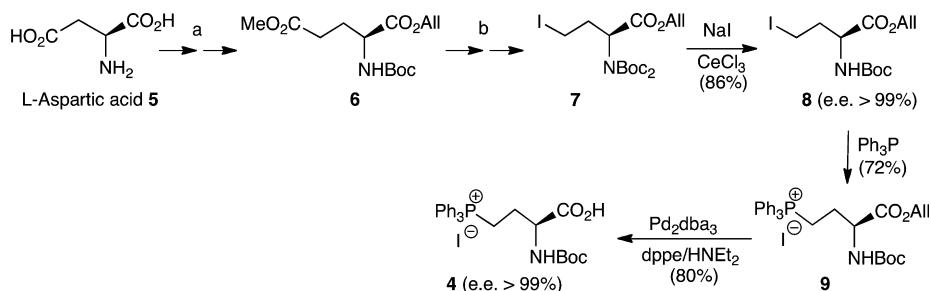
Figure 1. Wittig−Horner−Wadsworth−Emmons amino acid reagents.

Scheme 1. Synthesis of Chiral Amino Acid Wittig Reagent 4[a]

[a]Reagents and conditions: (a) (i) SOCl$_2$, MeOH, 85%; (ii) Boc$_2$O, Na$_2$CO$_3$, 75%; (iii) AllBr, K$_2$CO$_3$, 85%; (b) (i) Boc$_2$O, DMAP, 98%; (ii) DIBAL then NaBH$_4$, 75%; (iii) Ph$_3$P, I$_2$, Imd, 91%.

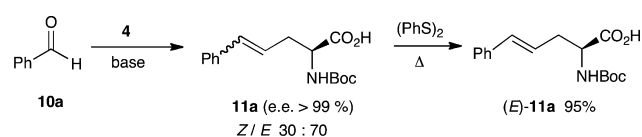both a free carboxylic function and the phosphonium moiety in the γ-position of the lateral chain. The goal was to avoid racemization or phosphine elimination, by deprotonation of the carboxylic acid or in the α-position or still on the amide group, respectively. We present herein the stereoselective synthesis of the phosphonium salt **4** from L-aspartic acid **5** and its application as Wittig reagent for the preparation of enantiopure γ,δ-unsaturated NHBoc-amino acids.[24b]

RESULTS AND DISCUSSION

Chiral amino acid phosphonium salt **4** was prepared in 60% overall yield by quaternization of triphenylphosphine with the γ-iodo NHBoc-amino allyl ester **8** and then deprotection to the free carboxylic acid using palladium-catalyzed conditions (Scheme 1).[25] The γ-iodo amino ester **8** was previously prepared from L-aspartic acid **5**, according to modified literature procedures with 75−98% chemical yield by step (Scheme 1).[26−31] It should be noted that the iodide **7** was prepared as a N,N-diBoc-amino ester derivative and then monodeprotected to its derivative **8**, by reaction with iodide ions in the presence of cerium salt,[31] in order to partially avoid this reaction by quaternization with the phosphine. The enantiomeric purities of the phosphonium salt allyl ester **9** and acid derivative **4** were checked using the chiral hexacoordinated phosphorus BIN-PHAT (Λ,R)-(1,1′-binaphthalene-2,2′diolato)(bis(tetrachlor-1,2-benzenediolato)phosphat(V)) anion.[32]

The Wittig reaction conditions of the amino acid phosphonium salt **4** were first investigated with the benzaldehyde **10a** (Scheme 2). When the experiments were performed in THF, using a strong base such as LiHMDS, LDA,

n-BuLi, or t-BuLi, the corresponding unsaturated amino acids **11a** were obtained with low yields and partially racemized. As the phosphonium salt **4** may act as a phase-transfer agent, we have envisaged to perform the reaction in heterogeneous conditions, using an inorganic weak base (Scheme 2, Table 1).[33]

**Table 1. Reaction of Wittig Reagent 4 with Benzaldehyde 10a under Phase-Transfer Conditions**[a]

entry	base	solvent	% yield[b]	% ee[c]
1	Cs$_2$CO$_3$	EtOH	6	
2	Cs$_2$CO$_3$	THF	8	
3	Cs$_2$CO$_3$	DMF	33	
4	Cs$_2$CO$_3$	PhCl	65[d]	99
5	Li$_3$PO$_4$	PhCl	6	
6	NaH[e]	PhCl	5	
7	K$_2$CO$_3$	dioxane	58[f]	99
8	K$_3$PO$_4$	PhCl	70[g]	99

[a]Reactions were performed at 90 °C during 15 h in 1.5 mL of solvent and with ratio **4**/**10a**/base = 1:1.5:6. [b]Isolated yield after purification by column chromatography. [c]Determined by HPLC on chiral column after esterification using TMSCHN$_2$.[34] [d]Reaction time 48 h. [e]Ratio **4**/**10a**/base = 1:1.5:.3 [f]Water is added to the medium with a ratio H$_2$O/**4** = 0.8. [g]**11a** was obtained as a mixture of Z/E isomers with a 30:70 ratio.

When the amino acid phosphonium salt **4** is heated during 15 h in EtOH or THF with the benzaldehyde **10a** in the presence of Cs$_2$CO$_3$ as base, the corresponding γ,δ-unsaturated amino acids **11a** were obtained in low yields (entries 1, 2). If the reaction was performed in DMF or chlorobenzene at 90 °C, the γ,δ-unsaturated amino acid **11a** was isolated with 33% and 65% yields, respectively (entries 3, 4). The use of Li$_3$PO$_4$ or NaH as base in chlorobenzene at 90 °C did not lead to the formation of the product **11a** (entries 5, 6). When K$_2$CO$_3$ is used in 1,4-dioxane and in the presence of 0.8 equiv of water,[33] **11a** was obtained in 58% yield (entry 7). Finally, the best result was obtained when the amino acid phosphonium salt **4** is heated during 15 h in chlorobenzene with benzaldehyde **10a** in

Scheme 2. Reaction of the Amino Acid Wittig Reagent 4 with Benzaldehyde 10a

the presence of dry K_3PO_4 (entry 8).[24b] In these conditions, the corresponding γ,δ-unsaturated NHBoc amino acid **11a** was obtained in 70% yield, as a Z/E mixture in the ratio 30:70, and with 99% ee for both geometric isomers (entry 8).

Interestingly, in these conditions, the phosphonium salt **4** has the double role to be a phase-transfer agent and to stabilize the α-carbanion (ylide **12**), as shown in Figure 2. Thus, the
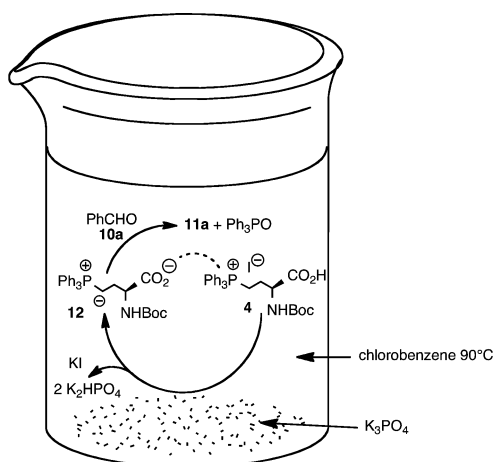

Figure 2. Proposed mechanism of the Wittig reaction in solid–liquid phase-transfer conditions.

phosphonium salt **4** interacts at the surface of the inorganic base, which deprotonates on one hand the carboxylic acid function and on the other hand the methylene substituent to afford the ylide **12** (Figure 2). In chlorobenzene, a non-dissociative solvent, the presence of phosphonium salt **4** must also help the formation of an ion pair with the carboxylate moiety, which allows better solubility and reactivity of the ylide **12** with the benzaldehyde **10a** (Figure 2). Despite the fact that **12** is a not stabilized ylide, the predominant formation of (E)-γ,δ-unsaturated NHBoc-amino acid **11a** was explained by the thermal isomerization under the reaction conditions (15 h, 90 °C).[35] Interestingly, the Z/E mixture **11a** was isomerized with unprotected carboxylic moiety, in pure (E)-γ,δ-unsaturated NHBoc-amino acid **11a**, by simple heating in the presence of diphenylsulfide (Scheme 2).[36] It should be noted that the unsaturated amino acid **11a**, which is obtained with a free carboxylic acid and a Boc protecting group, could be directly used in peptide synthesis.

The amino acid phosphonium salt **4** was used for the Wittig reaction with various aromatic or aliphatic aldehydes **10b–m** and 2,2,2-trifluoroacetophenone **10n** (Scheme 3, Table 2). In the optimized conditions, the reaction with the 4-trifluoromethyl, 4-nitro, 4-cyano, or 4-methoxy benzaldehydes **10b–e** leads to the corresponding γ,δ-unsaturated amino acids **11b–e** as a mixture of Z/E isomers in a ratio close to 20:80 and yields

Scheme 3. Synthesis of Unsaturated Amino Acids 11 Using Wittig Reagent 4
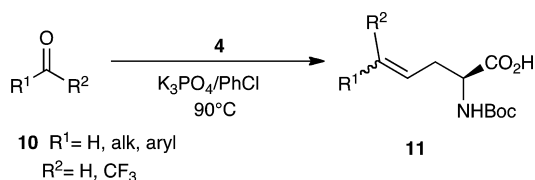
Table 2. Reaction of Wittig Reagent 4 with Various Carbonyl Derivatives 10[f]

Entry	R^1R^2CO **10**	γ,δ-unsaturated amino acids **11**[a]		
			% Yield[b]	% Z / E[c]
1	F_3C–C₆H₄–CHO **10b**	**11b**	98	10 : 90
2	NC–C₆H₄–CHO **10c**	**11c**	96	20 : 80
3	O_2N–C₆H₄–CHO **10d**	**11d**	75	15 : 85
4	MeO–C₆H₄–CHO **10e**	**11e**	67	24 : 76
5	furyl-CHO **10f**	**11f**	80	nd[d]
6	Fe ferrocenyl-CHO **10g**	**11g**	51[e]	50 : 50
7	PhCH₂CH₂-CHO **10h**	**11h**	57	nd[d]
8	$(CH_2O)_n$ **10i**	**11i**	55	-
9	pinacolboronate-C₆H₄–CHO **10j**	**11j**	57	25 : 75
10	OHC–C₆H₄–CHO **10k**	**11k**	85	nd[d]
11	PhCH=CH–CHO **10l**	**11l**	77	nd[d]
12	N_3–C₆H₄–CH=CH–CHO **10m**	**11m**	57	nd[d]
13	Ph–C(O)CF₃ **10n**	**11n**	81	37 : 63

[a]Enantiomeric purity of each unsaturated amino acid **11b–n** was determined by HPLC on chiral column after esterification with TMSCHN₂[34] and was superior to 99%. [b]Isolated yield after purification by column chromatography. [c]Determined by ^{1}H NMR. [d]Not determined.[40] [e]Yield as methyl ester. [f]The reactions were performed at 90°C during 15h in 1.5 mL of solvent and with the ratio **3**/**10**/K_3PO_4 = 1:1.5:6.

ranging from 67% to 98% (entries 1–4). The reaction of the furfural **10f** or ferrocene carboxaldehyde **10g** affords then the corresponding product **11f** (or **11g**) in 80% and 51% yield, respectively (entries 5, 6). The enantiomeric purity for both Z/E isomers **11b–g** was determined by HPLC on chiral column after esterification using TMSCHN₂ and was superior to 99% (entries 1–6). Moreover, when aliphatic aldehydes were used in this Wittig reaction, the corresponding γ,δ-unsaturated amino acids were also isolated in satisfactory yields. Thus, the

reaction of **4** with the 3-phenylpropanal **10h** afforded the γ,δ-unsaturated amino acids **11h** in 57% yield, whereas in the case of the paraformaldehyde **10i**, the NHBoc-allylglycine **11i** was obtained in 55% yield (entries 7, 8). The excellent reactivity of the Wittig reagent **4** toward aromatic aldehydes allows the synthesis of α-amino acids bearing functional groups. Thus, when **4** reacts with the 4-boronato-benzaldehyde **10j**, the corresponding unsaturated amino acid **11j** was obtained in 57% yield as a Z/E mixture in a ratio 25:75 (entry 9). Obviously, the boronato derivative **11j** presents a particular interest for the synthesis of modified amino acids using Suzuki−Miyaura cross-coupling reactions.[9,37] Noteworthy, the reaction of 2 equiv of **4** with the *m*-phthaldialdehyde **10k** leads to the corresponding bis-amino acid **11k** in 85% isolated yield (entry 10). On another hand, when α,β-unsaturated aldehydes were used, the Wittig reaction with the phosphonium salt **4** leads to the corresponding amino acid derivatives bearing a diene pattern on the lateral chain.

Very few examples of diene α-amino acids derivatives are reported to date.[38] Thus, the reaction of the *trans*-cinnamaldehyde **10l** or its azido derivative **10m** in the Wittig reaction with **4** led to the corresponding dienic α-amino acids **11l** (or **11m**) in 77% and 57% yield, respectively (entries 11 and 12). Again, it is interesting to note that the azido α-amino acid **11m** is a new useful building block for click chemistry.[39] Finally, in the reaction conditions developed, the Wittig reagent **4** reacts with the trifluoroacetophenone **10n** to afford the trifluoromethyl amino acid derivative **11n** as a Z/E mixture in a ratio of 37:63 and 81% yield (entry 13).

■ CONCLUSION

In summary, the stereoselective synthesis of a new amino acid phosphonium salt **4**, by quaternization of melting triphenylphosphine with the γ-iodo NHBoc-amino ester **8**, derived from L-aspartic acid **5**, has been described. The deprotection of the carboxylic acid function to afford the phosphonium salt **4** with a free carboxylic acid group was achieved in 80% yield by a palladium-catalyzed desallylation reaction. The use of **4** in the Wittig reaction with aromatic or aliphatic aldehydes and trifluoroacetophenone, under unusual solid−liquid phase-transfer conditions in chlorobenzene and in the presence of K_3PO_4 as weak base, affords the corresponding unsaturated amino acids **11** without racemization and in yield up to 98%. The γ,δ-unsaturated amino acids **11**, which are obtained as a Z/E mixture, can be isomerized by simple heating in the presence of diphenylsulfide. By reaction with substituted aldehydes, the Wittig reagent **4** thus makes it possible to graft various functionalized groups such as trifluoromethyl, cyano, nitro, ferrocenyl, boronato, or azido on the lateral chain of the amino acids **11**. In addition the reaction of **4** with α,β-unsaturated aldehydes leads to rarely described amino acids bearing a diene on the lateral chain. Finally, the phosphonium **4** appears to be a powerful new tool for the preparation of unsaturated and nonproteinogenic α-amino acids, directly usable for the synthesis of customized peptides.

■ EXPERIMENTAL SECTION

General Experimental Methods. All reactions were carried out under inert atmosphere. Solvents were dried and purified by conventional methods prior to use. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium/benzophenone and stored under argon. Dimethylformamide (DMF), acetonitrile (ACN), and ethanol (EtOH) were distilled from CaH_2 under argon prior to use.

Reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm E. Merck precoated silica gel plates. Flash chromatographies were performed with the indicated solvents using silica gel 60 (60AAC, 35−70 μm). NMR spectra (^{1}H, ^{13}C, ^{31}P) were recorded with 300 and 500 MHz apparatus, at ambient temperature using TMS as internal reference for ^{1}H and ^{13}C NMR and 85% phosphoric acid as external reference for ^{31}P NMR. Data are reported as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br.s = broad singlet, coupling constant(s) in Hertz, integration. Infrared spectra were recorded on a FTIR instrument. Melting points were measured on a Kofler melting points apparatus and are uncorrected. Optical rotation values were determined at 20 °C on a polarimeter at 589 nm (sodium lamp). Mass spectroscopies were performed under (ESI) conditions with a micro Q-TOF or HR/AM-MS detector. Elemental analyses were measured with a precision superior to 0.3% on a CHNS-O instrument apparatus. Li_3PO_4, K_3PO_4, and Cs_2CO_3 were previously dried by heating at 200 °C under vacuum, during 5 min. Chlorobenzene 99%, 1,4-doxane 99%, aldehydes **10a−h**, **10k−m**, paraformaldehyde 95% **10i**, 2,2,2-trifluoroacetophenone **10n**, L-aspartic acid **5**, 4-formylbenzeneboronic acid **10j**, and tris(dibenzylideneacetone)dipalladium were purchased from commercial sources and used without purification. Boc-L-β-methyl-aspartic acid was prepared in two steps from L-aspartic acid **5**, according to the procedures described in the literature.[26,27]

(*S*)-2-(*tert*-Butyloxycarbonylamino), 1-Allyl-4-methyl-succinate (6). This compound was prepared from Boc-L-β-methyl-aspartic acid, according to a modified literature procedure.[28] To a solution of Boc-L-β-methyl-aspartic acid (5.62 g, 22.7 mmol) in 70 mL of DMF were introduced K_2CO_3 (7.53 g, 54.5 mmol) and allyl bromide (3.9 mL, 45.4 mmol). After the mixture was stirred overnight, 70 mL of water was added, the aqueous layer was extracted with 3 × 75 mL of ethyl acetate, and the combined organic layers were dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by chromatography using a mixture petroleum ether/ethyl acetate (4:1) as eluent to afford the allyl ester **6** as a colorless oil (5.15 g, 79%). R_f: 0.29 (ethyl acetate/petroleum ether 1:4); $[\alpha]_D$ = +17.7 (*c* 0.7, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92−5.79 (m, 1H), 5.28 (dq, 1H, J = 1.4, 17.2 Hz), 5.20 (dq, 1H, J = 1.2, 10.4 Hz), 4.60 (dt, 2H, J = 1.3, 5.7 Hz), 4.57−4.53 (m, 1H), 3.65 (s, 3H), 2.98 (dd, 1H, J 4.6, 17.1 Hz), 2.79 (dd, 1H, J = 17.0, 4.7 Hz), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 170.7, 155.4, 131.5, 118.6, 80.1, 66.2, 52.0, 50.0, 36.6, 28.3. FTIR (neat) cm^{−1} 3370, 2980, 1716, 1502, 1439, 1367, 1339, 1286, 1246, 1209, 1161, 1049, 1026, 992. Analysis calcd for $C_{13}H_{21}NO_6$ (227.14): C 54.35, H 7.37, N 4.88. Found: C 54.50, H 7.38, N 4.93.

(*S*)-2-[Bis(*tert*-Butyloxycarbonyl)amino], Allyl-4-iodobutanoate (7). This compound was prepared from the aspartic ester derivative **6**, via compounds **I** then **II**, according to a modified literature procedure.[29,30]

(S)-2-[Bis(tert-Butyloxycarbonyl)amino], 1-Allyl-4-methyl-succinate (I). This compound was prepared from the allyl ester **6**, according to a modified literature procedure.[29,30] To a solution of the allyl ester **6** (4.86 g, 16.9 mmol) in 80 mL of acetonitrile were added successively DMAP (643 mg, 5.2 mmol) and Boc_2O (9.3 g, 42.6 mmol). After the mixture was stirred overnight at room temperature, the solvent was evaporated, and the residue was purified by chromatography with a mixture of petroleum ether/ethyl acetate (4:1) to afford the N,N-diBoc diester **I** as a colorless oil (5.76 g, 88%). R_f: 0.32 (ethyl acetate/petroleum ether 1:4); $[\alpha]_D$ = −54.1 (*c* 0.7, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90−5.79 (m, 1H), 5.47−5.42 (m, 1H), 5.28 (dq, 1H, J = 1.5, 17.2 Hz), 5.19 (dq, 1H, J = 1.3, 10.5 Hz), 4.59 (dt, 2H, J = 1.3, 5.6 Hz), 3.67 (s, 3H), 3.23 (dd, 1H, J = 7.1, 16.4 Hz), 2.71 (dd, 1H, J = 8.5, 16.4 Hz), 1.47 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 169.5, 151.6, 131.5, 118.3, 83.5, 66.1, 55.0, 51.9, 35.6, 27.9. FTIR (neat) cm^{−1} 2982−2954, 1742, 1702, 1458, 1439, 1368, 1314, 1269, 1243, 1168, 1142, 1116, 993, 934. Analysis calcd for $C_{18}H_{28}NO_8$ (387.19): C 55.80, H 7.54, N 3.62. Found: C 56.16, H 7.75, N 3.53.

(S)-2-[Bis(tert-Butyloxycarbonyl)amino], Allyl-4-hydroxybutanoate (II). This compound was prepared from diester **I** according to a modified literature procedure.[29,30] To a solution of diester **I** (2.2 g,

5.7 mmol) in 60 mL of distilled diethyl ether was introduced DIBAL (9 mL, 9 mmol) under argon at −78 °C. The mixture was stirred 1 h at −78 °C and hydrolyzed with 10 mL of distilled water at 0 °C. After 5 min, the mixture was filtered on Celite and washed with 3 × 25 mL of diethyl ether. After removal of the solvent, the crude product containing the aldehyde intermediate and traces of the corresponding alcohol **II** was dissolved in 50 mL of a mixture THF/H$_2$O (4:1), and NaBH$_4$ (225 mg, 5.9 mmol) was added. The mixture was stirred 30 min at 0 °C, and the aqueous layer was extracted with 3 × 75 mL of ethyl acetate. The organic layer was dried over MgSO$_4$, filtered and evaporated. The crude product was purified by chromatography with ethyl acetate/petroleum ether (1:4, then 3:7, and finally 1:1) as eluent, to afford the alcohol **II** as a colorless oil (1.27 g, 75%). R_f: 0.31 (ethyl acetate/petroleum ether 1:2); $[\alpha]_D$ = −27.9 (c 0.7, CHCl$_3$). ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.92−5.81 (m, 1H), 5.30 (dq, 1H, J = 1.5, 17.2 Hz), 5.20 (dq, 1H, J = 1.3, 10.4 Hz), 4.99 (dd, 1H, J = 4.7, 9.8 Hz), 4.59 (dt, 2H, J = 1.4, 5.5 Hz), 3.73−3.68 (m, 1H), 3.61−3.54 (m, 1H), 2.44−2.36 (m, 1H), 2.07−1.97 (m, 1H) 1.47 (s, 18H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 170.5, 152.5, 131.7, 118.2, 83.6, 65.8, 59.0, 55.6, 32.8, 27.9. FTIR (neat) cm^{-1} 3524, 2980−2934, 1740, 1700, 1457, 1368, 1272, 1254, 1144, 1119, 1049, 989. Analysis calcd for C$_{17}$H$_{29}$NO$_4$ (359.19): C 56.81, H 8.13, N 3.90. Found: C 56.52, H 8.32, N 3.93.

(S)-2-[Bis(tert-Butyloxycarbonyl)amino], Allyl-4-iodobutanoate (7).[29b,30] In a first flask, containing a solution of alcohol **II** (1.33 g, 3.7 mmol) in 20 mL of dry THF, was added imidazole (600 mg, 8.8 mmol). In a second flask containing Ph$_3$P (1.52 g, 5.8 mmol) in 15 mL of dry THF was added iodine (1.55 g, 6.1 mmol). The first solution was then added, and the resulting mixture was stirred for 2 h at room temperature. The reaction mixture was then hydrolyzed with 100 mL of 20% aqueous NaCl. The aqueous layer was extracted by 3 × 50 mL ethyl acetate. After drying over MgSO$_4$, filtration, and evaporation, the crude product was purified by chromatography using a mixture of ethyl acetate/petroleum ether (1:9) as eluent, to afford the iodo aminoester **7** as a colorless oil (1.6 g, 91%). R_f: 0.75 (ethyl acetate/petroleum ether 1:9); $[\alpha]_D$ = −44.6 (c 0.7, CHCl$_3$). ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.97−5.84 (m, 1H), 5.33 (dq, J = 1.5, 17.2 Hz, 1H), 5.24 (dq, 1H, J = 1.3, 10.5 Hz), 5.03 (dd, 1H, J = 5.5, 8.5 Hz), 4.63 (dt, 2H, J = 1.4, 5.5 Hz), 3.25−3.16 (m, 2H), 2.78−2.66 (m, 1H), 2.48−2.36 (m, 1H), 1.52 (s, 18H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 167.9, 150.2, 129.8, 116.5, 87.7, 64.1, 52.8, 32.6, 26.2, 0.0. FTIR (neat) cm^{-1} 2981−2936, 1747, 1704, 1479, 1457, 1368, 1236, 1171, 1131, 988. Analysis calcd for C$_{17}$H$_{29}$NO$_6$I (469.10): C 43.51, H 6.01, N 2.98. Found: C 43.31, H 6.24, N 2.92.

(S)-2-(tert-Butyloxycarbonylamino), Allyl-4-iodobutanoate (8).[24b] Finally, this compound was obtained from the iodo aminoester **7** according to a modified literature procedure.[31] To the solution of **7** (1.6 g, 3.4 mmol) in 20 mL of acetonitrile were added CeCl$_3$·7H$_2$O (1.3 g, 3.4 mmol) and NaI (513 mg, 3.4 mmol). The reaction mixture was stirred overnight at room temperature and hydrolyzed with 20 mL of water. The aqueous layer was extracted with 3 × 20 mL of ethyl acetate, and the organic layer was dried over MgSO$_4$. After evaporation, the crude product was purified by chromatography using a mixture of ethyl acetate/petroleum ether (1:4) as eluent. The iodo aminoester **8** was obtained as a pale yellow oil (831 mg, 86%). R_f: 0.31 (ethyl acetate/petroleum ether 1:4); $[\alpha]_D$ = +11.7 (c 0.5, CHCl$_3$). ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.95−5.82 (m, 1H), 5.31 (dd, 1H, J = 1.4, 17.2 Hz), 5.24 (dd, 1H, J = 1.1, 10.4 Hz), 5.05 (d, 1H, J = 6.2 Hz), 4.62 (d, 2H, J = 5.8 Hz), 4.34−4.32 (m, 1H), 3.18−3.13 (m, 2H), 2.43−2.37 (m, 1H) 2.23−2.10 (m, 1H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 171.9, 155.9, 132.0, 119.8, 80.9, 66.9, 55.0, 37.8, 28.9, 0.0. FTIR (neat), cm^{-1} 2981−2936, 1747, 1704, 1479, 1457, 1368, 1236, 1171, 1131, 988, 930, 853. Analysis calcd for C$_{12}$H$_{20}$NO$_4$I (369.09): C 39.04, H 5.46, N 3.79. Found: C 39.14, H 5.59, N 3.84.

(S)-2-[(tert-Butyloxycarbonyl)amino], Allyl-butanoate (9). A mixture of iodo aminoester **8** (1.1 g, 3.1 mmol) and triphenylphosphine (1.9 g, 7.1 mmol) was stirred without solvent under argon at 80 °C. After 2 h, 5 mL of toluene was added, followed by 30 mL of diethyl ether, after cooling to room temperature. The white solid was washed with 2 × 25 mL of diethyl ether and purified by column chromatography using acetone and

petroleum ether (7: 3) as eluent to afford phosphonium salt **9** as a pale yellow solid (1.22 g, 72%). R_f: 0.57 (acetone/petroleum ether 7: 3); mp 84−86 °C; $[\alpha]_D$ = −17.5 (c 0.4, CHCl$_3$). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.83−7.65 (m, 15H), 6.32 (d, 1H, J = 7.5 Hz) 5.89−5.78 (m, 1H), 5.29−5.15 (m, 2H), 4.60−4.53 (m, 3H), 3.95−3.79 (m, 1H) 3.73−3.58 (m, 1H), 2.30−2.26 (m, 2H) 1.39 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 170.7, 135.7, 135.2 (d, J = 3.0 Hz) 133.6 (d, J = 9.8 Hz) 131.7, 130.6 (d, J = 12.8 Hz), 118.6, 117.8 (d, J = 86.0 Hz), 80.0, 66.2, 53.2 (d, J = 17.3 Hz), 28.3, 23.8, 20.3 (d, J = 53.6 Hz); ^{31}P NMR (121 MHz, CDCl$_3$) δ +25.2 (s). FTIR (neat) cm^{-1} 3249, 3053−2870, 1699, 1648, 1587, 1508, 1486, 1437, 1391, 1366, 1340, 1309, 1251, 1229, 1158, 1111, 1052, 995. HRMS (ESI-Q-TOF) calcd for C$_{30}$H$_{35}$N$_1$O$_4$P$_1$ [M − I]$^+$: 504.2298, found 504.2278. The enantiomeric excess (>99%) was determined by ^{31}P NMR analysis using the BINPHAT as chiral reagent.[32]

(S)-2-[(tert-Butyloxycarbonyl)amino]-4-triphenylphosphonium Butanoic Acid (4).[24b] The desallylation of **9** was realized according to a modified literature procedure.[25] To a solution of phosphonium salt **9** (1.28 g, 2 mmol) in 20 mL of dry THF were successively added under argon Pd$_2$dba$_3$ (46 mg, 0.05 mmol) and dppe (40 mg, 0.1 mmol). After 5 min of stirring, HNEt$_2$ (0.42 mL, 4.2 mmol) was introduced, and the mixture was stirred at room temperature overnight. After hydrolysis, the crude product was extracted with CH$_2$Cl$_2$, and the combined organic layers were dried over MgSO$_4$, evaporated under vacuum, and purified by column chromatography with acetone and methanol (1:1) as eluent to afford the phosphonium salt **4** as a white solid (946 mg, 80%). R_f: 0.50 (acetone/MeOH 1:1); mp 151−153 °C; $[\alpha]_D$ = +48.5 (c 0.4, CHCl$_3$). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.77−7.70 (m, 3H), 7.64−7.52 (m, 12H), 6.27 (d, 1H J = 2.7 Hz), 4.08 (t, 1H, J = 3.6 Hz), 3.30−3.13 (m, 2H), 2.32−2.13 (m, 2H), 1.33 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 172.6, 156.0, 135.1 (d, J = 3.0 Hz), 133.3 (d, J = 9.8 Hz), 130.5 (d, J = 12.8 Hz), 118.3 (d, J = 86.0 Hz), 78.6, 54.9 (d, J = 17.3 Hz), 28.4, 25.7, 18.4 (d, J = 9.8 Hz); ^{31}P NMR (121 MHz, CDCl$_3$) δ +24.3 (s). FTIR (neat) cm^{-1} 3387, 3060−2932, 1695, 1605, 1483, 1438, 1386, 1365, 1251, 1161, 1112, 1053, 1025; HRMS (ESI-Q-TOF) calcd for C$_{27}$H$_{31}$N$_1$O$_4$P$_1$ [M − I]$^+$ 464.1985, found 464.1958.

Typical Procedure To Prepare γ,δ-Unsaturated Amino Acids (11) Using the Wittig Reagent (4).[24b] Aldehyde **10** (0.3 mmol) and dry K$_3$PO$_4$ (254 mg, 1.2 mmol) were successively added to a solution of phosphonium salt **4** (120 mg, 0.2 mmol) in chlorobenzene (1.5 mL). The reaction mixture was stirred for 15 h at 90 °C. After cooling to room temperature, the solution was hydrolyzed with distilled water (5 mL) and extracted with diethyl ether (3 × 5 mL). The aqueous layer was then acidified with KHSO$_4$ (1 M) to pH 3 and extracted with AcOEt (3 × 5 mL). The combined organic layers were dried over anhydrous MgSO$_4$ and evaporated. The crude residue was purified by chromatography on silica gel with a mixture of ethyl acetate/petroleum ether (3:7) containing 1% AcOH as eluent to afford the corresponding unsaturated α-amino acid **11**.

(S)-2-(tert-Butyloxycarbonylamino)-5-phenylpent-4-enoic Acid (11a). In the above conditions, 120 mg of phosphonium salt **3** and 42.4 mg of benzaldehyde **10a** afford the unsaturated α-amino acid **11a** as a pale yellow uncrystallized compound (42 mg, 72%) with a Z/E ratio 30/70; R_f: 0.52 (ethyl acetate/petroleum ether 3:7 + 1% acetic acid); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.38−7.22 (m, 5H), 6.63 (d, 0.3H, J = 11.7 Hz), 6.50 (d, 0.7H, J = 15.9 Hz), 6.23−6.08 (m, 0.7H), 5.69−5.60 (m, 0.3H), 5.12 (d, 0.7H, J = 7.8 Hz), 5.05 (d, 0.3H, J = 8.1 Hz), 4.51−4.49 (m, 0.7H), 4.38−4.28 (m, 0.3H), 2.98−2.92 (m, 0.6H), 2.81−2.65 (m, 1.4H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 176.5, 155.6, 136.8, 134.2, 132, 130.2, 129.7, 128.7, 128.6, 128.5, 128.4, 128.3, 127.6, 127.1, 126.4, 126.3, 125.6, 123.5, 80.4, 80.2, 53.1, 35.8, 31.1, 28.3. FTIR (neat) cm^{-1} 3422, 3026−2930, 1711, 1496, 1450, 1395, 1368, 1249, 1163, 1053, 1026, 966. HRMS (ESI-Q-TOF) calcd for C$_{16}$H$_{21}$N$_1$Na$_1$O$_4$ [M + Na]$^+$ 314.1363, found 314.1343. The enantiomeric excess >99% was determined by HPLC after esterification with TMSCHN$_2$ (Lux 5 μm cellulose-2, hexane/i-PrOH 98:2, 1.3 mL min^{-1}, λ = 210 nm, 20 °C, $t_{R(Z)\text{-}(S)}$ = 13.1 min, $t_{R(E)\text{-}(S)}$ = 16.5 min, $t_{R(Z)\text{-}(R)}$ = 23.3 min, $t_{R(E)\text{-}(R)}$ = 32.2 min).

(E)-(S)-2-(tert-Butyloxycarbonylamino)-5-phenylpent-4-enoic Acid (11a). To a solution of unsaturated amino acid **11a** (20 mg, 0.07 mmol) in 5 mL of dry THF was added (PhS)$_2$ (3 mg, 0.014 mmol). The mixture was heated under reflux for 15 h, to afford the corresponding (E)-unsaturated amino acid **11a** as a colorless uncrystallized compound (19 mg, 95%); R_f: 0.53 (ethyl acetate/petroleum ether 3:7 + 1% acetic acid); $[\alpha]_D$ = +61.0 (c 0.2, CHCl$_3$). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.29–7.12 (m, 5H), 6.41 (d, 1H, J = 15.9 Hz), 6.14–5.99 (m, 1H), 5.01 (d, 1H, J = 6.9 Hz), 4.40 (d, 1H, J = 3.3 Hz), 2.72–2.57 (m, 2H), 1.35 (s, 9H).

(S)-2-(tert-Butyloxycarbonylamino)-5-[4-trifluoromethyl)phenyl]-pent-4-enoic Acid (11b). In the above conditions, 120 mg of phosphonium salt **4** and 69.6 mg of 4-trifluoromethylbenzaldehyde **10b** afford the unsaturated α-amino acid **11b** as a white solid (57 mg, 98%) with a Z/E ratio 10:90; R_f: 0.33 (ethyl acetate/petroleum ether 3:7 + 1% acetic acid); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.58–7.53 (m, 2H), 7.43 (d, 2H, J = 8.1 Hz), 7.35 (d, 0.2H, J = 7.8 Hz), 6.62 (d, 0.1H, J = 11.4 Hz), 6.52 (d, 0.9H, J = 15.6 Hz), 6.27–6.22 (m, 0.9H), 5.88–5.71 (m, 0.1H), 5.17 (d, J = 7.8 Hz, 0.9H), 4.52–4.30 (m, 0.89 H), 4.23–4.21 (m, 0.1H), 2.80–2.76 (m, 1H), 2.70–2.68 (m, 1H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 176.5, 176.0, 156.8, 155.5, 132.8, 129.6, 129.5, 128.8, 128.6, 128.2, 127.7, 126.6, 126.4, 125.3 (q, J = 6.8 Hz), 125.3 (q, J = 271.7 Hz), 82.1, 80.6, 54.4, 53.0, 34.3, 28.2, 27.2. FTIR (neat) cm^{-1} 3352, 2973–2925, 1710, 1681, 1615, 1521, 1433, 1415, 1392, 1367, 1326, 1287, 1267, 1252, 1159, 1108, 1084, 1069, 1046, 1025. HRMS (ESI-Q-TOF) calcd for C$_{17}$H$_{19}$F$_3$NO$_4$ [M − H]$^-$ 358.1272, found 358.1256. The enantiomeric excess >99% was determined by HPLC on chiral column after esterification with TMSCHN$_2$ (Lux 5 μm cellulose-2, hexane/i-PrOH 95:5, 1 mL min^{-1}, λ = 210 nm, 20 °C, $t_{R(Z)-(S)}$ = 6.9 min, $t_{R(E)-(S)}$ = 8.2 min, $t_{R(Z)-(R)}$ = 10.6 min, $t_{R(E)-(R)}$ = 17.2 min).

(S)-2-(tert-Butyloxycarbonylamino)-5-(4-cyanophenyl)pent-4-enoic Acid (11c). In the above conditions, 120 mg of phosphonium salt **4** and 52 mg of 4-cyanobenzaldehyde **10c** afford the unsaturated amino acid **11c** as a white solid (60 mg, 96%), with a ratio Z/E 20:80; R_f: 0.31 (ethyl acetate/petroleum ether 3:7 + 1% acetic acid); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.27–7.24 (m, 2H), 7.20–7.17 (m, 2H), 6.72 (d, 0.2H, J = 6.3 Hz), 6.59 (d, 0.2H, J = 11.4 Hz), 6.50 (d, 0.8H, J = 15.6 Hz), 6.34–6.24 (m, 0.8H), 5.86–5.73 (m, 0.2H), 5.21 (d, 0.8H, J = 8.1 Hz), 4.52–4.48 (m, 0.8H), 4.32–4.30 (m, 0.2H), 2.88–2.78 (m, 1H), 2.72–2.62 (m, 1H), 1.43 (s, 9H) ; ^{13}C NMR (75 MHz, CDCl$_3$) δ 174.9, 155.4, 140.2, 132.3, 131.5, 131.4, 131.1, 130.1, 128.5, 128.3, 127.8, 127.1, 126.5, 125.8, 117.8, 117.9, 109.7, 109.6, 81.0, 79.6, 53.1, 51.9, 35.0, 29.0, 27.2. FTIR (neat) cm^{-1} 3416, 3135−2865, 2221, 1737, 1662, 1604, 1522, 1457, 1442, 1412, 1396, 1371, 1334, 1305, 1252, 1210, 1157, 1442, 1412, 1396, 1371, 1334, 1305, 1252, 1210, 1086, 1027. HRMS (ESI-Q-TOF) calcd for C$_{17}$H$_{20}$N$_2$NaO$_4$ [M + Na]$^+$ 339.1315, found 339.1299. The enantiomeric excess >99% was determined by HPLC after esterification with TMSCHN$_2$ (Lux 5 μm cellulose-2, hexane/i-PrOH 85:15, 1 mL min^{-1}, λ = 210 nm, 20 °C, $t_{R(Z)-(S)}$ = 16.3 min, $t_{R(E)-(S)}$ = 19.2 min, $t_{R(Z)-(R)}$ = 23.8 min, $t_{R(E)-(R)}$ = 32.1 min).

(S)-2-(tert-Butyloxycarbonylamino)-5-(4-nitrophenyl)pent-4-enoic Acid (11d). In the above conditions, 120 mg of phosphonium **4** and 60.4 mg of 4-nitrobenzaldehyde **10d** afford the unsaturated amino acid **11d** as a yellow uncrystallized compound (50 mg, 75%) with a Z/E ratio 15:85; R_f: 0.33 (ethyl acetate/petroleum ether 3:7 + 1% acetic acid); ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.14 (d, 2H, J = 8.4 Hz), 7.46 (d, 2H, J = 8.8 Hz), 7.16 (d, 0.15H, J = 7.8 Hz), 6.68 (d, 0.15H, J = 11.4 Hz), 6.56 (d, 0.85H, J = 15.6 Hz), 6.54–6.30 (m, 0.85H), 5.82–5.78 (m, 0.15H), 5.20 (d, 0.85H, J = 7.8 Hz), 4.56–4.54 (m, 1H), 2.89–2.83 (m, 1H), 2.78–2.65 (m, 1H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 175.3, 174.9, 155.8, 154.4, 149.9, 145.9, 145.6, 142.2, 133.8, 131.1, 130.2, 129.8, 128, 125.8, 122.9, 122.6, 81.3, 79.6, 53.2, 51.9, 35.1, 28.7, 27.2. FTIR (neat) cm^{-1} 3487, 3059−2817, 1703, 1484, 1453, 1436, 1413, 1386, 1366, 1311, 1220, 1167, 1107, 1064, 1024, 1002. HRMS (ESI-Q-TOF) calcd for C$_{16}$H$_{20}$N$_2$NaO$_6$ [M + Na]$^+$: 359.1214; found 359.1228. The enantiomeric excess >99% was determined by HPLC after esterification with TMSCHN$_2$ (Lux 5 μm cellulose-2, hexane/i-PrOH 90:10, 1 mL min^{-1}, λ = 210 nm, 20 °C,

$t_{R(Z)-(S)}$ = 16.2 min, $t_{R(E)-(S)}$ = 20.4 min, $t_{R(Z)-(R)}$ = 22.1 min, $t_{R(E)-(R)}$ = 34.2 min).

(S)-2-(tert-Butyloxycarbonylamino)-5-(4-methoxyphenyl)pent-4-enoic Acid (11e). In the above conditions, 120 mg of phosphonium salt **4** and 4-methoxybenzaldehyde **10e** (136 mg, 1 mmol) afford the amino acid **11e** as a pale yellow uncrystallized compound (43 mg, 67%), with a Z/E ratio 24: 76. R_f: 0.42 (ethyl acetate/petroleum ether 3:7 + 1% acetic acid); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.32–7.29 (m, 1H), 7.22–7.17 (m, 1H), 6.89–6.83 (m, 2H), 6.54 (d, 0.24H, J = 11.4 Hz), 6.43 (d, 0.76H, J = 15.6 Hz), 6.02–5.93 (m, 0.76H), 5.58–5.52 (m, 0.24H), 5.13–5.03 (m, 1H), 4.43–4.33 (m, 1H), 3.81 (s, 3H), 2.99–2.94 (m, 0.5H), 2.79–2.56 (m, 1.5H), 1.44 (s, 9H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 176.8, 159.2, 158.6, 155.8, 137.9, 133.7, 132.2, 130.0, 129.7, 129.0, 128.3, 127.5, 125.3, 123.9, 121.1, 114.0, 113.8, 80.6, 80.5, 55.3, 53.1, 35.7, 31.1, 28.3. FTIR (neat) cm^{-1} 3288, 2978−2838, 1713, 1578, 1512, 1456, 1441, 1394, 1368, 1289, 1248, 1174, 1111, 1043. HRMS (ESI-Q-TOF) calcd for C$_{17}$H$_{23}$N$_1$Na$_1$O$_5$ [M + Na]$^+$ 344.1468, found 344.1448. The enantiomeric excess >99% was determined by HPLC on chiral column after esterification with TMSCHN$_2$ (Lux 5 μm cellulose-2, hexane/i-PrOH 95:5, 1.5 mL min^{-1}, λ = 254 nm, 20 °C, $t_{R(Z)-(R)}$ = 8.3 min, $t_{R(E)-(R)}$ = 10.4 min, $t_{R(Z)-(S)}$ = 13.1 min, $t_{R(E)-(S)}$ = 16.7 min).

(S)-2-(tert-Butyloxycarbonylamino)-5-furylpent-4-enoic Acid (11f). In the above conditions, 120 mg of phosphonium salt **4** and 38.4 mg of 2-furaldehyde **10f** afford the unsaturated amino acid **11f** as a pale yellow uncrystallized compound (45 mg, 80%). R_f: 0.40 (ethyl acetate/petroleum ether 3:7 + 1% acetic acid); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.36 (dd, 1H, J = 1.2, 21.9 Hz), 7.20–7.17 (m, 0.4H), 6.41–6.35 (m, 3H), 6.10–6.00 (m, 0.6H), 6.21 (d, 1H, J = 3.3 Hz), 5.54–5.45 (m, 0.4H), 5.14–5.12 (m, 0.6H), 4.48–4.34 (m, 0.6H), 4.27–4.20 (m, 0.4H), 3.16- 2.90 (m, 1H), 2.78–2.58 (m, 1H), 1.45 (s, 9H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 176.8, 176.3, 155.7, 155.5, 152.6, 152.3, 142.0, 141.8, 123.1, 122.6, 122.2, 120.5, 111.2, 111.1, 110.2, 107.5, 81.7, 80.4, 53.1, 54.5, 35.5, 31.8, 28.3. FTIR (neat) cm^{-1} 3338, 2978−2931, 1780, 1694, 1511, 1455, 1393, 1367, 1254, 1157, 1349, 1017, 925, 863, 811, 735, 702, 653. HRMS (ESI-Q-TOF) calcd for C$_{14}$H$_{18}$N$_1$O$_5$ [M − H]$^-$ 280.1190, found 280.1188. The enantiomeric excess >99% was determined by HPLC after esterification by TMSCHN$_2$ (Lux 5 μm cellulose-2, hexane/i-PrOH 95:5, 1 mL min^{-1}, λ = 254 nm, 20 °C, $t_{R(Z)-and (E)-(S)}$ = 10.2 min, $t_{R(Z)-or (E)-(R)}$ = 14.5 min, $t_{R(E)-or (Z)-(R)}$ = 16.0 min).

(S)-Methyl-2-(tert-Butyloxycarbonylamino)-5-ferrocenylpent-4-enoate (11g). A 120 mg portion of phosphonium salt **4** and 214 mg (1 mmol, 5 equiv) of ferrocene-carboxaldehyde **10g** were stirred at 90 °C with 254 mg (1.2 mmol, 6 equiv) of K$_3$PO$_4$ during 16 h. The reaction mixture was hydrolyzed with distilled water (5 mL) and extracted with diethyl ether (3 × 5 mL). The aqueous layer was acidified with KHSO$_4$ (1 M) until pH = 3 and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over magnesium sulfate, and the solvent was evaporated. The residue was dissolved in 2 mL of a mixture of toluene/methanol (3:2), and 0.13 mL (0.25 mmol) of TMSCHN$_2$ was added. The reaction mixture was stirred 30 min at room temperature, and the solvent was evaporated. The residue was purified by chromatography with ethyl acetate/petroleum ether (3:7) as eluent. Methyl ester **11g** was obtained as an orange uncrystallized compound (30 mg, 51%) with a Z/E ratio 50:50. R_f: 0.42 (ethyl acetate/petroleum ether 1:4); ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.22 (d, J = 15.6 Hz, 0.5H), 6.26 (d, J = 11.8 Hz, 0.5H), 5.39–5.33 (m, 1H), 5.68–5.58 (m, 1H), 5.12–5.06 (m, 1H), 4.47–4.38 (m, 1H), 4.35–4.30 (2 m, 2H), 4.24–4.20 (2 m, 2H), 4.14–4.12 (2s, 5H), (2s, 3H), 2.87–2.47 (2 m, 2H), 1.47–1.46 (2s, 9H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 173, 172.6, 155.3, 155.2, 131.8, 130.1, 121.7, 120.4, 82.7, 81.0, 69.3, 69.0, 68.9, 68.8, 68.7, 68.6, 66.7, 66.6, 53.1, 53.0, 52.4, 52.3, 35.8, 31.7, 28.3. IR (cm^{-1}) 3390, 2927−2854, 1779, 1695, 1509, 1455, 1392, 1366, 1251, 1158, 1106, 1048, 1023, 1001, 821, 734, 662. HRMS (ESI-Q-TOF) calcd for C$_{21}$H$_{27}$FeNNaO$_4$ [M + Na]$^+$ 436.1182, found 436.1193. The enantiomeric excess was determined by HPLC (Lux 5 μm cellulose-2, hexane/i-PrOH 97:3, 0.8 mL min^{-1}, λ = 254 nm, 20 °C, $t_{R(Z)-(S)}$ = 27.4 min, $t_{R(E)-(S)}$ = 30.7 min, $t_{R(Z)-and (E)-(R)}$ = 43.1 min).

(S)-2-(tert-Butyloxycarbonylamino)-7-phenylhept-4-enoic Acid (11h). In the above conditions, 120 mg of phosphonium salt **4** and 120 mg (0.88 mmol, 4.4 equiv) of 3-phenylpropanal **10h** afford the unsaturated amino acid **11h** as an orange solid (36 mg, 57%); R_f: 0.48 (ethyl acetate/petroleum ether 3:7 + 1% acetic acid); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.34–7.27 (m, 2H), 7.23–7.11 (m, 3H), 5.68–5.62 (m, 1H), 5.40–5.32 (m, 1H), 4.95 (d, 1H, J = 7.2 Hz), 4.38–4.35 (m, 1H), 2.72–2.57 (m, 3H), 2.49–2.34 (m, 3H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 176.9, 155.8, 141.6, 134.8, 133.4, 128.7, 128.5, 128.3, 125.9, 123.3, 79.2, 53.0, 35.7, 34.3, 32.0, 30.9, 29.7, 29.2, 28.3. FTIR (neat) cm^{-1} 3235, 3077–2808, 2326, 1652, 1497, 1454, 1394, 1368, 1055, 983, 817, 736, 698, 649. HRMS (ESI-Q-TOF) calcd for C$_{18}$H$_{25}$NNaO$_4$ [M + Na]$^+$ 342.1676, found 342.1647. The enantiomeric excess >99% was determined by HPLC after esterification with TMSCHN$_2$ (Lux 5 μm cellulose-2, hexane/i-PrOH 95:5, 1 mL min^{-1}, λ = 254 nm, 20 °C, $t_{R(Z)\text{-or }(E)\text{-}(S)}$ = 6.9 min, $t_{R(E)\text{-or }(Z)\text{-}(S)}$ = 7.8 min, $t_{R(Z)\text{-or}(E)\text{-}(R)}$ = 10.2 min, $t_{R(E)\text{-or }(Z)\text{-}(R)}$ = 12.7 min).

(S)-2-(tert-Butyloxycarbonylamino)-4-pentenoic Acid (11i). In the above conditions, 120 mg of phosphonium salt **4** and 12 mg of paraformaldehyde **10i** afford the unsaturated amino acid **11i** as a colorless uncrystallized compound (24 mg, 55%); R_f: 0.39 (ethyl acetate/petroleum ether 3:7 + 1% acetic acid); $[\alpha]_D$ = +13.5 (c 0.2, CHCl$_3$, lit.[41] $[\alpha]_D$ = +14.5. ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.12 (d, 0.3H, J = 7.5 Hz). 5.87–5.69 (m, 1H), 5.36–5.16 (m, 2H), 5.04 (d, 0.7H, J = 7.5 Hz), 4.42–4.10 (m, 1H), 2.67–2.57 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 175.7, 155.5, 131.1, 118.4, 79.3, 51.8, 35.3, 27.4. FTIR (neat) cm^{-1} 3313, 3082–2932, 1703, 1662, 1509, 1439, 1394, 1368, 1250, 1157, 1050, 1024, 993, 920, 855, 778, 754, 739, 655. HRMS (ESI-Q-TOF) calcd for C$_{10}$H$_{17}$NNaO$_4$ [M + Na]$^+$ 238.1050, found 238.1039. The enantiomeric excess >99% was determined by HPLC after esterification with TMSCHN$_2$ (Lux 5 μm cellulose-2, hexane/i-PrOH 98:2, 1 mL min^{-1}, λ = 210 nm, 20 °C, $t_{R(S)}$ = 12.2 min, $t_{R(R)}$ = 20.2 min).

(S)-2-(tert-Butyloxycarbonylamino)-5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)]-pent-4-enoic Acid (11j). In the above conditions, 120 mg of phosphonium salt **4** and 93 mg of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde **10j**, previously prepared by reaction of pinacol with 4-formylbenzeneboronic acid,[42] afford the unsaturated amino acid **11j** as a colorless uncrystallized compound in 57% yield with a Z/E ratio 25:75; R_f: 0.40 (ethyl acetate/petroleum ether 3:7 + 1% acetic acid); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.41–7.15 (m, 4H), 6.63 (d, 0.25H, J = 12.3 Hz), 6.51 (d, 0.75H, J = 15.6 Hz), 6.25–6.10 (m, 0.75H), 5.73–5.61 (m, 0.25H), 6.18–5.16 (m, 1H), 5.13–4.48 (m, 1H), 2.80–2.67 (m, 2H), 1.44 (s, 9H), 1.36 (s, 12H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 176.1, 155.6, 139.5, 137.9, 135.1, 134.8, 134.2, 132.5, 131.6, 129.4, 129.0, 128.2, 128.0, 126.4, 125.6, 125.3, 124.8, 116.0, 83.8, 54.4, 53.1, 35.9, 31.2, 28.3, 24.8. FTIR (neat) cm^{-1} 3346, 2979–2931, 1714, 1608, 1515, 1496, 1455, 1397, 1358, 1321, 1270, 1214, 1143, 1089, 1052, 1019. HRMS (ESI) calcd for C$_{22}$H$_{32}$BNNaO$_6$ [M + Na]$^+$ 440.2219, found 440.2215. The enantiomeric excess >99% was determined by HPLC after esterification with TMSCHN$_2$ (Lux 5 μm cellulose-2, hexane/i-PrOH 90:10, 1 mL min^{-1}, λ = 210 nm, 20 °C, $t_{R(E)\text{-}(S)}$ = 6.9 min, $t_{R(Z)\text{-}(S)}$ = 7.8 min, $t_{R(E)\text{-}(R)}$ = 10.2 min, $t_{R(Z)\text{-}(R)}$ = 12.7 min,.

Bis-1,3-[(S)-2-(tert-Butyloxycarbonylamino)pent-4-enoic acid]-benzene (11k). In the above conditions, 120 mg of phosphonium salt **4** and 13.4 mg (0.1 mmol, 0.5 equiv.) of m-phthaldialdehyde **10k** afford the unsaturated amino acid **11k** as a white solid (86 mg, 85%); R_f: 0.23 (ethyl acetate/petroleum ether 3:7 + 1% acetic acid); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.18–7.14 (m, 2H). 7.11–7.08 (m, 2H), 7.07–7.01 (m, 1H), 6.54–6.35 (m, 2H), 6.06–6.01 (m, 1H), 5.71–5.63 (m, 1H), 5.32–5.26 (m, 1H), 4.70–4.14 (m, 2H), 2.89–2.59 (m, 4H), 1.44 (s, 18H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 175.9, 156.8, 155.6, 137.9, 137.1, 137.0, 134.1, 132.4, 129.0, 128.5, 128.3, 127.9, 127.5, 126.1, 126.0, 125,3, 80.4, 54.5, 53.1, 35.7, 31.3, 28.3. FTIR (neat) cm^{-1} 3555, 3407, 3056–3407, 2326, 2244, 2030, 1949, 1583, 1573, 1493, 1471, 1462, 1431, 1296, 1273, 1241, 1180, 1129, 1108, 1070, 1022. HRMS (ESI-Q-TOF) calcd for C$_{26}$H$_{36}$N$_2$NaO$_8$ [M + Na]$^+$ 527.2364, found 527.2372. The enantiomeric excess >99% was

determined by HPLC after esterification with TMSCHN$_2$ and hydrogenation (Lux 5 μm cellulose-2, hexane/i-PrOH 90: 10, 1 mL min^{-1}, λ = 210 nm, 20 °C, $t_{R(S,S)}$ = 14.3 min, $t_{R(R,S) + (S,R)}$ = 21.7 min, $t_{R(R,R)}$ = 32.2 min).

(S)-2-(tert-Butyloxycarbonylamino)-7-phenylhept-4,6-dienoic Acid (11l). In the above conditions, 120 mg of phosphonium salt **4** and 53 mg of trans-cinnamaldehyde **9l** afford the unsaturated amino acid **11l** as a white solid (42 mg, 66%); R_f: 0.53 (ethyl acetate/petroleum ether 3:7 + 1% acetic acid); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.36–7.18 (m, 5H), 7.03 (dd, 0.3H, J = 11.4, 15.6 Hz), 6.76 (dd, 0.7H, J = 10.2, 15.6 Hz), 6.62–6.49 (m, 1H), 6.38–6.27 (m, 0.7H), 5.73–5.70 (m, 0.3H), 5.45–5.42 (m, 0.7H), 5.20–5.04 (m, 1H), 4.53–4.45 (m, 0.7H), 4.33–4.14 (m, 0.3H), 2.94–2.47 (m, 2H), 1.47–1.44 (2s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 175.5, 175.2, 155.7, 154.5, 136.8, 136.1, 133.6, 133.5, 133, 131.9, 131.4, 130.9, 128, 127.6, 127.4, 127.2, 126.7, 126.5, 125.5, 125.3, 124.3, 124.0, 123.8, 122.5, 80.8, 79.4, 54.6, 53.1, 35.6, 31.9, 27.3. FTIR (neat) cm^{-1} 3319, 3083–3053, 1710, 1496, 1450, 1393, 1368, 1251, 1159, 1056, 1027, 989, 948, 920, 857, 807, 778, 752, 731, 694. HRMS (ESI-Q-TOF) calcd for C$_{18}$H$_{22}$NO$_4$ [M − H]$^-$ 316.1554, found 316.1560. The enantiomeric excess >99% was determined by HPLC after esterification with TMSCHN$_2$ (Lux 5 μm cellulose-2, hexane/i-PrOH, 95:5, 1 mL min^{-1}, λ = 210 nm, 20 °C, $t_{R(Z)\text{-or }(E)\text{-}(S)}$ = 20.1 min, $t_{R(E)\text{-or }(Z)\text{-}(S)}$ = 29 min, $t_{R(Z)\text{-or }(E)\text{-}(R)}$ = 32.2 min, $t_{R(E)\text{-or }(Z)\text{-}(R)}$ = 61.2 min).

(S)-2-(tert-Butyloxycarbonylamino)-7-(4-azidophenyl)hept-4,6-dienoic Acid (11m). In the above conditions, 120 mg of phosphonium salt **4** and 69.2 mg of (E)-4-azidophenylprop-2-enal **10m** afford the diene amino acid **11m** as a red solid (40 mg, 56%); R_f: 0.43 (ethyl acetate/petroleum ether 3:7 + 1% acetic acid); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.38 (dd, 2H, J = 8.4, 13.2 Hz). 6.70–6.65 (m, 0.53H), 6.56–6.42 (m, 1H), 6.97 (dd, 2H, J = 8.4, 3.0 Hz), 6.38–6.24 (m, 1H), 5.77–5.67 (m, 0.5H), 5.50–5.42 (m, 0.55H), 4.46–4.44 (m, 0.75H), 4.33–4.26 (m, 0.25H), 2.90–2.62 (m, 2H), 1.46–1.43 (2s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 175.3, 154.5, 138.1, 137.9, 133.5, 133.1, 132.3, 131.7, 131.6, 130.0, 128.1, 127.2, 126.9, 126.5, 124.3, 124.0, 122.2, 118.2, 79.4, 52.1, 29.5, 28.7, 27.3. FTIR (neat) cm^{-1} 3346, 2925–2854, 2114, 1706, 1598, 1504, 1454, 1393, 1367, 1284, 1259, 1157, 1127, 1053. HRMS (ESI-Q-TOF) calcd for C$_{18}$H$_{21}$N$_4$Na$_2$O$_4$ [M − H + 2Na]$^+$ 403.1358, found 403.1333. The enantiomeric excess >99% was determined by HPLC after esterification with TMSCHN$_2$ (Lux 5 μm cellulose-2, hexane/i-PrOH 95:5, 1 mL min-1, λ = 254 nm, 20 °C, $t_{R(Z)\text{-or }(E)\text{-}(S)}$ = 12.2 min, $t_{R(E)\text{-or}(Z)\text{-}(S) \text{ and }(Z)\text{-or }(E)\text{-}(R)}$ = 16.2 min, $t_{R(E)\text{-or }(Z)\text{-}(R)}$ = 30.4 min).

(S)-2-(tert-Butyloxycarbonylamino)-5-trifluoromethyl-5-phenyl-pent-4-enoic Acid (11n). In the above conditions, 120 mg of phosphonium salt **4** and 35 mg of 2,2,2-trifluoroacetophenone **10n** afford the unsaturated amino acid **11n** as a yellow solid in 81% yield with a Z/E ratio 37:63; R_f: 0.62 (ethyl acetate/petroleum ether 3:7 + 1% acetic acid); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.31–7.08 (m, 5H), 6.28 (t, 0.37H, J = 7.5 Hz), 5.90 (t, 0.63H, J = 7.5 Hz), 5.07 (d, 0.63H, J = 6.3 Hz), 4.36–4.17 (m, 1H), 2.99–2.84 (m, 0.63H), 2.84–2.74 (m, 0.63H), 2.56–2.50 (m, 0.37H), 2.38–2.35 (m, 0.37H), 1.18 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 175.7, 174.8, 156.6, 155.5, 135.9, 135.1, 134.7, 131.6, 129.6, 129.1, 129, 108.7, 128.6, 128.4, 128.3, 128.2, 125.5 (q, J = 10.8 Hz), 125.3 (q, J = 276.2 Hz), 82.3, 80.6, 53.0, 52.7, 32, 31.5, 29.7, 29.3, 28.2, 22.7. FTIR (neat) cm^{-1} 3348, 2965–2918, 1731, 1678, 1587, 1518, 1501, 1432, 1376, 1334, 1319, 1272, 1261, 1244, 1154, 1110, 1080, 1066, 1041, 1018. HRMS/MS (ESI) calcd for C$_{17}$H$_{19}$F$_3$N$_1$O$_4$ [M − H]$^-$ 358.1264, found 358.1261. The enantiomeric excess was determined by HPLC on chiral column after esterification with TMSCHN$_2$ (Lux 5 μm cellulose-2, hexane:i-PrOH 97:0.7 mL min^{-1}, λ = 254 nm, 20 °C, $t_{R(E)\text{-or }(Z)\text{-}(S)}$ = 10.7 min, $t_{R(Z)\text{-or }(E)\text{-}(S)}$ = 11.9 min, $t_{R(E)\text{-and }(Z)\text{-}(R)}$ = 21 min).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H, ^{13}C, and ^{31}P NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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