Palladium-Catalyzed Allylic Alkylations as Versatile Tool for Amino Acid and Peptide Modifications

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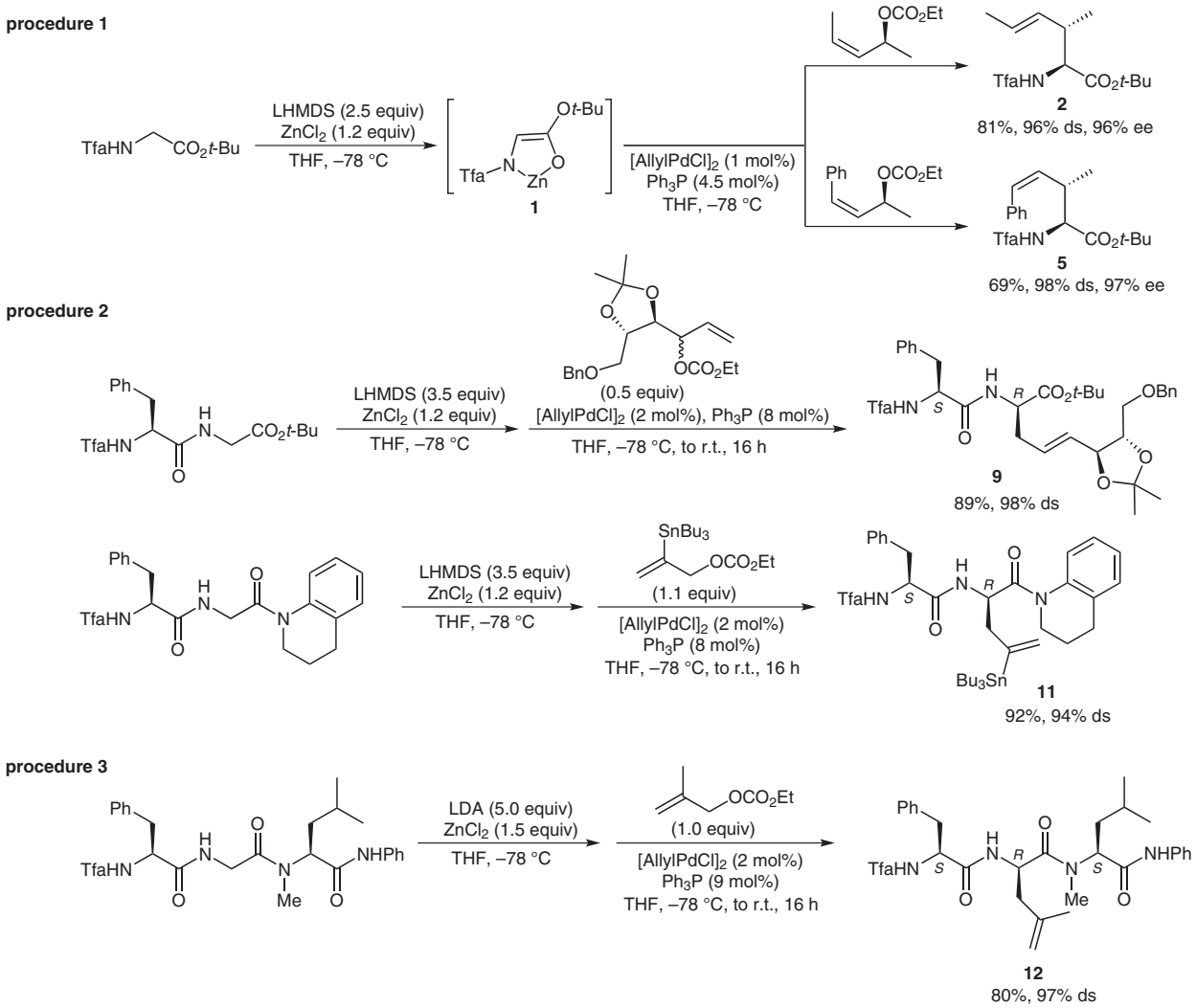
Abstract: Palladium-catalyzed allylic alkylations are especially suitable for the introduction of γ,δ-unsaturated side chains into amino acids and even peptides. Glycine ester enolates are generally used as nucleophiles in these reactions, they react at a very low temperature (–78 °C) to give the products of isomerization-free allylation. In reactions of *cis*-configured allylic substrates, the olefin geometry can be transferred to the product. Because the *syn* position of the corresponding *syn*/*anti* π-allyl complex formed in this case is more reactive, this isomerization-free protocol also allows regioselective and stereoselective allylations. Using stannylated allylic substrates gives metalated amino acid derivatives that are ideal substrates for subsequent Stille couplings or tin–iodine exchange reactions. If peptides are deprotonated with excess strong base, the corresponding ester or amide enolates formed can also be subjected to allylation; in this case the stereochemical outcome can be controlled by the peptide chain.

Key words: allylic alkylations, amino acids, enolates, peptides, peptide modifications, palladium



Scheme 1 Stereoselective palladium-catalyzed allylic alkylations for the modification of amino acids and peptides

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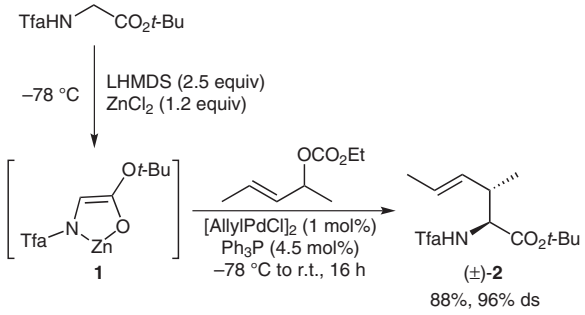
Introduction

π-Allyl–palladium complexes play an important role in modern organic synthesis;[1] with respect to their various synthetic applications, allylic substitution is probably one of the most popular. Herein, a π-allyl complex is attacked by a nucleophile such as an amine or a stabilized carbanion (in most cases malonate). In contrast to symmetrical malonates, unsymmetric nucleophiles, such as β-keto esters, are more critical, generally giving diastereomeric mixtures. Chelated enolates **1** (see Scheme 1 and Scheme 2), obtained by deprotonation of protected amino acid esters, are an exception; due to their fixed enolate geometry, their conversion often proceeds with a high degree of stereoselectivity. In addition, chelation causes a marked enhancement of thermal stability without decreasing the reactivity of these enolates. Excellent results are obtained in typical enolate reactions, such as aldol[2] or Michael additions,[3] as well as in palladium-catalyzed allylic alkylations.[4]

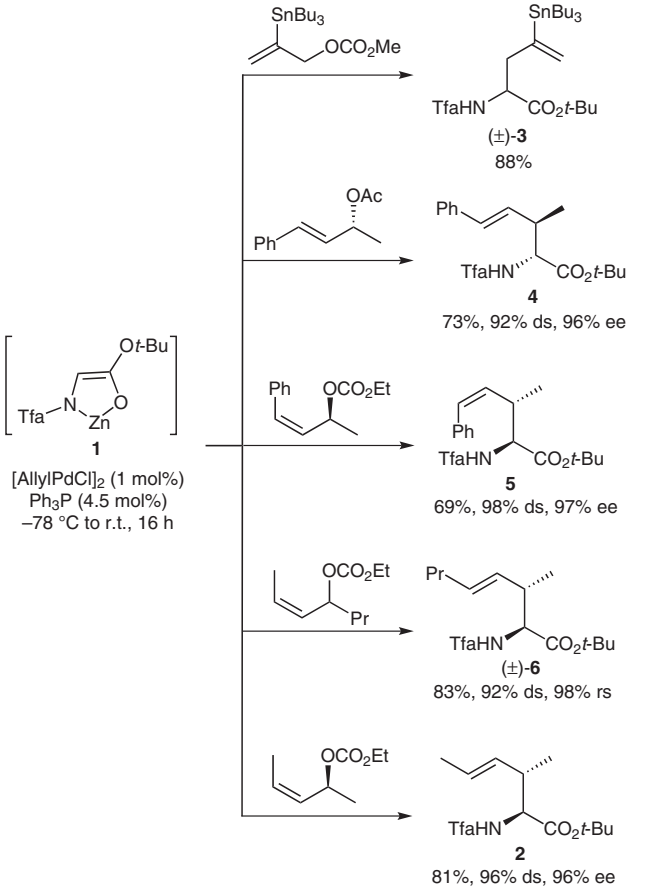
Besides allyl carbonates, the corresponding carboxylates can also be used, but with the more reactive carbonates the yields and selectivities are usually better. The trifluoroacetyl (Tfa) group is the best N-protecting group with respect to yield and selectivity. As a result of the high reactivity of the chelated enolates, allylations take place under very mild conditions at –78 °C or even below, this has an extremely positive effect on the selectivity of the reaction. In general, the *anti* products are formed with excellent stereoselectivity (Scheme 2).[5]



Scheme 2 Stereoselective palladium-catalyzed allylic alkylation of chelated glycine ester enolate **1**

Scope and Limitations

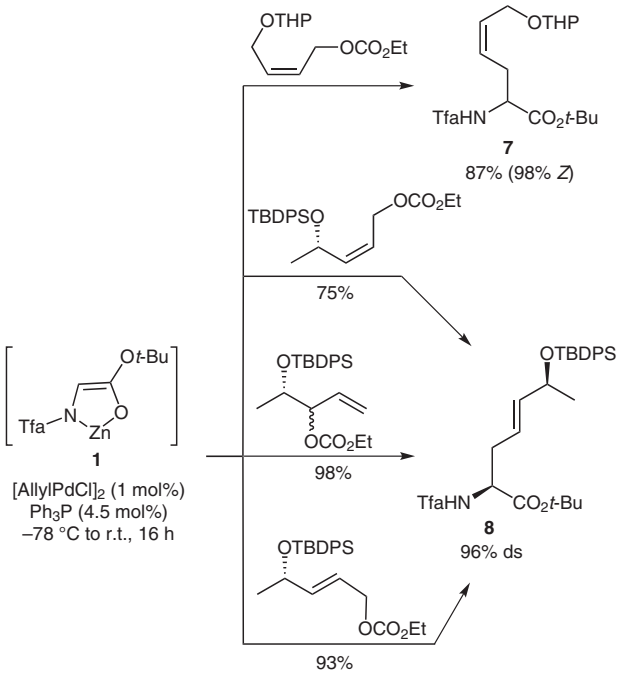
This protocol allows the straightforward introduction of a wide range of side chains into the glycine unit, but an even more flexible concept would be the introduction of a side chain that can be further modified at a later stage. This can easily be accomplished by using stannylated allylic substrates (Scheme 3), giving amino acids with a vinylstannane in the side chain, such as **3**,[6] which can be subjected to Stille couplings or tin–halogen exchange.[7]



Scheme 3 Isomerization-free regio- and stereoselective palladium-catalyzed allylic alkylation of chelated glycine ester enolate **1**

If allyl derivatives with different substituents are used, unsymmetrical π-allyl–palladium complexes are formed, which can be attacked by the nucleophile at both allylic positions. Although this can be problematic, these substrates also have the advantage that if optically active allyl substrates are used, the π-allyl–palladium complexes formed are chiral, and nucleophilic attack on these complexes provides optically active substitution products such as **4**. With the chelated enolate **1** an almost perfect transfer of chirality is observed.[5]

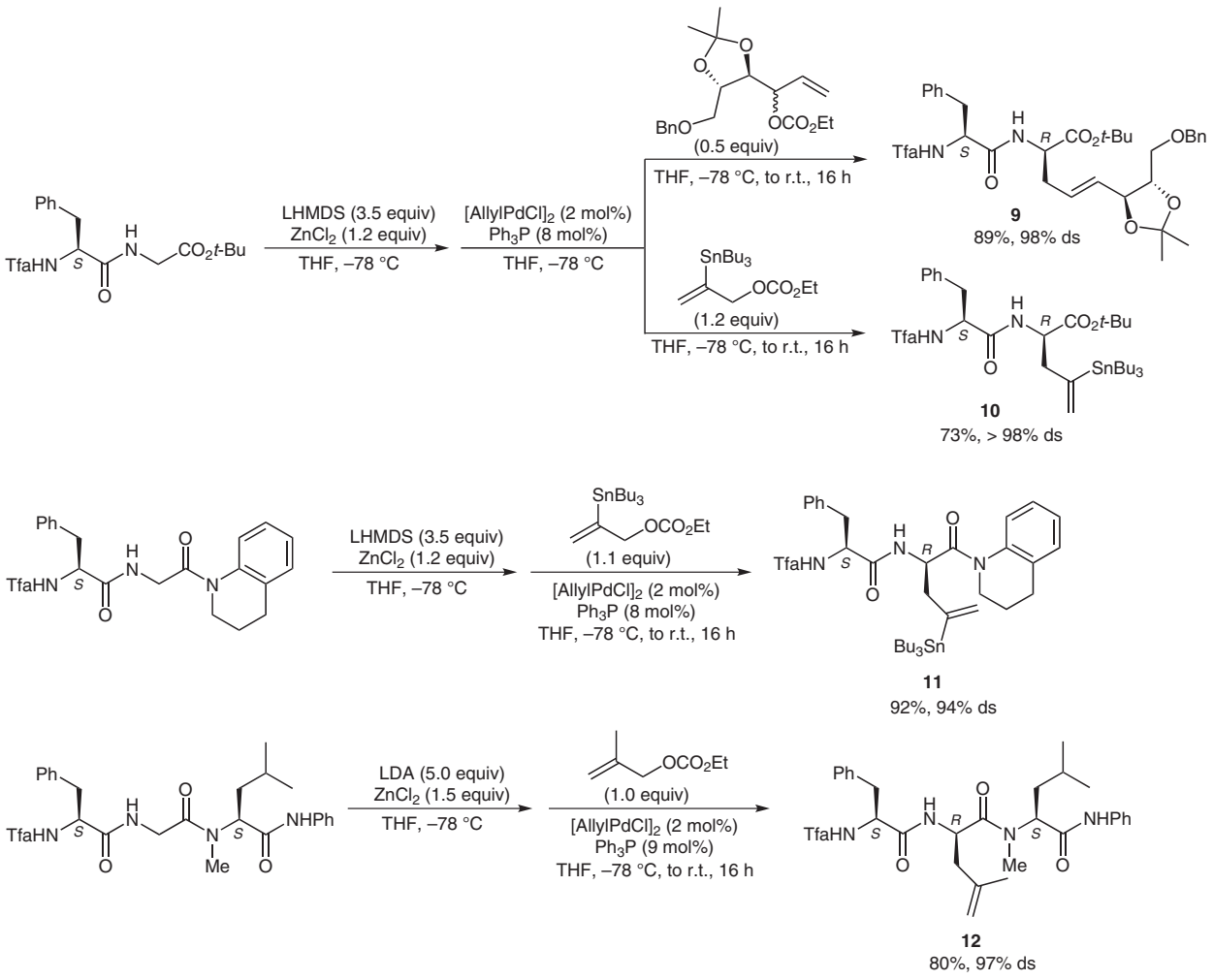
In general, the diastereoselectivities obtained with allylic acetates are worse in comparison to those obtained with carbonates. This can be explained by the higher reactivity of the carbonates, which react at –78 °C (or even lower). Therefore, the high reactivity of these enolates can also be used to suppress isomerization processes of the π-allyl complexes formed as intermediates.[8] The reaction with *Z*-carbonates almost exclusively yields the desired *Z*-substitution product **5**, with selectivities even higher than those obtained with the *E*-carbonates. In contrast, the corresponding acetates furnish *E*/*Z*-mixtures in lower yields. The selectivities are markedly worse than those obtained with the carbonates, clearly indicating that with acetates both processes, direct allylic substitution and isomerization, compete, while the carbonates react isomerization-free.[9]



Scheme 4 Allylic alkylation via terminal π-allyl–palladium complexes

In these cases the regioselectivity in the allylation step can be explained by the preferred formation of the conjugated double bond in, for example, **4** and **5**. Without such a conjugation effect (no aryl substituent) the formation of regioisomeric mixtures might be expected, but the *anti* position is more reactive allowing regioselective (rs) substitutions to give **6**.[10] This advantage can also be used to stereoselectively introduce allyl fragments bearing two identical substituents at the allylic positions in **2**,[9] which is only possible with *Z*-substrates, while *E*-substrates result in the formation of achiral π-allyl complexes.

Terminal π-allyl complexes show an even higher tendency towards isomerization than 1,3-disubstituted derivatives. But also with tetrahydropyranyl-protected (*Z*)-but-2-ene-1,4-diol carbonates the required amino acids **7** are obtained with near perfect transfer of the olefin geometry (Scheme 4).[11] Comparable results are obtained with chiral substrates, which also showed significant chiral induction from the allyl substrate to the α-position of the newly formed amino acid. The chiral induction depends on the steric demands of the protecting group, and the best results are obtained with the very demanding *tert*-butyldiphenylsilyl (TBDPS) group, but with such substrates isomerization occurs, giving *trans*-configured products **8**



Scheme 5 Stereoselective palladium-catalyzed allylic alkylation of peptide enolates

with excellent diastereoselectivity. In this case, the stereochemical outcome is independent of the allylic substrate used (*E* or *Z*, linear or branched allylic carbonates) as the reaction proceeds via the same π-allyl intermediate.[12]

The high isomerization tendency of terminal π-allyl complexes makes them good candidates for nucleophile controlled allylic alkylations. Therefore, this approach is especially suitable for the diastereoselective allylation of peptides, where the stereochemical outcome can be controlled by the peptide chain (Scheme 5). An *S*-amino acid in the peptide chain results in the generation of an *R*-stereogenic center in the allylation step giving **9**. The best results are obtained with peptide esters containing aromatic and sterically demanding amino acids.[13] With stannylated allyl carbonates the stannylated peptides **10** are obtained as a single stereoisomer.[14]

This protocol is not limited to peptide esters, generating a C-terminal ester enolate, but can also be applied to secondary peptide amides **11**. The results obtained with terminal amides are comparable to those obtained with esters.[15] This also allows stereoselective allylations in the middle of a peptide chain, as long as the glycine subunit is connected to a proline or an N-alkylated amino acid such as in the formation of **12**. Excellent enantioselectivities are obtained with all-*S*-configured peptides (double stereoinduction).[16]

Herein we describe three different procedures for the stereoselective allylic alkylation of glycine and peptide enolates. Procedure 1 is the standard procedure used for the allylation of glycine ester enolates. This protocol can be used for a very wide range of substrates and is generally applicable. Procedures 2 and 3 should be used for the modifications of peptide enolates, independently if ester or amide enolates are generated. These procedures mainly differ in the amount of base used, depending on the length of the peptide chain.

All reactions were carried out in oven-dried glassware (100 °C) under argon. All solvents were dried before use. THF was distilled from $LiAlH_4$ or Na. The products were purified by flash chromatography on silica gel. TLC: commercially precoated Polygram® SIL-G/UV 254 plates. Visualization was accomplished with UV-light, I_2, and $KMnO_4$ soln. Melting points are uncorrected. Selected signals in the NMR spectra for the minor isomers are extracted from the spectra of the isomeric mixture. Enantiomeric and diastereomeric excesses were determined by GC using a Chirasil-L-Val capillary column. Helium was used as carrier gas. Diastereomeric ratios were also determined by analytical HPLC using a Trentec Reprosil-100 Chiral-NR 8-mm column. Optical rotations were measured on a Perkin–Elmer polarimeter PE 341. Chemical ionization (CI) mass spectra were performed on a Finnigan MAT 95.

Palladium-Catalyzed Allylic Alkylations of Chelated Glycine Ester Enolate; General Procedure 1

A soln of LHMDS was prepared from HMDS (111 mg, 0.69 mmol) and 1.6 M BuLi (0.39 mL, 0.625 mmol) in THF (1 mL) at –20 °C. This soln was cooled to –78 °C, and then it was added to a soln of the protected amino acid ester (0.25 mmol) in THF (1 mL). After 20 min at –78 °C a soln of $ZnCl_2$ (38 mg, 0.275 mmol) in THF (1 mL) was added under vigorous stirring, and after an additional 30 min a soln of $[allylPdCl]_2$ (1 mg, 2.5 μmol, 1 mol%), Ph_3P (3 mg, 11.3 μmol, 4.5 mol%), and the corresponding allylic ester (0.5 mmol) in THF (3 mL) was added. The soln was stirred and warmed up to r.t. in the cooling bath overnight. Subsequently, the soln was diluted with Et_2O and hydrolyzed with 1 M $KHSO_4$ soln. The aqueous phase was extracted with Et_2O (2 ×), and the combined organic phases were dried (anhyd Na_2SO_4). After evaporation of the solvent, the crude product was purified by column chromatography (silica gel).

***tert*-Butyl (2*S*,3*S*,*E*)-3-Methyl-2-[(trifluoroacetyl)amino]hex-4-enoate (2)**[5b]

According to general procedure 1 using Tfa-Gly-O*t*-Bu (57 mg, 0.25 mmol) and ethyl (*S*,*Z*)-pent-3-en-2-yl carbonate (79 mg, 0.5 mmol) with purification by flash chromatography (hexanes–EtOAc, 9:1) to give ester **2** as a colorless oil; yield: 65 mg (0.22 mmol, 88%); ratio *anti*/*syn* 96:4; $[\alpha]_D^{20}$ +21.7 (*c* 1.0, $CHCl_3$, 96% ds, 96% ee).

GC (Chirasil-L-Val, 80 °C, isothermic): t_R = 17.39 (2*R*,3*R*), 17.95 (2*R*,3*S*), 23.21 (2*S*,3*S*), 24.60 min (2*S*,3*R*).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.03 (d, *J* = 6.9 Hz, 3 H), 1.45 (s, 9 H), 1.65 (d, *J* = 6.3 Hz, 3 H), 2.75 (m, 1 H), 4.42 (dd, *J* = 8.7, 4.7 Hz, 1 H), 5.24 (dd, *J* = 15.3, 7.7 Hz, 1 H), 5.52 (dqd, *J* = 15.3, 6.3, 1.0 Hz, 1 H), 6.65 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.4, 17.6, 27.7 (3 C), 39.4, 57.0, 82.8, 115.6 (J_{FC} = 286 Hz), 128.0, 129.3, 156.7 (J_{FC} = 37 Hz), 168.8.

Anal. Calcd for $C_{13}H_{20}F_3NO_3$ (295.30): C, 52.88; H, 6.83; N, 4.74. Found C, 52.85; H, 6.60; N, 4.71.

***tert*-Butyl 4-(Tributylstannyl)-2-[(trifluoroacetyl)amino]pent-4-enoate (3)**[7d]

According to general procedure 1 using Tfa-Gly-O*t*-Bu (57 mg, 0.25 mmol) and methyl 2-(tributylstannyl)allyl carbonate (83 mg, 0.205 mmol) with purification by flash chromatography (hexanes–EtOAc–Et_3N, 95:4:1) to give ester **3** as a colorless oil; yield: 100 mg (0.180 mmol, 88%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.81–0.96 (m, 15 H), 1.23–1.36 (m, 6 H), 1.49 (s, 9 H), 1.42–1.55 (m, 6 H), 2.49 (dd, *J* = 14.1, 9.4 Hz, 1 H), 2.85 (dd, *J* = 14.2, 9.1 Hz, 1 H), 4.36 (m, 1 H), 5.25 (s, J_{SnH} = 57 Hz, 1 H), 5.70 (s, J_{SnH} = 127 Hz, 1 H), 6.52 (d, *J* = 6.0 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.9 (J_{SnC} = 327 Hz), 13.4, 27.1 (J_{SnC} = 57 Hz), 28.7 (J_{SnC} = 20 Hz), 27.7, 43.5 (J_{SnC} = 40 Hz), 52.4, 82.8, 115.5 (J_{FC} = 285 Hz), 129.0, 149.0, 156.1 (J_{FC} = 37 Hz), 169.4.

Anal. Calcd for $C_{23}H_{42}F_3NO_3Sn$ (555.9): C, 49.66; H, 7.61; N, 2.52. Found: C, 49.94; H, 7.72; N, 2.62.

***tert*-Butyl (2*R*,3*R*,*E*)-3-Methyl-5-phenyl-2-[(trifluoroacetyl)amino]pent-4-enoate (4)**[5b]

According to general procedure 1 using Tfa-Gly-O*t*-Bu (57 mg, 0.25 mmol) and (*R*,*E*)-4-phenylbut-3-en-2-yl acetate (55 mg, 0.25 mmol) with purification by flash chromatography (hexanes–EtOAc, 9:1) to give ester **4** as a colorless solid; yield: 64 mg (0.18 mmol, 71%); ratio *anti*/*syn* 92:8. Recrystallization (Et_2O–hexanes) provided a diastereomerically pure white powder; mp 93–95 °C; $[\alpha]_D^{25}$ –12.5 (*c* 1.2, $CHCl_3$, 92% ds, 96% ee).

GC (Chirasil-L-Val, 145 °C, isothermic): t_R = 17.92 (2*R*,3*R*), 18.30 (2*R*,3*S*), 19.96 (2*S*,3*S*), 20.67 min (2*S*,3*R*).

Anal. Calcd for $C_{18}H_{22}F_3NO_3$ (357.37): C, 60.50; H, 6.20; N, 3.92. Found: C, 60.50; H, 6.39; N, 3.82.

(2*R*,3*R*)-4

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17 (d, *J* = 6.9 Hz, 3 H), 1.47 (s, 9 H), 3.00 (m, 1 H), 4.59 (dd, *J* = 8.4, 4.7 Hz, 1 H), 6.04 (dd, *J* = 15.9, 7.8 Hz, 1 H), 6.46 (dd, *J* = 15.9, 1.0 Hz, 1 H), 6.90 (d, *J* = 8.0 Hz, 1 H), 7.20–7.33 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.2, 28.0, 40.0, 57.3, 83.4, 115.7 (J_{FC} = 287 Hz), 126.2, 128.5, 128.6, 127.7, 132.2, 136.7, 157.0 (J_{FC} = 37 Hz), 169.5.

(2*S*,3*R*)-4

^{1}H NMR (300 MHz, $CDCl_3$): δ (selected signals) = 1.20 (d, *J* = 6.9 Hz, 3 H), 1.46 (s, 9 H), 2.87 (m, 1 H), 4.56 (m, 1 H), 6.02 (dd, *J* = 15.9, 7.8 Hz, 1 H), 6.41 (d, *J* = 15.9 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.3, 28.0, 40.5, 57.1, 83.5, 127.6, 131.9, 168.9.

***tert*-Butyl (2*S*,3*S*,*Z*)-3-Methyl-5-phenyl-2-[(trifluoroacetyl)amino]pent-4-enoate (5)**[5b]

According to general procedure 1 using Tfa-Gly-O*t*-Bu (57 mg, 0.25 mmol) and ethyl (*S*,*Z*)-4-phenylbut-3-en-2-yl carbonate (41 mg, 0.2 mmol) with purification by flash chromatography (hexanes–EtOAc, 95:5) to give ester **5** as a colorless solid; yield: 49 mg (0.138 mmol, 69%); ratio *anti*/*syn* 98:2. Recrystallization (Et_2O–hexanes) provided an enantiomerically pure, white solid; mp 78–79 °C; $[\alpha]_D^{23}$ +3.5 (*c* 2.6, $CHCl_3$, 99% ds, 99% ee).

GC (Chirasil-L-Val, 140 °C, isothermic): t_R = 11.03 (2*R*,3*S*), 11.84 (2*S*,3*R*), 12.96 (2*R*,3*R*), 15.09 min (2*S*,3*S*).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (s, 9 H), 1.66 (d, *J* = 4.7 Hz, 3 H), 3.59 (m, 1 H), 4.74 (t, *J* = 8.6 Hz, 1 H), 5.60–5.69 (m, 2 H), 6.88 (d, *J* = 8.6 Hz, 1 H), 7.19–7.34 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.54, 27.36 (3 C), 52.86, 56.75, 82.84, 115.52 (J_{FC} = 286 Hz), 126.05, 127.18 (2 C), 127.49, 128.20 (2 C), 129.49, 138.83, 156.37 (J_{FC} = 37 Hz), 168.80.

Anal. Calcd for $C_{18}H_{22}F_3NO_3$ (357.37): C, 60.50; H, 6.20; N, 3.92. Found: C, 60.42; H, 6.44; N, 3.99.

***tert*-Butyl (*E*)-3-Methyl-2-[(trifluoroacetyl)amino]oct-4-enoate (6)**[10]

According to general procedure 1 using Tfa-Gly-O*t*-Bu (114 mg, 0.50 mmol) and ethyl (*Z*)-hept-2-en-4-yl carbonate(68 mg, 0.40 mmol) with purification by flash chromatography (hexanes–EtOAc, 92:8) to give ester **6** as a colorless oil; yield: 106 mg (0.33 mmol, 83%); ratio *anti*/*syn* 92:8.

GC (Chira-Si-L-Val, 140 °C, T_0 [3 min] = 100 °C, 2 °C/min to *T* = 180 °C): t_R = 19.82 (2*R*,3*S*), 20.56 (2*S*,3*R*), 22.50 (2*R*,3*R*), 23.01 min (2*S*,3*S*).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 7.4 Hz, 3 H), 1.04 (d, *J* = 7.0 Hz, 3 H), 1.34 (qt, *J* = 7.4 Hz, 2 H), 1.45 (s, 9 H), 1.96 (td, *J* = 6.9 Hz, 2 H), 2.76 (m, 1 H), 4.41 (dd, *J* = 8.6, 4.4 Hz, 1 H), 5.22 (dd, *J* = 15.4, 7.7 Hz, 1 H), 5.52 (dt, *J* = 15.4, 6.6 Hz, 1 H), 6.64 (d, *J* = 7.7 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.5, 16.8, 22.4, 27.8, 34.6, 39.5, 57.2, 83.0, 115.8 (J_{FC} = 288 Hz), 128.4, 133.7, 157.0 (J_{FC} = 37 Hz), 169.1.

Anal. Calcd for $C_{15}H_{24}F_3NO_3$ (323.36): C, 55.72; H, 7.48; N, 4.33; found: C, 55.96; H, 7.46; N, 4.37.

***tert*-Butyl (*Z*)-6-(Tetrahydro-2*H*-pyran-2-yloxy)-2-[(trifluoroacetyl)amino]hex-4-enoate (7)**[11]

According to general procedure 1 using Tfa-Gly-O*t*-Bu (114 mg, 0.50 mmol) and ethyl (*Z*)-4-(tetrahydro-2*H*-pyran-2-yloxy)but-2-enyl carbonate (60 mg, 0.26 mmol) with purification by flash chromatography (hexanes–EtOAc, 85:15) to give ester **7** as a colorless oil; yield: 83 mg (0.22 mmol, 87%); ratio *Z*/*E* 98:2; dr 55:45.

Anal. Calcd for $C_{17}H_{26}F_3NO_5$ (381.39): C, 53.54; H, 6.87; N, 3.67. Found: C, 53.18; H, 6.74; N, 3.58.

(*Z*)-7

Major diastereomer

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46 (s, 9 H), 1.47–1.57 (m, 4 H), 1.68 (m, 1 H), 1.78 (m, 1 H), 2.67 (m, 2 H), 3.55 (m, 1 H), 3.81 (m, 1 H), 4.11 (m, 2 H), 4.44 (m, 1 H), 4.67 (m, 1 H), 5.48 (m, 1 H), 5.76 (m, 1 H), 7.52 (d, *J* = 6.9 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.9, 25.3, 27.9, 29.4, 30.2, 52.6, 61.9, 62.6, 83.0, 98.7, 115.6 (J_{FC} = 286 Hz), 127.7, 129.7, 156.4 (J_{FC} = 38 Hz), 169.4.

Minor diastereomer

^{1}H NMR (300 MHz, $CDCl_3$): δ (selected signals) = 1.46 (s, 9 H), 3.50 (m, 1 H), 3.96 (dd, *J* = 12.4, 7.1 Hz, 1 H), 4.27 (dd, *J* = 6.1, 2.4 Hz, 1 H), 4.59 (m, 1 H), 7.27 (d, *J* = 5.6 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.6, 28.3, 29.5, 30.4, 52.5, 61.5, 62.6, 83.2, 96.4, 126.4, 130.3, 169.2.

(*E*)-7

Major diastereomer

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46 (s, 9 H), 1.47–1.57 (m, 4 H), 1.68 (m, 1 H), 1.78 (m, 1 H), 2.55 (m, 1 H), 2.65 (m, 1 H), 3.48 (m, 1 H), 3.82 (m, 1 H), 3.91 (dd, *J* = 12.8, 6.2 Hz, 1 H), 4.15 (dd, *J* = 12.8, 5.4 Hz, 1 H), 4.52 (m, 1 H), 4.58 (m, 1 H), 5.54 (m, 1 H), 5.63 (ddd, *J* = 15.4, 6.2, 5.4 Hz, 1 H), 6.88 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.4, 25.4, 28.0, 30.6, 34.6, 52.6, 62.2, 67.0, 83.5, 97.9, 115.6 (J_{FC} = 286 Hz), 125.3, 132.1, 156.4 (J_{FC} = 38 Hz), 169.2.

Minor diastereomer

^{13}C NMR (75 MHz, $CDCl_3$): δ (selected signals) = 19.4, 62.2, 66.9, 83.5, 97.9, 132.1.

***tert*-Butyl (2*S*,6*S*,*E*)-6-(*tert*-Butyldiphenylsiloxy)-2-[(trifluoroacetyl)amino]hept-4-enoate (8)**[12b]

According to general procedure 1 using Tfa-Gly-O*t*-Bu (114 mg, 0.50 mmol) and (*S*,*E*)-4-(*tert*-butyldiphenylsiloxy)pent-2-enyl ethyl carbonate (120 mg, 0.301 mmol) with purification by flash chromatography (hexanes–EtOAc, 93:7) to give ester **8** as a colorless oil; yield: 153 mg (0.28 mmol, 93%); $[\alpha]_D^{20}$ +15.2 (*c* 1.1, $CHCl_3$, 96% ds, 96% ee).

HPLC (OD-H, hexane–*i*-PrOH, 99.75:0.25, flow: 1.0 mL/min): t_R = 6.58 (2*R*,6*R*), 7.12 (2*R*,6*S*), 10.03 (2*S*,6*S*), 12.01 min (2*S*,6*R*).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.03 (s, 9 H), 1.06 (d, *J* = 6.3 Hz, 3 H), 1.44 (s, 9 H), 2.47 (m, 1 H), 2.57 (m, 1 H), 4.25 (m, 1 H), 4.46 (m, 1 H), 5.30 (dt, *J* = 15.1, 7.8 Hz, 1 H), 5.56 (dd, *J* = 15.1, 5.1 Hz, 1 H), 6.78 (d, *J* = 6.9 Hz, 1 H), 7.33–7.40 (m, 6 H), 7.606 (d, *J* = 6.9 Hz, 1 H), 7.609 (d, *J* = 6.9 Hz, 1 H), 7.650 (d, *J* = 6.9 Hz, 1 H), 7.653 (d, *J* = 6.9 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2, 24.1, 26.9, 28.0, 34.0, 52.5, 69.3, 83.3, 115.6 (J_{FC} = 288 Hz), 120.6, 127.47, 127.48, 129.58, 129.59, 134.0, 134.4, 135.82, 135.84, 140.2, 156.4 (J_{FC} = 37 Hz), 169.20.

Anal. Calcd for $C_{29}H_{38}F_3NO_4Si$ (549.71): C, 63.36; H, 6.97; N, 2.55. Found: C, 63.09; H, 7.04; N, 2.70.

Palladium-Catalyzed Allylic Alkylations of Dipeptides; General Procedure 2

To a soln of HMDS (233 mg, 1.44 mmol) in anhyd THF (2 mL) was added dropwise 1.6 M BuLi in hexanes (0.82 mL, 1.31 mmol) at –78 °C. The cooling bath was removed and the soln was allowed to warm up to r.t. In a second flask $ZnCl_2$ (57 mg, 0.42 mmol) was carefully dried in vacuo with a heatgun. After cooling to r.t. the corresponding dipeptide (0.375 mmol) was added dissolved in anhyd THF (2 mL). The freshly prepared LHMDS soln was cooled to –78 °C and the $ZnCl_2$/peptide soln was slowly added via syringe. In a third flask $[allylPdCl]_2$ (1.8 mg, 5.0 μmol) and Ph_3P (5.9 mg, 22.5 μmol) were dissolved in anhyd THF (0.5 mL), allylic carbonate (0.20–0.45 mmol) was added and the catalyst/carbonate soln was transferred to the cold zinc enolate via syringe. The excess dry ice was removed from the cooling bath and the mixture was allowed to warm to r.t. After diluting with Et_2O, the mixture was quenched by

the addition of 1 M HCl (sat. NH_4Cl if substrates with acid labile groups were used). The aqueous layer was extracted with Et_2O (2 ×) and the combined organic layers were dried (Na_2SO_4). The solvent was evaporated and the residue was purified by column chromatography.

***tert*-Butyl *N*-(Trifluoroacetyl)-(*S*)-phenylalanyl-(2*R*,4*E*)-2-amino-5-[(4*S*,5*S*)-5-(benzyloxymethyl)-2,2-dimethyldioxolan-4-yl]pent-4-enoate (9)**[12c]

According to general procedure 2 using Tfa-Phe-Gly-O*t*-Bu (140 mg, 0.375 mmol) and 1-[(4*S*,5*S*)-5-(benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]allyl ethyl carbonate (70.0 mg, 0.20 mmol) and purification by flash chromatography (hexanes–EtOAc, 93:7) to give dipeptide ester **9** as a colorless oil; yield: 113 mg (0.18 mmol, 89%); dr 98:2.

HPLC (Reprosil 100 Chiral-NR 8 mm, hexane–*i*-PrOH, 98:2, 1.0 mL/min): t_R = 12.17 (*S*,*S*,*S*,*S*), 15.09 min (*S*,*R*,*S*,*S*).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36 (s, 9 H), 2.24 (ddd, *J* = 14.4, 5.8, 5.8 Hz, 1 H), 2.35 (ddd, *J* = 14.4, 5.5, 5.5 Hz, 1 H), 2.95 (dd, *J* = 13.6, 8.4 Hz, 1 H), 3.04 (dd, *J* = 13.6, 5.9 Hz, 1 H), 1.33 (s, 3 H), 1.32 (s, 3 H), 3.46 (dd, *J* = 10.3, 4.3 Hz, 1 H), 3.50 (dd, *J* = 10.3, 5.3 Hz, 1 H), 3.73 (ddd, *J* = 8.4, 5.0, 4.3 Hz, 1 H), 4.04 (dd, *J* = 8.4, 6.3 Hz, 1 H), 4.41 (ddd, *J* = 7.8, 5.5, 5.5 Hz, 1 H), 4.50–4.55 (m, 3 H), 5.32–5.34 (m, 2 H), 6.00 (br s, 1 H), 7.10–7.30 (m, 11 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.9, 27.0, 27.9, 35.0, 38.7, 52.1, 54.8, 69.6, 73.6, 79.0, 79.7, 82.8, 109.3, 115.6 (J_{FC} = 287 Hz), 127.5, 127.7, 127.8, 128.1, 128.4, 128.9, 129.2, 132.1, 135.3, 137.7, 156.5 (J_{FC} = 38 Hz), 168.5, 169.5.

HRMS (CI): *m*/*z* $[M - C_4H_9]^+$ calcd for $C_{29}H_{32}F_3N_2O_4$: 577.2162; found: 577.2191.

***tert*-Butyl *N*-(Trifluoroacetyl)-(*S*)-phenylalanyl-(*R*)-[2-(tributylstannyl)allyl]glycinate (10)**[14a]

According to general procedure 2 using Tfa-Phe-Gly-O*t*-Bu (562 mg, 1.5 mmol) and ethyl 2-(tributylstannyl)allyl carbonate (755 mg, 1.8 mmol) with purification by flash chromatography (hexanes–EtOAc–Et_3N, 95:4:1) to give dipeptide ester **10** as a colorless solid; yield: 765 mg (1.09 mmol, 73%); dr >98:2; mp 55–56 °C; $[\alpha]_D^{20}$ –6.3 (*c* 1.0, $CHCl_3$, >98% ds).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84 (t, *J* = 7.3 Hz, 9 H), 0.89 (t, *J* = 8.1 Hz, J_{SnH} = 50.8, 6 H), 1.27 (tq, *J* = 7.3, 7.3 Hz, 6 H), 1.35 (s, 9 H), 1.40–1.54 (m, 6 H), 2.27 (dd, *J* = 14.1, 8.1 Hz, 1 H), 2.49 (dd, *J* = 14.1, 6.2 Hz, 1 H),), 2.97 (dd, *J* = 13.8, 7.9 Hz, 1 H), 3.06 (dd, *J* = 13.8, 5.8 Hz, 1 H), 4.49 (ddd, *J* = 7.7, 7.7, 5.5 Hz, 1 H), 4.58 (ddd, *J* = 7.5, 7.5, 6.2 Hz, 1 H), 5.12 (d, *J* = 1.3 Hz, J_{SnH} = 59.5, 1 H), 5.53 (d, *J* = 1.1 Hz, J_{SnH} = 128.0, 1 H), 5.77 (d, *J* = 7.6 Hz, 1 H), 7.11–7.25 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.6 (J_{SnC} = 328 Hz), 13.7, 27.4 (J_{SnC} = 57 Hz), 27.9, 29.0 (J_{SnC} = 19.7 Hz), 38.5, 44.1 (J_{SnC} = 40.3 Hz), 52.6 (J_{SnC} = 12.4 Hz), 54.5, 82.5, 115.6 (J_{FC} = 288 Hz), 127.5, 128.3 (d, J_{SnC} = 23.6 Hz), 128.9, 129.2, 135.3, 149.6, 156.6 (J_{FC} = 37.6 Hz), 168.4, 170.5.

^{119}Sn NMR (149 MHz, $CDCl_3$): δ = –43.7.

Anal. Calcd for $C_{32}H_{51}F_3N_2O_4Sn$ (703.46): C, 54.64; H, 7.31; N, 3.98. Found: C, 54.41; H, 6.97; N, 3.95.

***N*-(Trifluoroacetyl)-(*S*)-phenylalanyl-(*R*)-[2-(tributylstannyl)allyl]glycine 3,4-Dihydroquinolinide (11)**[15]

According to general procedure 2 using Tfa-Phe-Gly-(3,4-dihydro)quinolinide (100 mg, 0.23 mmol) and ethyl 2-(tributylstannyl)allylcarbonate (104 mg, 0.25 mmol) with purification by flash chromatography (hexanes–EtOAc, 8:2) to give dipeptide amide **11** as a colorless oil; yield: 102 mg (0.21 mmol, 92%); dr 94:6.

HPLC (Reprosil, hexanes–*i*-PrOH 95:5, 1 mL/min): t_R = 6.88 (*S*,*S*), 8.07 min (*S*,*R*).

HRMS (CI): *m*/*z* $[M - C_4H_9]^+$ calcd for $C_{33}H_{43}F_3N_3O_3Sn$: 706.2279; found: 706.2268.

(*S*,*R*)-11

^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.75–0.87 (m, 15 H), 1.22–1.29 (m, 6 H), 1.39–1.45 (m, 6 H), 1.77–1.84 (m, 1 H), 1.94–2.02 (m, 1 H), 2.38 (dd, *J* = 13.7, 7.6 Hz, 1 H), 2.56–2.64 (m, 2 H), 2.76 (dt, *J* = 16.0, 6.5 Hz, 1 H), 2.96 (dd, *J* = 14.0, 10.0 Hz, 1 H), 3.09 (dd, *J* = 14.0, 5.0 Hz, 1 H), 3.30–3.34 (m, 1 H), 4.03–4.10 (m, 1 H), 4.71–4.73 (m, 1 H), 5.02–5.06 (m, 1 H), 5.17 (d, *J* = 2.4 Hz, J_{SnH} = 63.9, 1 H), 5.66 (d, *J* = 2.4 Hz, J_{SnH} = 134.9, 1 H), 7.13 (dt, *J* = 7.0, 1.5 Hz, 1 H), 7.17–7.20 (m, 2 H), 7.23–7.28 (m, 5 H), 7.52 (dd, *J* = 8.0, 1.5 Hz, 1 H), 8.18 (d, *J* = 8.0 Hz, 1 H), 9.19 (br s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 8.6 (J_{SnC} = 324 Hz), 12.6, 23.0, 25.4, 25.9 (J_{SnC} = 53 Hz), 27.8 (J_{SnC} = 19 Hz), 36.7, 42.2, 42.7 (J_{SnC} = 40 Hz), 48.8, 54.1, 115.2 (J_{FC} = Hz), 123.8, 124.6, 125.4, 125.8, 127.3, 127.4, 127.8, 128.5, 132.2, 136.6, 138.1, 149.1, 155.5 (J_{FC} = 36 Hz), 168.6, 170.3.

(*S*,*S*)-11

^{1}H NMR (500 MHz, DMSO-d_6): δ (selected signals) = 3.99–4.03 (m, 1 H), 7.46 (dd, *J* = 8.0, 1.0 Hz, 1 H), 8.13 (d, *J* = 8.0 Hz, 1 H), 9.05 (br s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ (selected signals) = 12.7, 23.1, 49.2, 53.8, 123.6, 128.4, 149.2, 168.7.

Palladium-Catalyzed Allylic Alkylations of Tripeptides; General Procedure 3

A 1.6 M BuLi soln (0.63 mL, 1.0 mmol) was added to a soln of *i*-Pr_2NH (0.145 mL, 1.1 mmol) in THF (0.5 mL) in a Schlenk flask at –20 °C. The cooling bath was removed and stirring was continued for further 10 min before the mixture was cooled again to –78 °C. In a second Schlenk flask a mixture of N-protected tripeptide (0.20 mmol) and $ZnCl_2$ (41.7 mg, 0.31 mmol) was dissolved in THF (3 mL). This soln was added to the LDA soln at –78 °C and the mixture was warmed up to –40 °C over 30 min, and then the soln was cooled again to –78 °C and stirred for a further 15 min. The palladium catalyst (1.46 mg, 4.0 μmol) and Ph_3P (4.8 mg, 18.3 μmol) were dissolved in THF (0.2 mL). After stirring for 10 min at r.t. the allyl substrate (0.20 mmol) was added to the yellow soln thus formed, and the resulting mixture was added slowly to the chelated enolate at –78 °C. The soln was allowed to warm up to r.t. overnight, before it was diluted with EtOAc and 1 M $KHSO_4$ was added. After extraction with EtOAc, the organic layers were dried (Na_2SO_4), concentrated in vacuo and the crude product was purified by flash chromatography.

***N*-(Trifluoroacetyl)-(*S*)-phenylalanyl-(*R*)-4,5-dehydroleucyl-(*S*)-*N*-methylleucine Anilide (12)**[16]

According to general procedure 3 using Tfa-Phe-Gly-MeLeu-NHPh (208 mg, 0.40 mmol) and ethyl methallyl carbonate (58 mg, 0.40 mmol) with purification by flash chromatography (hexanes–EtOAc, 8:2) to give tripeptide amide **12** as a colorless solid; yield: 183 mg (0.32 mmol, 80%); mp 112–113 °C; dr 97:3; $[\alpha]_D^{20}$ –128.0 (*c* 1.0, $CHCl_3$).

HPLC (Reprosil, hexane–*i*-PrOH, 9:1 to 7:3, 40 min, 1 mL/min, 252 nm): t_R = 16.16 (*S*,*S*), 20.48 min (*S*,*R*).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.6 Hz, 3 H), 0.96 (d, *J* = 6.6 Hz, 3 H), 1.67 (m, 1 H), 1.73 (s, 3 H), 1.88–1.98 (m, 2 H), 2.23 (dd, *J* = 13.9, 9.1 Hz, 1 H), 2.33 (dd, *J* = 14.0, 5.7 Hz, 1 H), 3.07 (s, 3 H), 3.09–3.13 (m, 2 H), 4.70–4.82 (m, 3 H), 4.86 (m, 1 H), 5.30 (dd, *J* = 10.0, 5.4 Hz, 1 H), 6.46 (d, *J* = 5.6 Hz, 1 H), 7.08 (t, *J* = 7.4 Hz, 1 H), 7.17 (m, 2 H), 7.25–7.35 (m, 6 H), 7.59 (d, *J* = 7.6 Hz, 2 H), 8.29 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 21.9, 23.2, 24.9, 31.0, 36.1, 38.3, 39.8, 48.3, 54.3, 56.1, 115.5 (J_{FC} = 287.4 Hz), 115.7, 120.0, 124.3, 127.5, 128.8, 128.9, 129.1, 135.2, 137.9, 139.2, 156.7 (J_{FC} = 37 Hz), 168.3, 169.6, 172.9.

HRMS (CI): *m*/*z* [M + H]$^+$ calcd for $C_{30}H_{37}F_3N_4O_4$: 575.2840; found: 575.2798.

Anal. Calcd for $C_{30}H_{37}F_3N_4O_4$ (574.63): C, 62.70; H, 6.49; N, 9.75. Found: C, 62.78; H, 6.79; N, 9.33.

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