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Stereoselective synthesis of dienylamines: from amino acids to *E*-alkene dipeptide isosters

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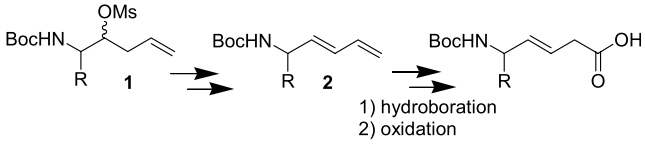
Abstract—A stereoselective approach to dienylamines is described, starting from enantiomerically enriched stannylated allylamines, which are in turn derived from amino acids. Conveniently the procedure allows to introduce diversity at 1-,2- and 4- positions of the final compounds. Conversion to vinylstannane has been extended to dipeptido aldehydes. The possible elaboration of 4-methyl substituted dienylamines to Boc-Gly-Ψ[(*E*)-CH=CH]-(L,D)-Ala and Boc-Phe -Ψ[(*E*)-CH=CH]-(L,D)-Ala dipeptide isosters is also shown.

1. Introduction

Dienylamines are a very interesting moiety, frequently, used in organic synthesis, as for instance in Diels Alder reactions.[1,2] They are versatile building blocks which can be transformed to a range of products by functionalization, reduction or oxidation of double bonds. In addition this unit is found in many bioactive molecules like streptogramine antibiotics,[3] and has been shown as key intermediate to *E*-alkene dipeptide isosters.[4]

trans-Disusbstituted alkene units have been introduced for the first time by Hann[5,6] as an ideal isosteric replacement for the backbone amide group of peptides as the C=C bond is inert to peptidases and the *trans* configuration mimics the conformational preference of a secondary amide. In addition this substitution does not diminish the conformational flexibility that is characteristics of a peptide.[7] The use of this isosteric replacement in peptides is thus, a very important tool in the development of new bioactive compounds and, affecting physical properties like folding and conformation,[8] can also serve as model for biological studies.

Basically, the synthesis of an *E*-alkene dipeptide isostere requires the preparation of a 5-amino-3-pentenoic acid bearing either one or two asymmetric centers in the α- and δ- position. Several methods have been reported to generate this class of compounds,[9–21] and especially Kessler and Kranz[4] showed how dienylamines **2**, which are generated by β-elimination of the corresponding mesyloxy derivative **1**, can be transformed into Phe-Gly *E*-alkene dipeptide isostere by regioselective hydroboration and subsequent oxidation (Scheme 1).



Scheme 1.

For all these reasons chiral pentadienylamines are an important synthetic goal, as it is addressed by several stereoselective approaches reported which include asymmetric nucleophillic additions to carbon–nitrogen double bond,[22] Julia[23] or Wittig-type chemistry,[1,24] cross coupling reactions between the C_3–C_4[25,26] or the C_5–C_6[27]atoms, indium mediated convertion of iodomethyl aziridine.[28] However, there is still a need for developing new convenient and practical approaches which are, if possible, designed to generate molecular diversity, compatible with the presence of sensitive functionalities and stereocenters on the substrates, and able to deliver the final compounds with total control of the geometry of the double bond.

We have already shown how chiral stannylated allylamines **3** can be efficiently obtained through the addition of stannylcuprate **4** on propargylamines **5** and coupled with

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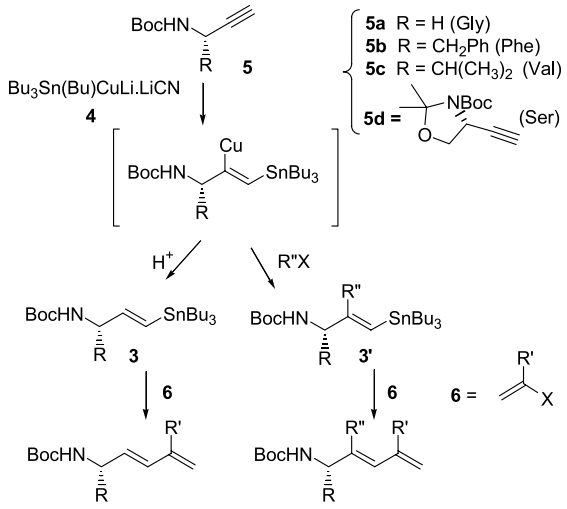
several electrophiles under Pd catalysis to afford a wide range of γ-substituted allylamines.[29] This protocol is mild, chemoselective and has worked remarkably well with chiral substrates, derived from naturally occurring amino acids.[30–32] Taking advantage of this approach, dienylamines could be simply obtained by coupling stannylallylamines **3** with vinylbromides **6** (see Scheme 2).

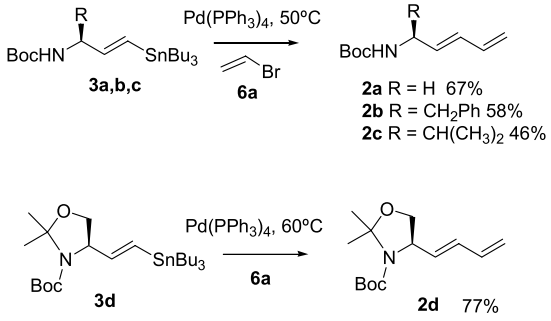


Scheme 2.

Although trivial, the value of this reaction scheme resides, in our opinion, in its flexibility since it allows to introduce three points of molecular diversification onto the dienylamine backbone. Substitution and configuration of the α-carbon can be determined, in fact, by choosing the appropriate starting amino acid, β-substitution can be achieved by quenching the intermediate vinylcuprates with different electrophiles and δ-substitution can be obtained through the coupling with α-branched vinylbromides **6** ($R' \neq H$). Thus, 1,2- or 1,4-disubstituted or 1,2,4-trisubstituted dienamines can be designed and possibly used as precursors for differently substituted *E*-alkene-dipeptide isosters.

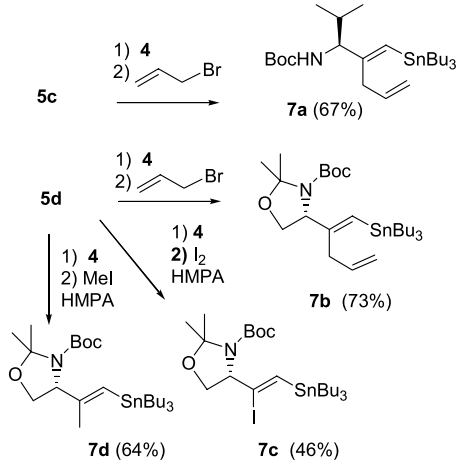
2. Results and discussion

In order to prove the feasibility of this approach, the reactivity of vinylstannanes **3a**,**b**,**c**,**d** with vinylbromide was studied. The required substrates were prepared from propargylamine **5a** and naturally occurring amino acids (phenylalanine **5b**, valine **5c** and serine **5d**) via standard methods.[33,29,30] According with the well known Stille procedure,[34] compounds **3a**,**b**,**c**,**d** were reacted with an excess of vinyl bromide **6a** in the presence of $Pd(PPh_3)_4$ as catalyst. Complete conversion of substrates into the coupled compounds **2a**,**b**,**c**,**d** was obtained performing the reaction in a sealed tube, at 50–60 °C, with excess of the electrophile and without solvent. ^1H NMR analysis of the crude mixture confirmed, as expected, that the coupling occurred with retention of configuration of the vinyl-tin bond, highlighting the method as a mild and efficient way for the preparation of α-branched dienylamines with an (*E*)-geometry. After work-up and chromatography, the final compounds were obtained in good yields (see Scheme 3).



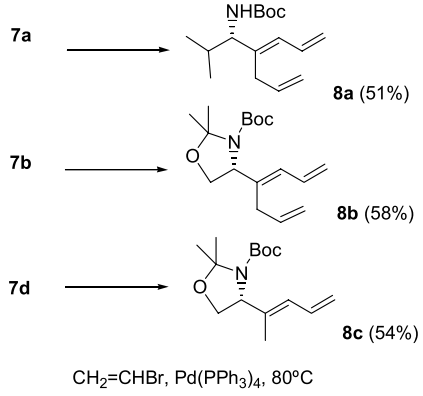
Scheme 3.

In the addition of stannylcuprate to triple bonds an intermediate vinylcuprate is generated which can be trapped with different electrophiles. This reactivity has been exploited in the past to obtain a range of β-substituted stannyl allylamines,[33] or enantiomerically enriched β-amino acrylates.[35] Certainly it can be also extended to prepare 1,2-disubstituted dienylamines. Aimed to show this, three different electrophiles have been used following addition of **4** onto amine **5c** or oxazolidine **5d**, as shown in Scheme 4.



Scheme 4.

Allylbromide gave excellent results affording more than 80% convertion to dienamine **7a** and **7b** in 95/5 regioisomeric mixture, as recovered by ^1H NMR analysis of the crude. Using a less powerful electrophilic partner, like MeI, addition of HMPA was required in order to obtain a good



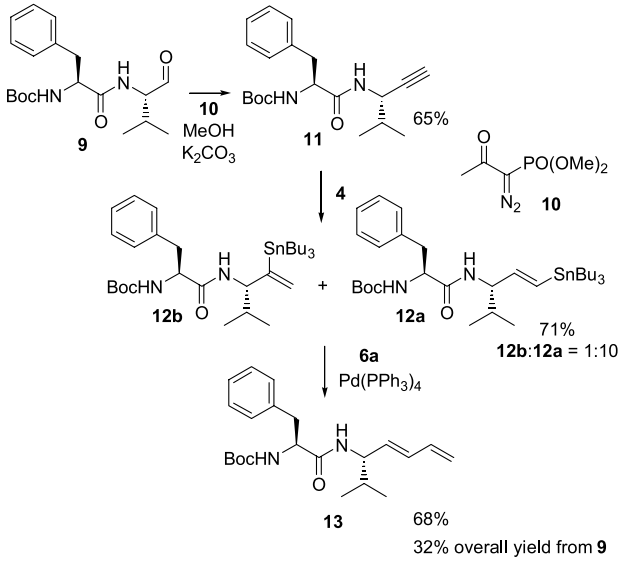
Scheme 5.

conversion into **7d**.[33] Trapping with I_2 in the presence of HMPA afforded **7c**, but in a 80/20 regiosomeric mixture and this was responsible for the lower yield observed. Final compounds **7a–d** were purified by flash chromatography and fully characterized.

2-Functionalized stannanes **7a**, **7b** and **7d** were also reacted with vinylbromide and transformed into the corresponding 1,2-disubstituted dienylmine **8a**,**b**,**c** as shown in Scheme 5.

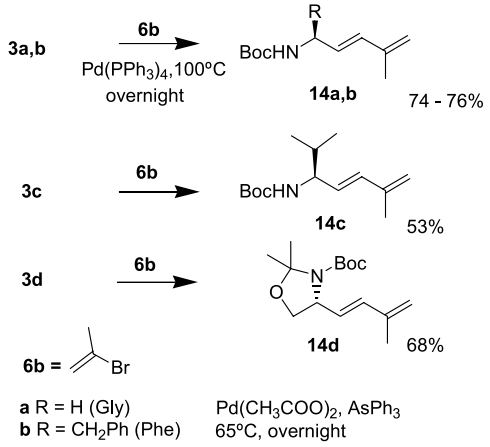
As we have already mentioned, the whole procedure, starting from amino aldehydes to give the target dienylamines, is very selective and requires mild conditions, which are compatible with functionalized substrates. It is known that the synthetic elaboration of dipeptides might be troublesome[36] because of their sensitivity, thus we thought to verify if our route could be extended to a dipeptido aldehyde like **9**,[36,37] aiming to obtain alkyne **11** and vinylstannane **12a**. Both these compounds can be regarded as very useful chiral building blocks to make selective transformations on a dipeptide structure.

When aldehyde **9** was reacted with oxopropyldiazophosphonate **10**,[38] alkyne **11** was obtained in 65% yield after purification on column chromatography (Scheme 6). No α-epimerization at the stereogenic center next to the carbonyl was observed, as confirmed by ^1H and ^{13}C NMR spectra of the crude mixture, where only one diastereoisomer was present. Reaction with stannylcuprate **4** gave a mixture of stannylated dipeptide **12a** and its regioisomer **12b** in a 10:1 ratio. Although the two regioisomer were not separated by flash chromatography, the mixture could be used in coupling reactions, due to the higher reactivity of isomer **12a**.[33] Reaction with vinylbromide, for instance, gave, after purification, dienylamine **13** in good yield (see Scheme 6) as a single diastereoisomer.



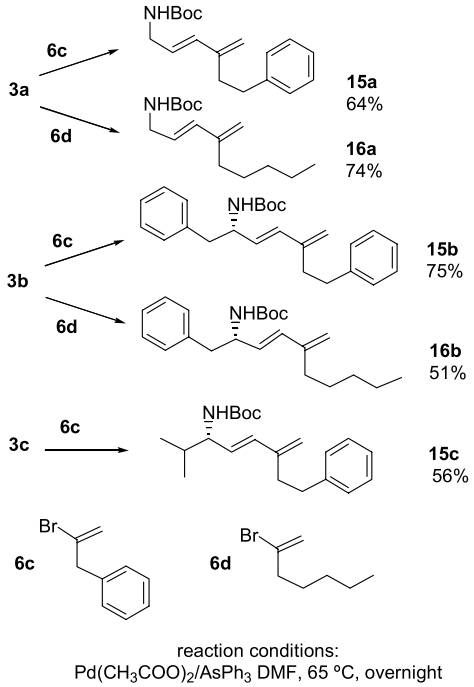
Scheme 6.

In view of accessing a wider molecular diversification, we finally examined the coupling with 2-branched vinylbromides: this would result in δ-substituted dienyl amines. Commercially available 2-bromopropene **6b** was selected to test the reactivity of our substrates (Scheme 7). Although an higher reaction temperature (100 °C), a longer reaction time and excess of electrophile were required, the corresponding 4-methyl dienes, **14a–b**, were recovered and isolated in good yields.



Scheme 7.

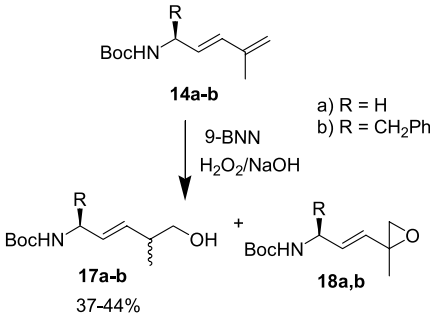
On the contrary, amine **3c** and oxazolidine **3d** reacted sluggishly and the corresponding coupling products could be isolated only in poor yield. Hence, we decided to look for milder conditions. It is known that ligands of reduced donicity usually lead to much faster coupling,[39] consequently when tri(2-furyl)phosphine or $AsPh_3$ are used together with $Pd(CH_3COO)_2$, the reaction can be performed at a lower temperature. Indeed, both these catalysts when reacted with **3c**,**d** promoted the coupling and the best results were finally found using $AsPh_3/Pd(CH_3COO)_2$ in DMF at 65 °C. Using these reaction conditions, compounds **14c**,**d** were obtained in good yields after purification.



Scheme 8.

Stannanes **3a**,**b**,**c** were also reacted with 2-bromo,4-phenyl-but-1-ene **6c** and with 2-bromo,4-methyl-hept-1-ene **6d**, in turn prepared by reaction of 1,2-dibromopropene with benzyl magnesium chloride or with $Bu_2CuLi\cdot LiCN$. Five new amines, **15a**,**b**,**c** and **16a**,**b** were consequently obtained and isolated after column chromatography, as shown in Scheme 8.

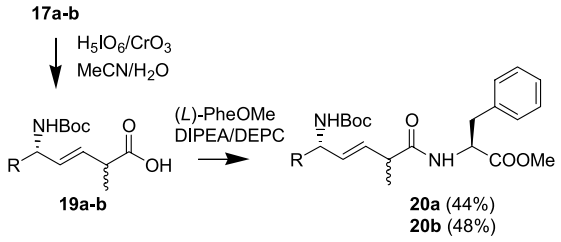
As we previously pointed out, dienamines have been shown to be key intermediates for the synthesis of *E*-alkene dipeptide isosters. In particular, dienamine **2b** was used for the synthesis of Phe-Ψ[(*E*)-CH=CH]-Gly type isoster.[4] The same procedure, if applied to 4-substituted dienamines, can usefully widen the field of target compounds. For instance, if dienamines **14a–b** are used as starting material, the corresponding Gly-Ψ[(*E*)-CH=CH]-Ala and Phe-Ψ[(E)-CH=CH]-Ala isosteres can be obtained. To verify this hypothesis we converted compounds **14a–b** into the corresponding primary alcohols **17a–b** in the reported conditions.[4] Regioselective hydroboration with 9-borabicyclo[3.3.1]-nonane (9-BBN) followed by treatment with $NaOH/H_2O_2$ (see Scheme 9) gave the target alcohols, although in poor yield. Unfortunately in both cases, variable amounts of a by-product were recovered in the ^1H NMR of crude mixture. These were finally identified as the corresponding epoxides **18a**,**b**. Nevertheless, alcohols **17a**,**b** were isolated and fully characterized. Concerning **17b**, it was obtained as a 1/1 mixture of diastereoisomers as shown by some diagnostic signals in the 400 MHz ^1H NMR spectrum. In particular, the more shielded of the two vinylic protons was splitted into two double doublets of the same intensity and two separated doublets ($\delta=0.93$, $\delta=0.90$) were observed for the methyl too. This was also split into two separate signals at $\delta=16.04$ and $\delta=16.15$ pmm in the ^{13}C NMR spectrum.



Scheme 9.

The two diastereoisomers **17b** were not separated and, after flash chromatography, were used for an oxidative step. Rapid and clean oxidation to Boc-Gly-Ψ[(E)-CH=CH]-(*rac*)-Ala **18a**, and Boc-(L)-Phe-Ψ[(E)-CH=CH]-(*rac*)-Ala **18b** occurred using periodic acid (H_5IO_6) as stoichiometric oxidant together with a catalytic amount of CrO_3.[40]

For characterization purposes, these were coupled with (L)-phenylalanine methyl ester to give tripeptide isosters Boc-Gly-Ψ[(E)-CH=CH]-(*rac*)-Ala-(L)-Phe-OMe **19a** and Boc-(L)-Phe-Ψ[(E)-CH=CH]-(*rac*)-Ala-(L)-Phe-OMe **19b** (see Scheme 10).



Scheme 10.

3. Conclusions

In conclusion stannylated allylamines have been confirmed as valuable chiral building blocks which can be elaborated into dienylamines. Due to the mild and selective procedure employed, the method has been proved to be appropriate also when applied to sensitive substrates like dipeptido aldehydes. We had then access to stannylated dipeptido derivatives which can be very useful building blocks. Transformation of dienamines into *E*-dipeptide isosters was estabilished in two cases and isoster of kind AA-Ψ[(E)-CH=CH]-(*rac*)-Ala were obtained by hydroboration/oxidation of the precursors 4-methyl pentadienylamines. Further improvement of the whole process using selective hydroboration methods is currently under investigation.

4. Experimental

4.1. General methods

Ethereal extracts were dried with Na_2SO_4. Reactions were monitored by TLC on SiO_2; detection was made using a $KMnO_4$ basic solution. Flash column chromatography[41] was performed using glass columns (10–50 mm wide) and SiO_2 (230–400 mesh). ^1H NMR were recorded at 200, 300 or 400 MHz. For those compounds which are present as slowly interconverting rotamers, ^1H NMR experiments were performed at 50 °C and signals of the averaged spectrum are reported when possible. ^{13}C NMR spectra were recorded at 50.3 MHz. Chemical shifts were determined relative to the residual solvent peak ($CHCl_3$, δ 7.26 ppm for ^1H NMR; $CHCl_3$, δ 77.0 ppm for ^{13}C NMR). FTIR spectra were registered in CH_2Cl_2 solution (CaF_2). Mass spectra were obtained at a 70 eV ionization potential and are reported in the form *m*/*z* (intensity relative to base=100). Polarimetric measurements were performed at $\lambda=589$ nm, and the temperature is specified case by case.

Amines **3a–c**,[33,29,30] oxazolidine **3d**,[30] and dipeptide aldehyde **9**[36] were prepared according to the literature. $Pd[P(Ph_3)_4]$ was freshly prepared and stored under nitrogen. Starting materials are commercially available unless otherwise stated. All commercial reagents were used without further purification. THF was dried by distillation over sodium benzophenone ketyl. CH_2Cl_2 was dried over $CaCl_2$, and stored over 4 Å molecular sieves. DMF was distilled over $CaCl_2$, and stored over 4 Å molecular sieves. Petroleum ether, unless specified, is the 40–70 °C boiling fraction.

4.2. Coupling with vinyl bromide 6a: general procedure

A catalytic amount (0.01 equiv) of freshly prepared $Pd[P(Ph_3)]_4$ was poured into a sealed flask under nitrogen atmosphere, together with excess of vinyl bromide **6a**. Amine **3a–d** (1 equiv) was then added and the reaction mixture heated and reacted for a variable time, depending on the substrate. After the starting material was completely consumed the excess of electrophile was evaporated and the recovered material diluted with ether and treated with a aqueous KF saturated solution. After filtration and extraction with ether the organic phase was washed with brine and dried. The crude obtained after evaporation of the solvent was purified by flash chromatography.

4.2.1. (2*E*)-Penta-2,4-dienyl-carbamic acid *tert*-butyl ester 2a. Vinylbromide (0.5 mL) was reacted with **3a** (90 mg, 0.2 mmol) at 55 °C for 10 h. Purification [petroleum ether/ethyl acetate = 7:1] gave 26 mg of pure **2a** (67%) as a colorless oil.

Compound (**2a**): ^{1}H NMR (200 MHz) δ: 1.44 [s, 9H]; 3.72–3.78 [br m, 3H]; 4.53 [br s, 1H]; 5.04 [br d, 1H, J = 10.4 Hz]; 5.16 [br d, 1H, J = 16.8 Hz]; 5.64–5.71 [m, 1H]; 6.11–6.17 [m, 1H, J_{AB} = 15.8 Hz]; 6.25–6.34 [m, 1H, J_{AB} = 15.8 Hz]. ^{13}C NMR (50.3 MHz) δ: 28.25; 42.12; 79.33; 117.13; 130.20; 132.00; 136.10; 155.66. MS *m*/*z* (%): 127 (9); 57 (100). Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.37; H, 9.31; N, 7.73.

4.2.2. (2*E*),(1*S*)-(1-Benzyl-penta-2,4-dienyl)-carbamic acid *t*-butyl ester 2b. Vinylbromide (0.5 mL) was reacted with **3b** (110 mg, 0.2 mmol) at 50 °C for 20 h. Purification [petroleum ether/ethyl acetate = 6:1] gave 30 mg of pure **2b** (58%) as a pale yellow oil. ^{1}H NMR was in agreement with those previously reported.[4]

Compound (**2b**). ^{13}C NMR (50.3 MHz) 28.40; 33.21; 62.07; 79.12; 111.58; 115.82; 117.33; 127.67; 132.56; 135.96; 139.11; 147.20; 155.45. $[\alpha]_D^{24}$ +4.5 (*c* 1.0, $CHCl_3$).

4.2.3. (2*E*),(1*S*)-(Isopropyl-penta-2,4-dienyl)-carbamic acid *t*-butyl ester 2c. Vinylbromide (0.5 mL) was reacted with **3c** (100 mg, 0.2 mmol) at 50 °C for 20 h. After Purification [petroleum ether/ethyl acetate = 10:1] gave 21 mg of pure **2c** (46%) as a colorless oil.

Compound (**2c**): ^{1}H NMR (200 MHz) δ: 0.88 [d, J = 5.8 Hz, 3H]; 0.90 [d, J = 5.8 Hz, 3H]; 1.44 [s, 9H]; 1.58–1.88 [m, 1H]; 3.97 [br s, 1H]; 4.37–4.58 [m, 1H]; 5.05 [br d, J = 8.8 Hz, 1H]; 5.18 [dd, J = 14.0, J = 2.0 Hz, 1H]; 5.58 [dd, J = 14.6, J = 6.2 Hz, 1H]; 6.08–6.41 [m, 2H]. ^{13}C NMR (50.3 MHz) δ: 18.04; 18.74; 28.46; 32.70; 58.15; 79.28; 116.75; 131.49; 133.13; 136.41; 155.44. MS *m*/*z* (%): 225 (4); 57 (100). $[\alpha]_D^{28}$ +5.2 (*c* 0.35, $CHCl_3$). Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29; N, 6.22. Found: C, 69.42; H, 10.32; N, 6.26.

4.2.4. (4*R*)-2,2-Dimethyl-4-[(*E*)-buta-1,3-dienyl)]-oxazolidine-3-carboxylic acid tert-butyl ester 2d. Vinylbromide (0.5 mL) was reacted with **3d** (135 mg, 0.2 mmol) at 60 °C for 20 h. Purification [petroleum ether/ethyl acetate = 5:1] gave 51 mg of pure **2d** (77%) as an oil. Spectroscopic data were in agreement with those previously reported.[42] $[\alpha]_D^{20}$ +20.2 (*c* 1.85, $CHCl_3$) {lit. $[\alpha]_D^{21}$ +21.2 (*c* 1.93, $CHCl_3$)}.

4.3. Trapping with electrophiles: general procedure

Stannylcuprate was prepared as reported[43] using CuCN (1 equiv), BuLi (1.6 M in hexane, 2 equiv) and n-Bu_3SnH (1.0 equiv). Substrate **5** (1 equiv) was then added and, after warming at −30 °C, reacted with the electrophile. After usual workup the corresponding 2-substituted stannylated amines were recovered and purified by flash chromatography.

4.3.1. (1*S*)-(1-Isopropyl-2-tributylstannanylmethylene-pent-4-enyl)-carbamic acid *t*-butyl ester 7a. CuCN (38 mg, 0.4 mmol), BuLi (0.50 mL, 0.8 mmol) and n-Bu_3SnH (116 mg, 0.4 mmol) were reacted with **5c** (92 mg, 0.4 mmol) and, after warming at −30 °C, with allylbromide (72 mg, 0.6 mmol) for 12 h. Purification [petroleum ether/ethyl acetate (20:1)], gave **7a** as a colorless oil (139 mg, 67%).

Compound (**7a**): ^{1}H NMR (200 MHz) δ: 0.79–0.94 [m, 15H + 6H]; 1.43 [s, 9H]; 1.20–1.51 [m, 12H]; 1.78–1.96 [m, 1H]; 2.82 [d, J = 6.6 Hz]; 3.86–4.00 [m, 1H]; 4.48–4.62 [br. d, J = 10.8 Hz, 1H]; 4.98–5.20 [m, J_{AB} = 16.4, J_{AX} = 9.9, J_{BX} = 1.6 Hz]; 5.68 [d, J = 0.8 Hz, 1H]; 5.69–5.86 [m, J_{AB} = 16.4, J_{AX} = 9.9 Hz, 1H]. ^{13}C NMR (50.3 MHz) δ: 10.24; 13.64; 17.21; 20.21; 27.24; 28.37; 29.14; 30.04; 42.13; 61.43; 78.80; 116.34; 124.36; 136.90; 155.18; 155.51. MS *m*/*z* (%): 416 (10); 57 (100). FTIR ν_{max}: 3434, 1712. $[\alpha]_D^{21}$ −4.7 (*c* 1.18, $CHCl_3$).

4.3.2. (4*R*)-2,2-Dimethyl-4-{1-[(*E*)-1-tributyl-stannanyl-methylidene]-but-3-enyl}-oxazolidine-3-carboxylic acid *tert*-butyl ester 7b. CuCN (88 mg, 1.0 mmol), BuLi (1.25 mL, 2.0 mmol) and n-Bu_3SnH (290 mgl, 1.0 mmol) were reacted with oxazolidine **5d** (218 mg, 0.97 mmol) and, after warming at −30 °C, with allylbromide (180 mg, 1.5 mmol) for 12 h. Purification [petroleum ether/ethyl acetate (gradient)], gave **7b** as a colorless oil (392 mg, 73%).

Compound (**7b**): ^{1}H NMR (400 MHz, 50 °C) δ: 0.89 [t, J = 7.6 Hz, 9H]; 0.89–0.94 [m, 6H]; 1.26–1.36 [m, 12H]; 1.38–1.58 [m, 15H]; 2.80–2.85 [m, J_{AB} = 8.0, J_{AX} = 14.8, 1H]; 2.91–2.96 [m, J_{AX} = 14.8, J_{BX} = 6.4 Hz, 1H]; 3.70–3.73 [m, J_{AX} = 2.8, J_{AB} = 8.8 Hz]; 4.06–4.02 [m, J_{BX} = 6.8, J_{AB} = 8.8 Hz, 1H]; 4.26–4.42 [br m, 1H]; 5.02–5.05 [dd, J_{cis} = 10.0, J_{gem} = 1.6 Hz, 1H]; 5.13–5.09 [br d, J_{trans} = 17.2 Hz, 1H]; 5.69–5.78 [m, 1H]; 5.81 [s, $J_{Sn\text{-}H}$ = 36.2 Hz, 1H). ^{13}C NMR (50.3 MHz) δ: 10.30; 13.67; 23.34; 25.59; 27.29; 28.40; 29.20; 41.82; 62.34; 68.51; 79.38; 94.32; 116.40; 122.68; 136.50; 151.98; 153.51. MS *m*/*z* (%): 500 (2); 57 (100). FTIR ν_{max}: 1692, 1388. $[\alpha]_D^{21}$ −25.2 (*c* 0.98, $CHCl_3$).

4.3.3. (4*R*)-2,2-Dimethyl-4-{1-[(*Z*)-1-iodo-2-tributyl-stannyl]-vinyl}-oxazolidine-3-carboxylic acid *tert*-butyl ester 7c. CuCN (45 mg, 0.5 mmol), BuLi (0.65 mL, 1.0 mmol) and n-Bu_3SnH (148 mg, 0.5 mmol) were reacted with oxazolidine **5d** (113 mg, 0.5 mmol) and then with HMPA (0.2 mL) and a solution of I_2 (122 mg, 0.5 mmol) in THF (2 mL). Temperature was raised at −30 °C and the

reaction mixture stirred overnight. Purification [petroleum ether/ethyl acetate = 30:1] gave 143 mg of **7c** (46%) as an yellow oil.

Compound (**7c**): ^{1}H NMR (400 MHz, 50 °C) δ: 0.90 [t, J = 7.2 Hz, 9H]; 1.30–1.57 [m, 6H + 9H + 18H]; 3.91–3.94 [m, J_{AB} = 8.8, J_{AX} = 3.2 Hz,, 1H]; 4.02–4.05 [m, J_{AB} = 8.8, J_{BX} = 7.2 Hz, 1H]; 4.39–4.45 [br m, 1H]; 7.13 [s, $J_{Sn\text{-}H}$ = 45.2 Hz, 1H]. ^{13}C NMR (50.3 MHz) δ: 10.65; 13.66; 23.55; 25.88; 27.25; 28.29; 29.06; 68.37; 69.96; 80.04; 95.42; 124.77; 139.45; 151.77. MS *m*/*z* (%): 587 (2); 57 (100). ν_{max}: 1712. $[\alpha]_D^{21}$ 0.00 (*c* 0.62, $CHCl_3$).

4.3.4. (4*R*)-2,2-Dimethyl-4-{1-[(*E*)-1-methyl-2-tributylstannyl]-vinyl}-oxazolidine-3-carboxylic acid *tert*-butyl ester 7d. CuCN (45 mg, 0.5 mmol), BuLi (0.65 mL, 1.0 mmol) and *n*-Bu_3SnH (146 mg, 0.5 mmol) were reacted with oxazolidine **5d** (108 mg, 0.5 mmol) together with HMPA (0.2 mL). Temperature was raised at −25 °C, methyliodide (112 mg, 0.8 mmol) was added and stirred overnight. Purification [petroleum ether/ethyl acetate (gradient)] gave **7d** as a pale yellow oil (167 mg, 64%).

Compound (**7d**): ^{1}H NMR (400 MHz, 55 °C) δ: 0.86–0.91 [t, J = 7.2 Hz, 15H]; 1.26–1.35 [m, 6H]; 1.41–1.52 [m, 21H]; 1.75 [s, 3H]; 3.67–3.70 [m, J_{AB} = 8.8, J_{AX} = 1.6 Hz, 1H]; 4.03–4.09 [m, J_{AB} = 8.8, J_{BX} = 7.2 Hz, 1H]; 4.21–4.37 [br m, 1H]; 5.67 [s, $J_{Sn\text{-}H}$ = 65.6 Hz, 1H]. ^{13}C NMR (50.3 MHz) δ: 13.62; 20.76; 23.37; 25.73; 27.22; 28.25; 28.35; 29.01; 65.26; 68.38; 79.33; 94.29; 11.28; 122.74; 152.212. MS *m*/*z* (%): 474 (4); 57 (100). ν_{max}: 1708. $[\alpha]_D^{26}$ −30.3 (*c* 1.0, $CHCl_3$).

4.3.5. (1*S*)-(2-Allyl-1-isopropyl-penta-2,4-dienyl)-carbamic acid *t*-butyl ester 8a. Vinylbromide (0.5 mL) was reacted with 85 mg (0.2 mmol) of **7a** at 80 °C for 20 h. Purification [petroleum ether/ethyl acetate = 5:1] gave pure **8a** as a colorless oil (28 mg, 51%).

Compound (**8a**): ^{1}H NMR (200 MHz) δ: 0.84–0.95 [m, 6H, CH_3 (*i*-Pr)]; 1.42 [s, 9H, *t*-Boc]; 1.56–1.68 [m, 1H, CH (*i*-Pr)]; 2.73–2.93 [m, 2H, CH_2C=]; 3.72–3.92 [m, 1H, (C1)–H]; 4.53 [br s, 1H, NH]; 4.90–5.24 [m, 2H + 2H, C(5)–H + CH_2=]; 5.70–5.84 [m, 1H, CH=]; 5.97 [d, J = 11.0 Hz, 1H, C(3)–H]; 6.46–6.65 [m, 1H, C(4)–H]. ^{13}C NMR (50.3 MHz) δ: 17.28; 20.27; 28.40; 33.21; 37.78; 62.07; 79.12; 115.83; 127.68; 132.57; 135.97; 147.21; 155.45. MS *m*/*z* (%): 209 (7); 57 (100). $[\alpha]_D^{24}$ −9.7 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{16}H_{27}NO_2$: C, 72.41; H, 10.25; N, 5.28. Found: C, 72.54; H, 10.48; N, 5.22.

4.3.6. (4*R*)-2,2-dimethyl-4-[(*E*)-1-allyl-buta-1,3-dienyl]-oxazolidine-3-carboxylic acid *tert*-butyl ester 8b. Vinylbromide (0.5 mL) was reacted with 110 mg (0.2 mmol) of **7b** at 80 °C for 20 h. Purification [petroleum ether/ethyl acetate = 5:1] gave **8b** as a colorless oil (34 mg, 58%).

Compound (**8b**): ^{1}H NMR (400 MHz, 50 °C) 1.52 [s, 9H]; 1.68 [br s, 6H]; 2.85–2.93 [br m, J_{AB} = 15.6 Hz, 1H]; 2.99–3.05 [m, J_{AB} = 15.6, J_{BX} = 3.0 Hz, 1H]; 3.75–3.78 [m, J_{AB} = 9.1, J_{AX} = 3.1 Hz, 1H]; 4.04–4.08 [m, J_{AB} = 9.1, J_{BX} = 7.0 Hz, 1H]; 5.05–4.96[br m,1H]; 5.00–5.03 [m, 1H]; 5.05–5.11 [m, 2H]; 5.18 [dd, J = 16.8, 1.8 Hz, 1H]; 5.72–5.83 [m, 1H]; 6.03 [br d, J = 10.8 Hz, 1H]; 6.52–6.61 [m, 1H]. ^{13}C NMR (50.3 MHz) δ: 23.21; 25.19; 28.36; 37.01; 62.51; 67.87; 79.71; 94.36; 115.90; 116.77; 117.51; 127.28 132.40; 135.66; 152.22. MS *m*/*z* (%): 237 (5); 57 (100). $[\alpha]_D^{21}$ −25.2 (*c* 0.98, $CHCl_3$). Anal. Calcd for $C_{17}H_{27}NO_3$: C, 69.59; H, 9.28; N, 4.77. Found: C, 69.46; H, 9.41; N, 4.63.

4.3.7. (4*R*)-2,2-Dimethyl-4-[(*E*)-1-methyl-buta-1,3-dienyl)-oxazolidine-3-carboxylic acid *tert*-butyl ester 8c. Vinylbromide (0.5 mL) was reacted with 104 mg (0.2 mmol) of **7d** at 80 °C for 20 h. Purification [petroleum ether/ethyl acetate = 5:1] gave **8c** as a pale yellow oil (27 mg, 54%).

Compound (**8c**): 1.52 [s, 9H]; 1.69 [br s, 6H]; 1.75 [s, 3H]; 3.75–3.78 [m, J_{AB} = 8.8, J_{AX} = 2.8 Hz, 1H]; 4.08–4.13 [m, J_{AB} = 8.8, J_{BX} = 3.9 Hz, 1H]; 4.32–4.37 [br m,1H]; 4.87–4.90 [m, 1H]; 4.93–4.96 [m, 2H]; 5.97 [br d, J = 10.8 Hz, 1H]; 6.68 [dt, J = 10.8, 16.8 Hz, 1H]. ^{13}C NMR (50.3 MHz) δ: 17.9; 23.21; 25.19; 28.26; 32.41; 62.82; 65.43; 79.64; 94.36; 116.53; 131.22; 132.81; 136.10; 152.34. MS *m*/*z* (%): 211 (8); 57 (100). Anal. Calcd for $C_{15}H_{25}NO_3$: C, 67.38; H, 9.42; N, 5.24. Found: C, 67.25; H, 9.34; N, 5.36.

4.4. Synthetic elaboration of dipeptido aldehydes

4.4.1. {(*S*)-1-[(*S*)-1-Isopropyl-prop-2-ynylcarbamoyl]-2-phenyl-ethyl}-carbamic acid *tert*-butyl ester 11. Aldehyde **9** (606 mg, 1.7 mmol) was dissolved into MeOH (12 mL) together with diazophosphonate**10**,[38] (535 mg, 2.8 mmol). After cooling at 0 °C, K_2CO_3 (490 mg) was added and the reaction left at this temperature for 1 h, then at RT for 3 h. After hydrolysis (NH_4Cl saturated solution), MeOH was evaporated and the aqueous residue extracted with ethyl acetate (3 × 15 mL). The organic phase was washed with water and brine, then dried and evaporated. Purification [petroleum ether/ethyl acetate = 3:1] gave **11** (386 mg, 1.1 mmol, 65%) as a white solid.

Compound (**11**): mp 125–127 °C. ^{1}H NMR (200 MHz) δ: 0.80 [d, J = 6.5 Hz, 3H]; 0.89 [d, J = 6.5 Hz, 3H]; 1.41 [s, 9H]; 1.66–1.86 [m, 1H]; 2.20 [d, J = 2.2 Hz, 1H]; 3.04–3.10 [m, 2H]; 4.26–4.36 [m, 1H]; 4.56–4.64 [m, 1H]; 4.85–5.05 [m, 1H]; 6.08 [br d, J = 8.4 Hz, 1H]; 7.34–7.19 [m, 5H]. ^{13}C NMR (50.3 MHz) δ: 17.16; 18.56; 28.15; 32.30; 38.37; 46.89; 55.72; 71.96; 80.11; 81.10; 126.83; 128.58; 129.24; 136.55; 155.38; 170.42. MS *m*/*z* (%): 271 (5); 120 (100). ν_{max}: 3420, 3302, 1712, 1675. $[\alpha]_D^{24}$ +0.96 (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{20}H_{28}N_2O_3$: C, 69.74; H, 8.19; N, 8.13. Found: C, 69.92; H, 8.32; N, 8.03.

4.4.2. {(*S*)-1-[(*E*)-(*S*)-1-Isopropyl-3-tributylstannanyl-allylcarbamoyl)-2-phenyl-ethyl}-carbamic acid *tert*-butyl ester 12a. Stannylcuprate was prepared using CuCN (55 mg, 0.6 mmol), BuLi (1.6 M, 0.75 mL, 1.2 mmol) and *n*-Bu_3SnH (178 mg, 0.6 mmol). Compound **11** (199 mg, 0.6 mmol) was added and reacted under stirring for 15 min. Usual workup afforded 435 mg of crude which, after purification [petroleum ether/ethyl acetate, gradient], gave 262 mg of a of **12a** + **12b** (95:5 mixture) as a pale yellow oil (71%).

Compound (**12a**): ^{1}H NMR (200 MHz) δ: 0.62–1.00 [m, 15H+6H]; 1.20–1.74 [m, 1H+12H]; 1.42 [s, 9H]; 3.00–3.14 [m, 2H]; 4.22–4.41 [m, 1H+1H]; 4.90–5.10 [br m, 1H]; 5.66–5.84 [m, J_{AB}=19.2, J_{BC}=4.4 Hz, 1H+1H]; 5.93 [d, J_{AB}=19.2 Hz, 1H]; 7.17–7.30 [m, 5H]. ^{13}C NMR (50.3 MHz) δ: 9.34; 13.57; 17.57; 18.34; 27.13; 28.15; 28.95; 31.88; 38.26; 56.23; 58.63; 80.04; 126.83; 128.63; 129.29; 136.55; 136.72; 145.46; 155.32; 170.38. MS *m*/*z*: 580 (4); 505 (100). ν_{max}: 3422, 1712, 1675.

4.4.3. {(*S*)-1-[(*E*)-(*S*)-1-Isopropyl-penta-2,4-dienyl-carbamoyl]-2-phenyl-ethyl}-carbamic acid *tert*-butyl ester 13. Vinylbromide (0.5 mL) was reacted with **12a**+**12b** (96 mg, 0.15 mmol) at 80 °C for 72 h. Purification [petroleum ether/ethyl acetate=5:1] gave **13** (38 mg, 68%) as a colorless oil.

Compound (**13**): ^{1}H NMR (200 MHz) δ: 0.80–0.89 [m, 6H]; 1.42 [s, 9H]; 1.50–1.86 [m, 1H]; 2.96–3.20 [m, 2H]; 4.20–4.39 [m, 1H+1H]; 4.90–5.19 [m, 2H+1H]; 5.48 [dd, J=15.2, 6.1 Hz, 1H]; 5.92 [br d, J=9.2 Hz, 1H]; 6.04 [dd, J=14.6, 10.2 Hz, 1H]; 6.15–6.36 [m, 1H]; 7.11–7.28 [m, 5H]. ^{13}C NMR (50.3 MHz) δ: 17.28; 18.45; 28.24; 32.23; 38.13; 55.80; 56.48; 80.29; 117.11; 126.91; 128.71; 129.30; 129.34; 132.00; 136.28; 136.60; 155.39; 170.58. MS *m*/*z*: 315 (2); 57 (100). $[\alpha]_D^{24}$ −26.4 (*c* 1.5). Anal. Calcd for $C_{22}H_{32}N_2O_3$: C, 70.94; H, 8.66; N, 7.52. Found: C, 71.12; H, 8.42; N, 7.22.

4.5. Coupling with 2-substituted-vinylbromides 6b,c,d

4.5.1. Synthesis of electrophiles.

4.5.1.1. (3-Bromo-but-3-enyl)-benzene 6c. 2,3-Dibromopropene (400 mg, 2 mmol) was dissolved in ether (5 mL) and reacted with benzyl magnesium chloride (1.0 M in ether, 2.5 mL, 2.5 mmol) at RT, overnight. Workup gave 360 mg of crude which were used without further, purification.

Compound (**6c**): ^{1}H NMR (200 MHz) δ: 2.72–2.76 [m, 2H]; 2.85–2.89 [m, 2H]; 5.39 [d, J=1.8 Hz, 1H]; 5.51 [d, J=1.8 Hz, 1H]; 7.18–7.30 [m, 5H]. ^{13}C NMR (50.3 MHz) δ: 34.23; 43.13; 116.91; 125.72; 128.13; 128.27; 133.35; 140.09. MS *m*/*z*: 209/211 (2/2); 91 (100).

4.5.1.2. 2-Bromo-hept-1-ene 6d. A slurry of CuCN (180 mg, 2 mmol) in THF (5 mL) was cooled at −78 °C and reacted with BuLi (1.6 M, 2.5 mL, 4 mmol) for 1 h. 2,3-dibromopropene (400 mg, 2 mmol) was added at −30 °C and reacted overnight. After workup 286 mg of crude were obtained and used without further, purification.

Compound (**6d**): ^{1}H NMR (200 MHz) δ: 0.90 [t, J=6.6 Hz, 3H]; 1.18–1.41 [m, 4H]; 1.44–1.62 [m, 2H]; 2.41 [t, J=7.0 Hz, 2H]; 5.37 [d, J=1.6 Hz, 1H]; 5.45–5.56 [m, 1H]. ^{13}C NMR (50.3 MHz) δ: 14.22; 22.62; 27.33; 31.40; 41.43; 112.81; 131.82. MS *m*/*z*: 178/176 (6/5); 122/120 (44/43).

4.5.2. Coupling: general procedure. $Pd(CH_3COO)_2$ (0.03 equiv) and $AsPh_3$ (0.12 equiv) were mixed in DMF at 65 °C for 1 h. Electrophile **6** (2 equiv) was added and the mixture degassed, then reacted with amine **3** (1 equiv) for 20 h. After DMF was evaporated, the recovered material was diluted with ether and treated with a KF saturated solution. The mixture was filtered, extracted with ether and the organic phase washed with brine and dried. The crude obtained after evaporation was purified by flash chromatography.

4.5.2.1. [(*E*)-4-Methyl-penta-2,4-dienyl]-carbamic acid tert-butyl ester 14a. 2-Bromo-propene **6b** (2.0 mmol, 0.25 mL) was reacted with **3a** (430 mg, 1.0 mmol) in DMF (2.0 mL). Purification [petroleum ether/ethyl acetate=10:1] gave **14a** (153 mg, 76%) as a pale yellow oil.

Compound (**14a**): ^{1}H NMR (200 MHz) δ: 1.44 [s, 9H]; 1.82 [s, 3H]; 3.77–3.83 [m, 2H]; 4.61 [br s, 1H]; 4.92–4.99 [m, 2H]; 5.62 [dt, J_{AB}=15.6, J=5.8 Hz, 1H]; 6.23 [d, J_{AB}=15.6 Hz, 1H]. ^{13}C NMR (50.3 MHz) δ: 18.53; 28.35; 42.45; 79.38; 116.40; 126.15; 134.20; 143.41; 155.93. MS *m*/*z*: 141 (8); 57 (100). Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.85; H, 9.56; N, 7.11.

4.5.2.2. [(*E*)-(*S*)-1-Benzyl-4-methyl-penta-2,4-dienyl]-carbamic acid *tert*-butyl ester 14b. 2-Bromo-propene **6b** (0.5 mmol, 0.1 mL) was reacted with **3b** (100 mg, 0.2 mmol) in DMF (1.0 mL). Purification [petroleum ether/ethyl acetate=10:1] gave **14b** (43 mg, 74%) as a thick oil.

Compound (**14b**): ^{1}H NMR (200 MHz) δ: 1.40 [s, 9H]; 1.80 [s, 3H]; 2.83–2.89 [m, 2H]; 4.37–4.52 [m, 1H]; 4.82–4.97 [m, 2H]; 5.52–5.63 [m, J_{AB}=15.6 Hz, 1H]; 6.19 [d, J_{AB}=15.6 Hz, 1H]. 7.38–7.12 [m, 5H]. ^{13}C NMR (50.3 MHz) δ: 18.59; 28.33; 41.97; 53.07; 79.41; 116.52; 126.43; 128.30 (×2); 129.54; 132.89; 137.43; 141.22; 155.12. MS *m*/*z* (%): 231 (10); 140 (100); 96 (100). $[\alpha]_D^{24}$ 3.3 (*c* 1.5, $CHCl_3$). Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.37; H, 8.68; N, 4.96.

4.5.2.3. [(*E*)-(*S*)-1-Isopropyl-4-methyl-penta-2,4-dienyl]-carbamic acid *tert*-butyl ester 14c. 2-Bromo-propene **6b** (0.5 mmol, 0.1 mL) was reacted with **3c** (100 mg, 0.2 mmol) in DMF (1.0 mL). Purification [petroleum ether/ethyl acetate=10:1] gave **14c** (25 mg, 53%) as a colorless oil.

Compound (**14c**): ^{1}H NMR (200 MHz) δ: 0.83 [d, J=5.2 Hz, 3H]; 0.87 0.83 [d, J=5.2 Hz, 3H]; 1.45 [s, 9H]; 1.72–1.84 [m, 1H]; 1.83 [s, 3H]; 3.94–4.09 [m, 1H]; 4.41–4.57 [m, 1H]; 4.95 [br s, 2H]; 5.51 [dd, J=6.6, 15.8 Hz, 1H]; 6.23 [d, J=15.8 Hz, 1H]. MS *m*/*z* (%): 182 (10); 57 (100). $[\alpha]_D^{23}$ −4.4 (*c* 0.9, $CHCl_3$). Anal. Calcd for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 70.34; H, 10.19; N, 5.92

4.5.2.4. 2,2-Dimethyl-4-[(*R*)-(*E*)-3-methyl-buta-1,3-dienyl]-oxazolidine-3-carboxylic acid *tert*-butyl ester 14d. 2-Bromo-propene **6b** (0.5 mmol, 0.15 mL) was reacted with **3d** (104 mg, 0.2 mmol). Purification [petroleum ether/ethyl acetate=10:1] gave **14d** (34 mg, 68%) as a colorless oil.

Compound (**14d**): ^{1}H NMR (400 MHz, 50 °C) δ: 1.47 [s, 9H]; 1.56 [s, 3H]; 1.64 [s, 3H]; 1.84 [s, 3H]; 3.79 [dd, J=

2.4, 8.8 Hz 1H]; 4.11 [dd, $J=6.4$, 8.8 Hz 1H]; 4.23–4.31 [m, 1H]; 5.00 [br s, 2H]; 5.64 [dd, $J=7.6$, 15.6 Hz, 1H]; 6.28 [d, $J=15.6$ Hz, 1H]. ^{13}C NMR (50.3 MHz) δ: 22.97; 23.69; 28.89; 30.31; 59.37; 68.41; 80.04; 95.23; 116.38; 128.77; 130.87; 141.19; 155.56. MS *m/z* (%): 211 (8); 57 (100). Anal. Calcd for $C_{15}H_{25}NO_3^{\cdot}$: C, 67.38; H, 9.42; N, 5.24. Found: C, 67.48; H, 9.63; N, 5.33.

4.5.2.5. [(*E*)-4-Methylene-6-phenyl-hex-2-enyl]-carbamic acid *tert*-butyl ester 15a. Vinylbromide **6c** (93 mg, 0.4 mmol) was reacted with **3a** (100 mg, 0.2 mmol). Purification [petroleum ether/ethyl acetate=15:1] gave **15a** (41 mg, 64%) as a pale yellow oil.

Compound (**15a**): ^{1}H NMR (200 MHz) δ: 1.45 [s, 9H]; 2.45–2.53 [m, 2H]; 2.76–2.84 [m, 2H]; 3.77–3.83 [m, 2H]; 4.53 [br s, 1H]; 4.88–5.10 [m, 2H]; 5.69 [dt, $J=16.1$, 6.0 Hz, 1H]; 6.19 [dt, $J=16.1$ Hz]; 7.16–7.33m, 5H]. ^{13}C NMR (50.3 MHz) δ: 28.46; 33.99; 34.67; 42.70; 79.46; 115.71; 125.60; 128.27; 128.33; 130.81; 133.50; 137.41; 144.71; 155.62. MS *m/z* (%): 230 (7); 91 (100). Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.16; H, 8.68; N, 4.74.

4.5.2.6. [(*E*)-(*R*)-1-Benzyl-4-methylene-6-phenyl-hex-2-enyl]-carbamic acid *tert*-butyl ester 15b. Vinylbromide **6c** (91 mg, 0.4 mmol) was reacted with **3b** (123 mg, 0.2 mmol). Purification [petroleum ether/ethyl acetate=20:1] gave **15b** (65 mg, 75%) as a pale yellow oil.

Compound (**15b**): ^{1}H NMR (200 MHz) δ: 1.43 [s, 9H]; 2.42–2.50 [m, 2H]; 2.73–2.89 [m, 2H+2H]; 4.39–4.66 [m, 1H+1H]; 4.79–5.08 [m, 2H]; 5.66 [dd, $J=5.8$, 16.2 Hz, 1H]; 6.15 [d, $J=16.2$ Hz, 1H]; 7.15–7.34 [m, 10H]. ^{13}C NMR (50.3 MHz) δ: 28.29; 34.08; 34.60; 41.90; 52.12; 79.41; 115.88; 125.80; 126.41; 128.25; 128.31; 128.89; 129.49; 129.51; 132.08; 133.16; 137.38; 144.60; 155.07. MS *m/z* (%): 321 (5); 91 (100). ν_{max}: 3434, 1710. $[\alpha]_D^{26}$ −40.4 (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{25}H_{31}NO_2$: C, 79.54; H, 8.28; N, 3.71. Found: C, 79.58; H,8.19; N, 3.76.

4.5.2.7. [(*E*)-(*R*)-1-Isopropyl-4-methylene-6-phenyl-hex-2-enyl]-carbamic acid *tert*-butyl-ester 15c. Vinylbromide **6c** (68 mg, 0.3 mmol) was reacted with **3c** (70 mg, 0.15 mmol). Purification [petroleum ether/ethyl acetate=15:1] gave **15c** (27 mg, 58%) as a colorless oil.

Compound (**15c**): ^{1}H NMR (200 MHz) δ: 0.89 [d, $J=6.6$ Hz, 3H]; 0.91 [d, $J=6.6$ Hz, 3H]; 1.45 [s, 9H]; 1.64–1.84 [m, 1H]; 2.45–2.52 [m, 2H]; 2.76–2.83 [m, 2H]; 4.01 [br s, 1H]; 4.47 [br s, 1H]; 4.96–5.01 [m, 1H]; 5.58 [dd, $J=6.6$, 16.2 Hz, 1H]; 6.18 [d, $J=16.2$ Hz, 1H]. ^{13}C NMR (50.3 MHz) δ: 18.35; 18.81; 28.46; 29.73; 32.85; 34.69; 38.78; 57.93; 79.31; 115.42; 125.83; 128.29 (x2); 130.80; 132.64; 144.79; 155.12. MS *m/z* (%): 287 (4); 91 (100). $[\alpha]_D^{23}$ −5.3=1.3 $CHCl_3$). Anal. Calcd for $C_{21}H_{31}NO_2$: C, 76.55; H, 9.48; N, 4.25. Found: C, 76.71; H, 9.53; N, 4.33.

4.5.2.8. [(*E*)-4-methylene-non-2-enyl]-carbamic acid *tert*-butyl-ester 16a. Vinyl-bromide **6d** (76 mg, 0.4 mmol) was reacted with **3a** (100 mg, 0.2 mmol). Purification [petroleum ether/ethyl acetate=15:1] gave **16a** (42 mg, 74%) as a colorless oil.

Compound (**16a**): ^{1}H NMR (400 MHz) δ: 0.89 [t, $J=5.6$ Hz, 3H]; 1.21–1.42 [m, 6H]; 1.45 [s, 9H]; 2.16 [t, $J=7.6$ Hz, 3H]; 3.85–3.76 [br m, 1H]; 4.56 [br s, 1H]; 4.90–5.00 [m, 2H]; 5.67 [dt, $J=15.4$, 6.0 Hz, 1H]; 6.16 [d, $J=15.4$ Hz, 1H]. ^{13}C NMR (50.3 MHz) δ: 14.04; 22.52; 27.83; 28.39; 31.79; 32.05; 42.75; 79.33; 115.15; 125.33; 133.84; 145.68; 155.18. MS *m/z* (%): 197 (2); 57 (100). Anal. Calcd for $C_{15}H_{27}NO_2$: C, 71.10; H, 10.74; N, 5.53. Found: C, 70.83; H,10.66; N, 5.59.

4.5.2.9. [(*E*)-(*R*)-1-benzyl-4-methylene-non-2-enyl]-carbamic acid *tert*-butyl-ester 16b. Vinyl-bromide **6d** (78 mg, 0.4 mmol) was reacted with **3b** (116 mg, 0.2 mmol). Purification [petroleum ether/ethyl acetate=15:1] gave **16b** (38 mg, 51%) as a colorless oil.

Compound (**16b**): ^{1}H NMR (400 MHz) δ: 0.98 [t, $J=6.6$ Hz, 3H]; 1.33–1.55 [m, 6H]; 1.48 [s, 9H]; 2.21 [t, $J=7.8$ Hz, 2H]; 2.90–2.99 [m, 2H]; 4.56 [br s, 1H]; 4.88–5.12 [m,2H]; 5.68 [dd, $J=6.0$, 15.6 Hz, 1H]; 6.17 [d, $J=15.6$ Hz, 1H]; 7.22–7.38 [m, 5H]. ^{13}C NMR (50.3 MHz) δ: 14.05; 22.52; 27.88; 28.30; 31.75; 31.10; 41.99; 52.98; 79.20; 115.27; 126.42; 128.69; 128.90; 129.58; 132.36; 137.43; 145.60; 155.11. MS *m/z* (%): 287 (6); 57 (100). ν_{max}: 3432, 1706. $[\alpha]_D^{28}$ −0.6 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{22}H_{33}NO_2$: C, 76.92; H, 9.68; N, 4.08. Found: C, 76.87; H, 9.63; N, 4.04.

4.6. Synthesis of Boc-Gly-ψ[(*E*)-CH=CH]-(*rac*)-Ala-(L)-Phe-OMe 19a and Boc-(L)-Phe-ψ[(*E*)-CH=CH]-(*rac*)-Ala-(L)-Phe-OMe 19b

4.6.1. Reduction: general procedure. Dienamines **14a**,**b** (1 equiv) were dissolved in THF and stirred overnight with 9-BBN (0.5M in THF, 1 equiv), then treated with NaOH (0.1 M) and H_2O_2 (35%, 0.1 mL), heated at 50°C and reacted for 1 h. After dilution with ethyl acetate and washing with K_2CO_3 saturated solution, the organic phase was dried, evaporated and purified by flash chromatography.

4.6.1.1. [(*E*)-(*R,S*)-(4-methyl-5-hydroxy-pent-2-enyl)-carbamic acid tert-butyl ester (17a). Dienamine **14a** (180 mg, 0.9 mmol) in THF (1.5 mL) was reacted with 9-BBN (0.9 mmol), then with NaOH and H_2O_2 (35%, 0.1 mL). Purification [petroleum ether/ethyl acetate=10:1] gave **17a** (86 mg, 44%) as an oil.

Compound (**17a**): ^{1}H NMR (200 MHz) δ: 0.97 [d, $J=7.0$ Hz, 3H]; 1.43 [s, 9H]; 1.89 [br s, 1H]; 2.30 [sept, $J=7.0$ Hz, 1H]; 3.34-3.56 [m, 2H]; 3.61-3.84 [m, 2H]; 4.75 [br s, 1H]; 5.30-5.71 [m, 2H]. ^{13}C NMR (50.3 MHz) δ: 16.23; 28.35; 39.28; 42.57; 67.11; 79.40; 127.68; 134.78; 155.81. MS *m/z* (%): 127 (57); 56 (100). Anal. Calcd for $C_{11}H_{21}NO_3$: C, 61.37; H, 9.83; N. 6.51. Found: C, 61.55; H, 9.79; N, 6.53.

4.6.1.2. [(*E*)-(*1S*)-(*4R,S*)(1-Benzyl-4-methyl-5-hydroxy-pent-2-enyl)-carbamic acid tert-butyl ester (17b). Dienamine **14b** (202 mg, 0.7 mmol) in THF (1.5 mL) was reacted with 9-BBN (0.7 mmol), then with NaOH and H_2O_2 (35%, 0.1 mL). Workup and purification [petroleum ether/ethyl acetate=10:1] gave **17b** as a 1:1 diastereomeric mixture (79 mg, 37%).

Compound (**17b**): ^{1}H NMR (400 MHz) δ: 0.90 (0.93) [d, J=6.8 Hz, 3H]; 1.40 (1.41) [s, 9H]; 2.19–2.40 [m, 1H]; 2.66–2.97 [m, 2H]; 3.16–3.32 [m, 1H]; 3.33–3.48 [m, 1H]; 4.27–4.33 [br Fm, 1H]; 4.57 [br d, 1H]; 5.33–5.24 (5.31–5.21) [m, J_{AB}=15.4, J_{BX}=7.4 Hz, 1H]; 5.34–5.49 [m, J_{AB}=15.4, J_{AX}=6.2 Hz, 1H]; 7.40–7.10 [m, 5H]. ^{13}C NMR (50.3 MHz) δ: 16.04 (16.15); 24.57; 28.32; 39.44; 41.60 (41.67); 53.78; 66.94; 79.50; 126.50; 128.34; 129.49; 131.01 (131.22); 137.61 (137.86); 155.18 (155.27). MS *m/z* (%): 158 (43); 91 (92); 56 (100). Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N. 4.59. Found: C, 70.64; H, 8.77; N, 4.63.

4.6.2. Oxidation: general procedure. A stock solution of H_5IO_6 (0.4 M, 2.5 equiv) and CrO_3 (0.5% mol) in wet acetonitrile was added dropwise to a cooled solution of amino alcohols **17a**,**b** in wet acetonitrile. The reaction mixture was stirred for 30 min. then quenched with phosphate buffer. After dilution with ethyl acetate the organic layer was separated, washed with brine/aqueous $NaHSO_3$ (0.4 M)/brine and then dried. Crude acids **19a**,**b** were dissolved in CH_2Cl_2, cooled at 0 °C and reacted with (L)-phenylalanine methyl ester (1.5 equiv), DIPEA (3 equiv) and diethylcyanophosphonate at room temperature overnight. Dilution with ethyl acetate, washing with water and evaporation afforded crude **20a**,**b** which were purified by flash chromatography.

4.6.2.1. Boc-Gly-ψ-[(*E*)-CH=CH]-(*rac*)-Ala-(*S*)-Phe-OMe (19a). Oxidation of **17a** (67 mg, 0.3 mmol) and coupling with (L)-phenylalanine methyl ester (94 mg, 0.45 mmol) gave, after purification [petroleum ether/ethyl acetate=1:3], **19a** (53 mg, 44%) as a white solid.

Compound (**19a**): ^{1}H NMR (200 MHz) δ: 1.22 (1.23) [d, J=7.0 Hz, 3H]; 1.45 (1.46) [s, 9H]; 2.83–3.00 [m, 1H]; 3.04–3.19 [m, 2H]; 3.64–3.75 [m, 2H]; 3.73 [s, 3H]; 4.53 [br s, 1H]; 4.76–5.89 [m, 1H]; 5.51–5.60 [m, 2H]; 6.01 [br s, 1H]; 7.03–7.19 [m, 5H]. ^{13}C NMR (50.3 MHz) δ: 17.57; 28.42; 32.54; 42.31; 43.90; 52.87 (52.34); 55.97; 79.28; 127.11; 128.47; 129.22; 129.49; 131.53; 136.22; 156.12; 171.89; 173.34.

4.6.2.2. Boc-(L)Phe-ψ-[(*E*)-CH=CH]-(*rac*)-Ala-(*S*)-Phe-OMe (19b). Oxidation of **17b** (63 mg, 0.20 mmol) and coupling with (L)-phenylalanine methyl ester (83 mg, 0.43 mmol) gave, after purification [petroleum ether/ethyl acetate=1:3], **19b** (46 mg, 48%) as a white solid.

Compound (**19b**): ^{1}H NMR (200 MHz) δ: 1.16 [d, J=6.8 Hz, 3H]; 1.40 (1.39) [s, 9H]; 2.76–3.19 [m, 2H+1H+2H]; 3.72 [s, 3H]; 4.22–4.47 [m+ br s, 1H+1H]; 4.67–4.76 [m, 1H]; 5.46–5.12 [m, 2H]; 6.03 [br s, 1H]; 7.03–7.29 [m, 10H]. ^{13}C NMR (50.3 MHz) δ: 173.32; 171.92; 155.04; 137.25; 135.99; 132.53; 130.13; 129.47; 129.24; 128.45; 128.34; 127.03; 126.47; 79.49; 53.11; 52.98; 52.29; 43.93 (43.86); 41.51; 37.73; 28.39; 17.13 (16.97).

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