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PAPER

Highly stereoselective modifications of peptides *via* Pd-catalyzed allylic alkylation of internal peptide amide enolates†‡

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Pd-catalyzed allylations are excellent tools for stereoselective peptide modifications, showing several advantages compared to normal alkylations. Reactions of internal peptide amide enolates with Pd–allyl complexes proceed not only with high yields of up to 86%, they show also high regio- and diastereoselectivities (88–99%), giving rise to the *trans*-configured products. Therefore, this protocol is a powerful synthetic tool for the synthesis of natural product and drug molecules.

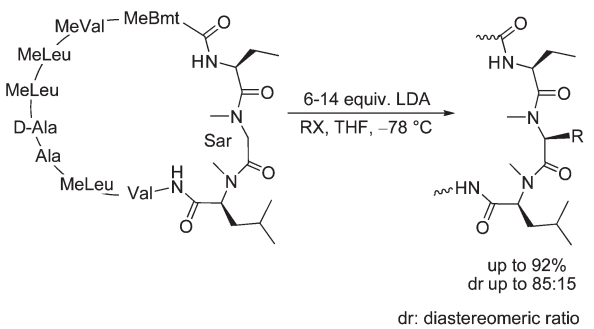
Introduction

Bacteria or marine organisms are an excellent source of peptide- and cyclopeptide-based natural products, containing a wide range of unusual amino acids.[1] Many of these contain also *N*-alkylated and (*R*)-amino acids as building blocks. In most cases, these secondary metabolites show interesting biological properties, and therefore some of them found application as drugs[2] or at least as lead structures for drug development. For the optimization of such lead structures highly flexible and modular concepts are desired. For example, the direct introduction of a side chain onto a given peptide, or the manipulation of a suitable functionalized side chain, represents a powerful alternative to classical peptide synthesis, since a multitude of modified analogues can be prepared from only one parent peptide precursor.[3]

While the modification of a functionalized side chain in general is not a big problem,[4] the direct introduction of a side chain onto a given peptide is not a trivial issue. Especially the stereoselective introduction of side chains was an unsolved problem in most cases so far. In principle, peptide-incorporated glycine cations,[5] radicals[6] as well as anions can be generated as reactive intermediates for further modifications. Especially the last approach was investigated intensively by Seebach *et al.*[7] Probably the most spectacular success was the regio- as well as stereoselective alkylation of the sarcosine (sar) subunit in cyclosporine (Scheme 1).[8] At this position, the secondary amide allowed the formation of an amide enolate, which could be reacted with electrophiles such as alkyl halides. Here, one face of the enolate is probably shielded by the deprotonated peptide ring, and therefore the attack of the electrophile occurs preferentially from the face opposite to the peptide ring. It should be mentioned that even with a large excess of base, no epimerization of the peptide occurs, because the *N*-methylated amino acids are not deprotonated for steric reasons, and the unmethylated amino acids are protected by deprotonation of the acidic NH-bonds.[7] In contrast to such cyclic peptides, modifications of linear peptides generally proceed unselectively, because of the high flexibility of the peptide chain.[9]

Our group has been also investigating stereoselective peptide modifications for some time, with the aim to apply these modifications to natural product and drug synthesis. Our major goal is to transfer the chiral information of a given peptide chain *via* metal peptide complexes to the newly formed stereogenic center.

We recognized that besides the chelate–enolate Claisen rearrangements[10] also palladium-catalyzed allylations of peptides give high yields and selectivities (Scheme 2).[11] In all examples investigated so far, an (*S*)-amino acid generated an (*R*)-amino acid and *vice versa*.[12] At the beginning, these reactions were limited to peptide esters, but recently we could show that such stereoselective allylic alkylations are also possible with



Scheme 1 Stereoselective cyclopeptide modifications according to Seebach *et al.*

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† Dedicated to Prof. Th. Eicher on the occasion of his 80th birthday.

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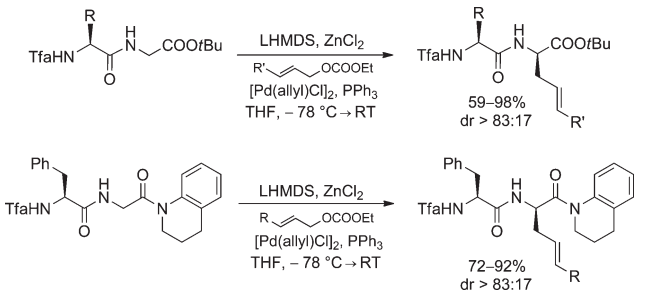
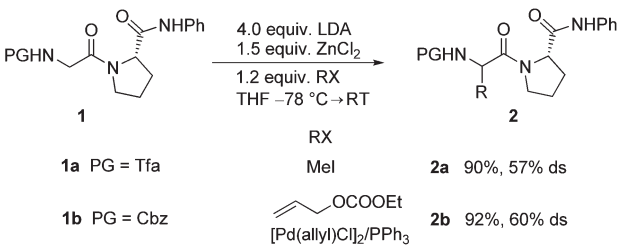


Scheme 2 Stereoselective peptide modifications *via* allylic alkylations.



Scheme 3 Modifications of proline dipeptides.

secondary amide enolates.[13] Originally, we began our investigations with alkylations of different protected (Cbz, Boc, Ts, Tfa) secondary dipeptide amides to figure out the best conditions for the required amide enolate modifications. Although good yields (70–90%) were obtained with all protecting groups used, no selectivity was observed in any case, independent of the alkylating agent used. Therefore, we switched to the Pd-catalyzed allylic alkylation which proved to be much better suited for stereoselective modifications than simple alkylations.[12] Based on our previous observations made with amino acid[14] and peptide ester enolates,[15] we chose the trifluoroacetyl (Tfa-) protected peptides as substrates. And indeed, with a wide range of allyl carbonates the allylation products were obtained in high yields and good diastereoselectivities, providing the (*S*,*R*)-configured peptides preferentially (Scheme 2).

Results and discussion

With these results in hand, we next tried to transfer these reaction conditions also to proline-containing tripeptides. As long as the stereogenic center of the proline has no influence on the stereochemical outcome of the allylation, one might have a chance to get similar results also with these larger peptides. Therefore, as a control experiment, we subjected dipeptides **1**[16] to both, a methylation and an allylic alkylation (Scheme 3). Both reactions proceeded very well, and, as we hoped, without significant selectivity.

This was an excellent precondition to switch to the corresponding tripeptides such as **3** (Table 1). And indeed, the results were comparable to those obtained with the dipeptides. Although both, LHMDS as well as LDA, can be used as a base, in the case of the tripeptides the stronger base LDA gave slightly better yields.

The stannylated allyl carbonate (entry 3) is an especially interesting substrate, not only because it provided only one stereoisomer, but also because the stannylated peptide **7c** is an ideal substrate for subsequent peptide modification *via* Stille couplings.[12]

In all other examples investigated so far the diastereoselectivity was in the range of 90% or better, relatively independent of the substitution pattern in the allylic substrate. The only exception was a functionalized substrate having an additional stereogenic center adjacent to the π-allyl complex formed (entry 4). Probably this has an influence on the stereoselectivity,[17] and we assume that we observe a mismatched situation here. Interestingly, in this case only the linear substitution product (**7d**$_l$) was formed, while the other monosubstituted linear substrates gave mixtures of linear (**7**$_l$) and branched products (**7**$_b$), while also here the linear product was the predominant one (entries 5–7).

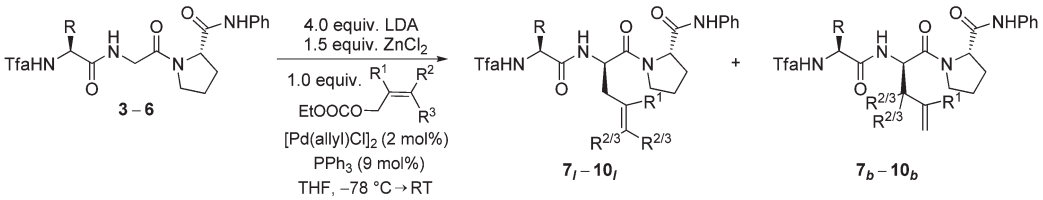
It should be mentioned that only the formation of the *trans*-configured product was observed by NMR, also with *cis*-configured substrates (entry 7). This clearly indicates that the π–σ–π-isomerization of the π-allyl intermediate is faster than the nucleophilic attack of the peptide enolate, which is in contrast to reactions of chelated amino acid ester enolates.[18] But with respect to the steric demand of the peptide enolates, this is not surprising. They react at slightly higher temperatures (−55 °C) than the amino acid ester enolates (−78 °C), allowing the isomerization to occur.

Disubstituted allylic substrates behave differently when compared to the monosubstituted ones. Isoprenyl acetate, for example, surprisingly gave rise to a significant amount of the branched product with a quaternary center at the β-position of the newly formed amino acid (entry 8). Obviously, a nucleophilic attack in an S_N1-type fashion is favored over the generally observed S_N2-type process.[19] Both regioisomers were formed with the same high diastereoselectivity and we assume that this is also true for the other examples, where we could determine only one stereoisomer for the minor branched products (entries 5–7). To prove the generality of our process we subjected also some other tripeptides (**4**–**6**) to allylations using methallyl carbonate (entries 9–11). The yields obtained were comparable in the range of 80% (±5%). While the Ile-peptide **6** was slightly less selective, with the *tert*-leucine (**7**) and the tyrosine derivative (**8**) the diastereomeric ratio (dr) exceeded 20 : 1, and it was difficult to identify the second diastereomer.

Therefore, for analytical purposes, we subjected peptides **3**–**6** also to "normal" allylations using methallyl bromide (Scheme 4). The yields obtained were comparable to the Pd-catalyzed process, but the allylations proceeded completely unselective. This clearly demonstrates the power and the advantages of the Pd-catalyzed version. Catalytic hydrogenations of these peptides gave rise to the leucine-peptides, which could be used to determine the configuration of the peptide formed. Also here, the N-terminal (*S*)-amino acid induces an (*R*)-configured amino acid and therefore an (*S*,*R*,*S*)-configuration can be assumed for the peptides **7**–**10**.

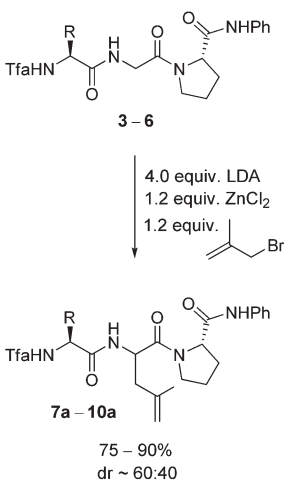
Although the C-terminal proline of the dipeptides **1** had no significant effect on the stereochemical outcome of the allylation reaction, in principle one might expect some influence of the C-terminal chiral amino acids as well. Therefore, we replaced the proline by *N*-alkylated leucine (*R* and *S*) and investigated the allylation of substrates **11** and **12** using methallyl carbonate (Table 2, entries 1 and 2). Two (*S*)-amino acids flanking the

Table 1 Modifications of tripeptide amides **3–6**



Entry	Substrate	R	R^1	R^2	R^3	Yield (%)	Product	Ratio[a] *l* : *b*	dr
1	**3**	Bn	Me	H	H	82	**7a**	—	92 : 8
2	**3**	Bn	Ph	H	H	73	**7b**	—	88 : 12
3	**3**	Bn	$SnBu_3$	H	H	75	**7c**	—	>99 : 1
4	**3**	Bn	H		H	67	**7d**	100 : 0	81 : 19
5	**3**	Bn	H	*n*Pr	H	75	**7e**	87 : 13	90 : 10
6	**3**	Bn	H	Ph	H	86	**7f**	96 : 4	92 : 8
7	**3**	Bn	H	H	$CH_2OTBDMS$	70	**7g**	93 : 7	97 : 3
8	**3**	Bn	H	Me	Me	54	**7h**	46 : 54	92 : 8[b]
9	**4**	*i*Bu	Me	H	H	80	**8a**	—	88 : 12
10	**5**	*t*Bu	Me	H	H	84	**9a**	—	96 : 4
11	**6**	*p*-MeOBn	Me	H	H	85	**10a**	—	96 : 4

[a] *l*: Linear product; *b*: branched product. [b] Diastereoselectivity of both products (*l* and *b*).



Scheme 4 Allylation of tripeptide amide enolates.

glycine led to the expected (*S*,*R*,*S*)-configured product **16a** with excellent diastereoselectivity (matched case), whereas a combination of an (*S*)- and an (*R*)-amino acid was completely unselective, resulting in the formation of product **17** as a nearly 1 : 1 mixture of both diastereomers (mismatched case). To show the generality of the observed stereoselectivity, the (*S*,*S*)-*N*-benzylated substrate **13** was also subjected to allylic alkylation. Despite the sterically crowded environment around the glycine unit the allylated product was obtained in quite acceptable yield with very high diastereoselectivity (entry 3). Next the employment of a sterically more hindered TMBDMSO-substituted allylic substrate was attempted with tripeptide **11** and provided the expected product **16b** with excellent diastereoselectivities in a slightly lower yield (entry 4). The variation of the N-terminal amino acid in the tripeptides containing a C-terminal *N*-methylleucine (**14**, **15**) had a relatively little influence on the diastereoselectivity (entries 5 and 6), giving rise to the (*S*,*R*,*S*)-products with ds values of 91–99%, being slightly lower for the alanine-containing peptide.

Furthermore Boc- and Cbz-protected analogues of tripeptides **11**, **14** and **15** were tested as substrates in the Pd-catalyzed tripeptide allylation with methallyl carbonate. The reactions proceeded with similar diastereoselectivities as with the Tfa-protected peptides but gave significantly lower yields (38–41%) along with several by-products (data not shown).

The absolute configuration of the allylation products **16–20** was confirmed by total hydrolysis, followed by derivatization of the fragments, GC-analysis on a chiral stationary phase (L-Chirasil-Val) and comparison with racemic references.

Conclusion

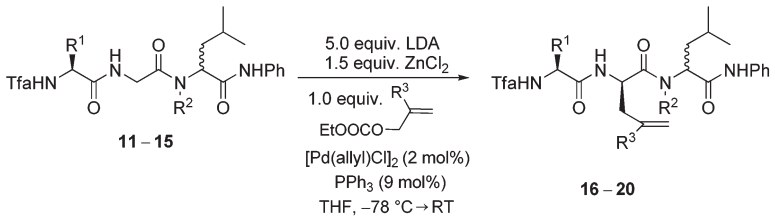
In conclusion, we have shown that the Pd-catalyzed allylation is an excellent tool for stereoselective peptide modifications, being clearly superior to normal alkylations. The reactions proceed not only in high yields, but also high regio- and diastereoselectivities, and *trans*-products are formed exclusively. Therefore, this is a powerful synthetic tool for natural product and drug synthesis. Further investigations using even larger peptides are currently in progress.

Experimental

General remarks

Optical rotations were measured with a Perkin-Elmer polarimeter (Model 341) at 20 °C using a sodium vapor lamp (λ = 589 nm). ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AC-400 [400 MHz (^{1}H) and 100 MHz (^{13}C)] spectrometer in $CDCl_3$. Compounds which showed a mixture of rotamers at room

Table 2 Modifications of tripeptide amides **11–15**



Entry	Substrate	R^1	R^2	R^3	Leu	Yield (%)	Product	dr
1	**11**	Bn	Me	Me	*S*	80	**16a**	97 : 3
2	**12**	Bn	Me	Me	*R*	78	**17**	49 : 51
3	**13**	Bn	Bn	Me	*S*	66	**18**	94 : 6
4	**11**	Bn	Me	$CH_2OTBDMS$	*S*	56	**16b**	97 : 3
5	**14**	Me	Me	Me	*S*	70	**19**	89 : 11
6	**15**	*i*Pr	Me	Me	*S*	71	**20**	>99 : 1

temperature, their spectra were recorded with a Bruker DRX-500 [500 MHz (^{1}H) and 125 MHz (^{13}C)] spectrometer at 80 °C (353 K) in DMSO-d_6. HRMS were recorded with a Finnigan MAT 95 spectrometer using a CI technique. Peptide substrates **3–6** and **11–15** were obtained by standard peptide coupling reactions. Diastereomeric ratios were measured using HPLC (Merck Hitachi) using a silica gel or Reprosil column. Total hydrolyses of tripeptides were carried out with 6 M HCl at 130 °C for 24 h, followed by esterification with *n*-propanol/cat. 4 M HCl at 110 °C and subsequent perfluoroacylation with trifluoroacetic anhydride/methyl trifluoroacetate (1 : 1) at 130 °C for 10 min. The fragments were separated on a chiral GC (L-Chirasil-Val, 80 °C, 4 min, 80–110 °C, 4 °C min^{-1}, 110–180 °C, 5 °C min^{-1}), detected with FID and identified by comparison with racemic references. Elemental analyses were performed at the Saarland University.

General procedure for palladium-catalyzed allylic alkylations of dipeptides

n-BuLi (1.6 M, 0.50 mL, 0.81 mmol) was added to a solution of HMDS (0.18 mL, 0.87 mmol) in THF (0.4 mL) in a Schlenk flask at −20 °C and stirred for 20 min. The cooling bath was removed and stirring was continued for a further 10 min before cooling again to −78 °C. In a second Schlenk flask a mixture of *N*-protected dipeptide (0.23 mmol) and $ZnCl_2$ (37.7 mg, 0.28 mmol) was dissolved in THF (1 mL). The solution was added to the LHMDS solution at −78 °C and stirring was continued for 30 min at −78 °C. A solution was prepared from the palladium catalyst (1.7 mg, 4.6 μmol) and triphenylphosphine (20.7 μmol) in THF (0.2 mL) and stirred at room temperature for 10 min before the allyl carbonate (0.16 mmol) was added. The resulting solution was added slowly to the chelated enolate at −78 °C. The mixture was allowed to warm up to room temperature overnight. The solution was diluted with ethyl acetate before 1 M $KHSO_4$ was added. After extraction with ethyl acetate the organic layers were dried over Na_2SO_4, concentrated *in vacuo* and the crude product was purified by column chromatography.

***N*-Benzyloxycarbonyl-(*R*/*S*)-allylglycyl-(*S*)-prolinanilide (2b).** According to the procedure for palladium-catalyzed allylic alkylations of dipeptides **2b** was obtained from **1b** (100 mg, 0.262 mmol) in 92% yield (101.5 mg, 0.241 mmol). Major diastereomer (60%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.14 (bs, 1 H, N*H*), 7.37 (d, J = 8.0 Hz, 2 H, Ar*H*), 7.26–7.18 (m, 5 H, Ar*H*), 7.21 (t, J = 8.0 Hz, 2 H, Ar*H*), 6.96 (t, J = 8.0 Hz, 1 H, Ar*H*), 5.73 (d, J = 8.4 Hz, 1 H, N*H*), 5.64 (m, 1 H, C*H*═CH_2), 5.01–4.93 (m, 4 H, PhCH_2, CH═CH_2), 4.67 (dd, J = 8.0, 2.0 Hz, 1 H, NC*H*), 4.54 (q, J = 8.0 Hz, 1 H, NHC*H*), 3.65 (m, 1 H, NCH_2), 3.55 (m, 1 H, NCH_2), 2.50–2.31 (m, 3 H, CH_2CH═CH_2, CH_2), 2.10 (m, 1 H, CH_2), 1.94 (m, 1 H, CH_2), 1.80 (m, 1 H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0 (*C*═O), 168.5 (*C*═O), 155.8 (O*C*═O), 138.0 (Ar*C*), 136.1 (Ar*C*), 131.6 (*C*H═CH_2), 128.7 (Ar*C*), 128.4 (Ar*C*), 128.1 (Ar*C*), 128.0 (Ar*C*), 123.8 (Ar*C*), 119.6 (Ar*C*), 119.4 (CH═*C*H_2), 66.9 (Ph*C*H_2), 60.6 (N*C*HCO), 51.9 (NH*C*HCO), 47.5 (N*C*H_2), 37.0 (*C*H_2CH═CH_2), 26.6 (*C*H_2), 25.0 (*C*H_2). HRMS (CI) *m*/*z* calcd for $C_{24}H_{28}N_3O_4$ [M + H]$^+$ 422.2080; found 422.2089. Minor diastereomer (40%, mixture with major diastereomer): ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.01 (bs, 1 H, N*H*), 7.59 (d, J = 8.0 Hz, 2 H, Ar*H*), 7.37–7.25 (m, 7 H, Ar*H*), 7.06 (d, J = 7.6 Hz, 1 H, Ar*H*), 5.78 (m, 1 H, C*H*═CH_2), 5.38 (d, J = 6.0 Hz, 1 H, N*H*), 5.22 (d, J = 15.6 Hz, 1 H, CH═CH_2), 5.20 (d, J = 9.6 Hz, 1 H, CH═CH_2), 5.14 (d, J = 12.0 Hz, 1 H, PhCH_2), 5.03 (d, J = 12.0 Hz, 1 H, PhCH_2), 4.78 (dd, J = 6.8, 1.2 Hz, 1 H, NC*H*), 4.52 (q, J = 6.8 Hz, 1 H, NHC*H*), 3.94 (t, J = 7.6 Hz, 1 H, NCH_2), 3.58 (q, J = 7.6 Hz, 1 H, NCH_2), 2.59–2.53 (m, 2 H, CH_2CH═CH_2), 2.46 (m, 1 H, CH_2), 2.19–1.92 (m, 3 H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7 (*C*═O), 168.9 (*C*═O), 156.3 (O*C*═O), 138.1 (Ar*C*), 135.9 (Ar*C*), 132.0 (*C*H═CH_2), 128.6 (Ar*C*), 128.4 (Ar*C*), 128.1 (Ar*C*), 127.9 (Ar*C*), 123.9 (Ar*C*), 120.0 (Ar*C*), 119.4 (CH═*C*H_2), 67.0 (Ph*C*H_2), 61.1 (N*C*HCO), 52.4 (NH*C*HCO), 47.3 (N*C*H_2), 35.8 (*C*H_2CH═CH_2), 28.3 (*C*H_2), 24.4 (*C*H_2). HRMS (CI) *m*/*z* calcd for $C_{24}H_{28}N_3O_4$ [M + H]$^+$ 422.2080; found 422.2078. HPLC (silica, hexane–EtOAc = 60 : 40, 1 mL min^{-1}, 254 nm): t_R (60%) = 15.23 min, t_R (40%) = 20.72 min.

General procedure for palladium-catalyzed allylic alkylations of tripeptides

n-BuLi (1.6 M, 0.51 mL, 0.81 mmol) was added to a solution of DIPA (0.11 mL, 0.84 mmol) in THF (0.4 mL) in a Schlenk flask

at −20 °C. The cooling bath was removed and stirring was continued for a 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 solution was added to the LDA solution at −78 °C and the mixture was warmed up to −40 °C within 30 min, before the solution was cooled again to −78 °C and stirred for a further 15 min. The palladium catalyst (1.46 mg, 4.0 μmol) and triphenylphosphine (4.8 mg, 18.3 μmol) were dissolved in THF (0.2 mL). After stirring for 10 min at room temperature the allyl substrate (0.20 mmol) was added to the yellow solution formed, and the resulting mixture was added slowly to the chelated enolate at −78 °C. The solution was allowed to warm up to room temperature overnight, before it was diluted with ethyl acetate and 1 M $KHSO_4$ was added. After extraction with ethyl acetate, the organic layers were dried over Na_2SO_4, concentrated *in vacuo* and the crude product was purified by flash chromatography.

***N*-Trifluoroacetyl-(*S*)-phenylalanyl-(*R*)-(2-methylallyl)-glycyl-(*S*)-prolinanilide (7a).** According to the general procedure for palladium-catalyzed allylic alkylations of tripeptides **7a** was obtained from **3** (100 mg, 0.204 mmol) in 82% yield (91.2 mg, 0.167 mmol). Major diastereomer (92%): $[\alpha]_D^{20} = -102.5°$ (c = 0.5, $CHCl_3$). M.p. 150–152 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.79 (s, 1 H, N*H*), 7.57 (d, J = 7.2 Hz, 2 H, Ar*H*), 7.28–7.25 (m, 6 H, Ar*H*, N*H*), 7.12 (d, J = 7.6 Hz, 2 H, Ar*H*), 7.06 (t, J = 7.2 Hz, 1 H, Ar*H*), 6.83 (d, J = 6.0 Hz, 1 H, N*H*), 4.83 (s, 1 H, C═CH_2), 4.80 (q, J = 7.2 Hz, 1 H, NHC*H*), 4.78 (s, 1 H, C═CH_2), 4.69 (dd, J = 6.0, 2.4 Hz, 1 H, NC*H*), 4.60 (m, 1 H, NHC*H*), 3.95 (m, 1 H, NCH_2), 3.53 (m, 1 H, NCH_2), 3.11–2.99 (m, 2 H, PhCH_2), 2.44 (m, 1 H, CH_2), 2.37 (dd, J = 14.0, 5.2 Hz, 1 H, CH_2C═CH_2), 2.26 (dd, J = 14.0, 9.2 Hz, 1 H, CH_2C═CH_2), 2.15 (m, 1 H, CH_2), 2.05 (m, 2 H, CH_2), 1.75 (s, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3 (*C*═O), 169.7 (*C*═O), 168.9 (*C*═O), 156.7 (q, $^2J_{C,F}$ = 36.5 Hz, CF_3*C*O), 139.5 (*C*═CH_2), 137.8 (Ar*C*), 135.2 (Ar*C*), 129.1 (Ar*C*), 128.8 (Ar*C*), 127.4 (Ar*C*), 124.3 (Ar*C*), 120.0 (Ar*C*), 115.5 (q, $^1J_{C,F}$ = 286.0 Hz, *C*F_3), 115.4 (C═*C*H_2), 61.3 (N*C*HCO), 54.4 (NH*C*HCO), 50.0 (NH*C*HCO), 47.4 (N*C*H_2), 39.6 (*C*H_2C═CH_2), 38.5 (PhCH_2), 28.8 (*C*H_2), 24.4 (*C*H_2), 21.9 (*C*H_3). HRMS (CI) *m*/*z* calcd for $C_{28}H_{32}F_3N_4O_4$ $[M + H]^+$ 545.2376; found: 545.2355. Minor diastereomer (8%): $[\alpha]_D^{20}$ = −116.8° (c = 0.5, $CHCl_3$). M.p. 239–240 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (s, 1 H, N*H*), 8.49 (bs, 1 H, N*H*), 7.61 (d, J = 8.8 Hz, 1 H, Ar*H*), 7.43 (d, J = 7.6 Hz, 2 H, Ar*H*), 7.26–7.17 (m, 5 H, Ar*H*), 7.06–7.01 (m, 3 H, Ar*H*, N*H*), 5.26 (m, 1 H, NC*H*), 5.05 (m, 1 H, NC*H*), 4.65 (dd, J = 8.0, 3.6 Hz, 1 H, NC*H*), 4.44 (s, 1 H, C═CH_2), 4.32 (s, 1 H, C═CH_2), 3.89–3.77 (m, 2 H), 3.03 (dd, J = 13.6, 4.8 Hz, 1 H, PhCH_2), 2.87 (dd, J = 13.6, 8.8 Hz, 1 H, PhCH_2), 2.49 (dd, J = 13.6, 3.2 Hz, 1 H, CH_2C═CH_2), 2.31 (m, 1 H, CH_2C═CH_2), 2.26–2.20 (m, 2 H, CH_2), 2.15–2.06 (m, 2 H, CH_2), 1.61 (s, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2 (*C*═O), 169.3 (*C*═O), 169.2 (*C*═O), 155.0 (q, $^2J_{C,F}$ = 37.4 Hz, CF_3*C*O), 138.9 (*C*═CH_2), 138.1 (Ar*C*) , 135.4 (Ar*C*), 129.1 (Ar*C*), 128.7 (Ar*C*), 128.4 (Ar*C*), 127.4 (Ar*C*), 123.9 (Ar*C*), 119.3 (Ar*C*), 115.6 (q, $^1J_{C,F}$ = 285.1 Hz, *C*F_3), 115.5 (C═CH2), 60.9 (N*C*HCO), 53.9 (NH*C*HCO), 49.3 (NH*C*HCO), 47.6 (N*C*H_2), 41.2 (*C*H_2C═CH2), 39.7 (PhCH_2), 28.8 (*C*H_2), 24.9 (*C*H_2), 21.9 (*C*H_3). HRMS (CI) *m*/*z* calcd for $C_{28}H_{32}F_3N_4O_4$ $[M + H]^+$ 545.2376; found 545.2368. $C_{28}H_{31}F_3N_4O_4$ (544.57) calcd C 61.76, H 5.74, N 10.29; found C 61.14, H 5.72, N 9.78. HPLC (silica, hexane–EtOAc = 50 : 50, 1 mL min^{-1}, 254 nm): t_R (8%) = 9.47 min, t_R (92%) = 13.51 min.

***N*-Trifluoroacetyl-(*S*)-phenylalanyl-(*R*)-[(2-tributylstannyl)allyl]-glycyl-(*S*)-prolinanilide (7c).** According to the general procedure for palladium-catalyzed allylic alkylations of tripeptides **7c** was obtained from **3** (100 mg, 0.204 mmol) in 75% yield (125.5 mg, 0.153 mmol). $[\alpha]_D^{20} = -65.6°$ (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76 (s, 1 H, N*H*), 7.59 (d, J = 7.6 Hz, 2 H, Ar*H*), 7.28–7.18 (m, 6 H, Ar*H*, N*H*), 7.11 (dd, J = 8.0, 2.0 Hz, 2 H, Ar*H*), 7.04 (t, J = 7.6 Hz, 1 H, Ar*H*), 6.52 (d, J = 5.2 Hz, 1 H, N*H*), 5.70 (dd, J = 231.6, 1.6 Hz, 1 H, C═CH_2), 5.28 (dd, J = 58.0, 1.6 Hz, 1 H, C═CH_2), 4.76 (q, J = 7.2 Hz, 2 H, NC*H*), 4.70 (dd, J = 7.8, 2.0 Hz, 1 H, NC*H*), 4.48 (dt, J = 8.5, 5.7 Hz, 1 H, NC*H*), 3.94 (m, 1 H, NCH_2), 3.51 (m, 1 H, NCH_2), 3.08 (dd, J = 14.0, 6.8 Hz, 1 H, PhCH_2), 3.01 (dd, J = 14.0, 6.8 Hz, 1 H, PhCH_2), 2.63 (dd, J = 13.6, 5.7 Hz, 1 H, CH_2C═CH_2), 2.42 (m, 2 H, CH_2C═CH_2, CH_2), 2.06 (m, 3 H, CH_2), 1.50 (m, 6 H, SnCH_2CH_2), 1.35 (m, 6 H, CH_2CH_3), 0.94 (m, 15 H, SnCH_2, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0 (*C*═O), 169.6 (*C*═O), 168.9 (*C*═O), 156.8 (q, $^2J_{C,F}$ = 37.4 Hz, CF_3*C*O), 148.9 (CH$_2$═*C*Sn), 137.9 (Ar*C*), 135.2 (Ar*C*), 129.9 (Ar*C*), 129.1 (Ar*C*), 128.8 (Ar*C*), 128.7 (*C*H$_2$═CSn), 127.4 (Ar*C*), 124.2 (Ar*C*), 120.1 (Ar*C*), 115.5 (q, $^1J_{C,F}$ = 289.7 Hz, *C*F_3), 61.4 (N*C*HCO), 54.2 (NH*C*HCO), 50.1 (NH*C*HCO), 47.5 (N*C*H_2), 41.9 (*C*H_2C═CH_2), 38.1 (PhCH_2), 29.0 ($J_{C,Sn}$ = 19.8 Hz, SnCH_2*C*H_2), 28.8 (*C*H_2), 27.4 ($J_{C,Sn}$ = 56.5 Hz, *C*H$_2$CH$_3$), 24.3 (*C*H$_2$), 13.6 (CH$_2$*C*H$_3$), 9.7 ($J_{C,Sn}$ = 328.6 Hz, Sn*C*H$_2$). HRMS (CI) *m*/*z* calcd for $C_{39}H_{57}F_3N_4O_4Sn$ $[M + H]^+$ 821.3276; found 821.3259. HPLC (silica, hexane–EtOAc = 70 : 30, 1 mL min^{-1}, 254 nm): t_R = 10.24 min.

***N*-Trifluoroacetyl-(*S*)-phenylalanyl-(*R*)-[3-(2,2-dimethyl-1,3-dioxolan-4-yl)allyl]-glycyl-(*S*)-prolinanilide (7d).** According to the general procedure for palladium-catalyzed allylic alkylations of tripeptides **7d** was obtained from **3** (200 mg, 0.409 mmol) in 67% yield (173.2 mg, 0.274 mmol). Major diastereomer (81%): $[\alpha]_D^{20} = -29.0°$ (c = 1.0, CH_3OH). M.p. 70–72 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (s, 1 H, N*H*), 7.57–7.48 (m, 4 H, Ar*H*, N*H*), 7.31–7.22 (m, 5 H, Ar*H*), 7.13 (d, J = 6.4 Hz, 2 H, Ar*H*), 7.07 (t, J = 6.4 Hz, 1 H, Ar*H*), 5.63 (dt, J = 15.5, 6.5 Hz, 1 H, CH$_2$C*H*═CH), 5.56 (dd, J = 15.5, 6.4 Hz, 1 H, CH$_2$CH═C*H*), 4.85 (q, J = 6.8 Hz, 1 H, NHC*H*), 4.68 (dd, J = 7.6, 2.0 Hz, 1 H, NC*H*), 4.62 (q, J = 6.8 Hz, 1 H, NHC*H*), 4.43 (m, 1 H, CH═CHC*H*O), 4.06 (dd, J = 8.0, 6.0 Hz, 1 H, CH_2O), 3.84 (m, 1 H, CH_2O), 3.54 (m, 2 H, NCH_2), 3.11 (dd, J = 14.0, 6.8 Hz, 1 H, PhCH_2), 3.05 (dd, J = 14.0, 7.2 Hz, 1 H, PhCH_2), 2.44–2.32 (m, 3 H, CH_2, CH_2CH═CH), 2.18–1.97 (m, 3 H, CH_2), 1.40 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5 (*C*═O), 169.7 (*C*═O), 168.9 (*C*═O), 156.6 (q, $^2J_{C,F}$ = 37.4 Hz, CF_3*C*O), 137.8 (Ar*C*), 135.3 (Ar*C*), 132.6 (CH$_2$CH═*C*H), 129.1 (Ar*C*), 128.7 (Ar*C*), 128.6 (Ar*C*), 128.5 (CH$_2$*C*H═CH), 127.5 (Ar*C*), 124.2 (Ar*C*), 119.9 (Ar*C*), 115.5 (q, $^1J_{C,F}$ = 286.1 Hz, *C*F_3), 109.3 (O*C*O), 76.2 (CH═CH*C*HO), 69.1 (*C*H$_2$O), 61.2 (N*C*HCO), 54.3

(NHCHCO), 51.3 (NHCHCO), 47.4 (NCH$_2$), 38.4 (PhCH$_2$), 34.3 (CH$_2$CH=CH), 28.7 (CH$_2$), 26.5 (CH$_3$), 25.6 (CH$_3$), 24.3 (CH$_2$). HRMS (CI) *m/z* calcd for $C_{29}H_{32}F_3N_4O_5$ [M − C_3H_6O + H]$^+$ 573.2325; found 573.2300. Minor diastereomer (19%): $[\alpha]_D^{20}$ = −30.6° (*c* = 0.5, $CHCl_3$). M.p. 88–90 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.90 (s, 1 H, NH), 7.48 (d, *J* = 8.8 Hz, 2 H, ArH), 7.34–7.28 (m, 5 H, ArH), 7.19–7.07 (m, 5 H, ArH, NH), 5.57 (dt, *J* = 15.5, 7.2 Hz, 1 H, CH$_2$CH=CH), 5.43 (dd, *J* = 15.5, 6.7 Hz, 1 H, CH$_2$CH=CH), 4.82 (q, *J* = 7.2 Hz, 1 H, NHCH), 4.76–4.70 (m, 2 H, NHCH), 4.21 (q, *J* = 6.8 Hz, 1 H, CH=CHCHO), 3.80 (dd, *J* = 8.0, 8.0 Hz, 1 H, CH$_2$O), 3.86–3.61 (m, 2 H, NCH$_2$), 3.35 (dd, *J* = 8.0, 8.0 Hz, 1 H, CH$_2$O), 3.09 (dd, *J* = 13.8, 6.5 Hz, 1 H, PhCH$_2$), 3.03 (dd, *J* = 13.8, 7.0 Hz, 1 H, PhCH$_2$), 2.58–2.44 (m, 2 H, CH$_2$CH=CH), 2.35 (m, 1 H, CH$_2$), 2.22 (m, 1 H, CH$_2$), 2.10–1.93 (m, 2 H, CH$_2$), 1.37 (s, 3 H, CH$_3$), 1.34 (s, 3 H, CH$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9 (C=O), 168.6 (C=O), 168.3 (C=O), 137.9 (ArC), 135.1 (ArC), 132.7 (CH$_2$CH=CH), 129.2 (ArC), 129.0 (ArC), 128.7 (CH$_2$CH=CH), 127.5 (ArC), 126.8 (ArC), 124.2 (ArC), 119.5 (ArC), 109.2 (OCO), 76.1 (CH=CHCHO), 69.0 (CH$_2$O), 60.4 (NCHCO), 54.4 (NHCHCO), 50.6 (NHCHCO), 47.7 (NCH$_2$), 38.6 (PhCH$_2$), 35.2 (CH$_2$CH=CH), 29.7 (CH$_2$), 26.6 (CH$_3$), 25.7 (CH$_3$), 25.1 (CH$_2$). HRMS (CI) *m/z* calcd for $C_{29}H_{32}F_3N_4O_5$ [M − C_3H_6O + H]$^+$ 573.2325; found 573.2300. HPLC (silica, hexane–EtOAc = 50 : 50, 1 mL min^{-1}, 254 nm): t_R (19%) = 26.85 min, t_R (81%) = 46.20 min.

***N*-Trifluoroacetyl-(*S*)-*tert*-leucyl-(*R*)-(2-methylallyl)-glycyl-(*S*)-prolinanilide (9a).** According to the general procedure for palladium-catalyzed allylic alkylations of tripeptides **9a** was obtained from **5** (100 mg, 0.219 mmol) in 84% yield (93.8 mg, 0.184 mmol). Major diastereomer (96%): $[\alpha]_D^{20}$ = −54.6° (*c* = 0.5, $CHCl_3$). M.p. 82–83 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.88 (s, 1 H, NH), 7.52 (d, *J* = 7.6 Hz, 2 H, ArH), 7.27 (t, *J* = 7.6 Hz, 2 H, ArH), 7.07 (t, *J* = 7.6 Hz, 1 H, ArH), 6.96 (d, *J* = 8.9 Hz, 1 H, NH), 6.75 (d, *J* = 6.4 Hz, 1 H, NH), 4.92 (s, 1 H, C=CH$_2$), 4.86 (s, 1 H, C=CH$_2$), 4.77 (m, 1 H, NCH), 4.72 (dd, *J* = 8.0, 1.2 Hz, 1 H, NHCH), 4.35 (d, *J* = 8.9 Hz, 1 H, NHCH), 3.92 (m, 1 H, NCH$_2$), 3.52 (m, 1 H, NCH$_2$), 2.49 (m, 1 H, CH$_2$), 2.45–2.39 (m, 2 H, CH$_2$C=CH$_2$), 2.15 (m, 1 H, CH$_2$), 2.10 (m, 1 H, CH$_2$), 1.96 (m, 1 H, CH$_2$), 1.80 (s, 3 H, C=CCH$_3$), 0.98 (s, 9 H, C(CH$_3$)$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2 (C=O), 168.9 (C=O), 168.7 (C=O), 156.8 (q, $^2J_{C,F}$ = 37.2 Hz, CF$_3$CO), 139.7 (C=CH$_2$), 137.8 (ArC), 128.8 (ArC), 124.2 (ArC), 120.0 (ArC), 115.6 (q, $^1J_{C,F}$ = 286.2 Hz, CF$_3$), 115.4 (C=CH$_2$), 61.2 (NCHCO), 60.5 (NHCHCO), 50.0 (NHCHCO), 47.3 (NCH$_2$), 39.9 (CH$_2$C=CH$_2$), 35.4 (C(CH$_3$)$_3$), 28.3 (CH$_2$), 26.4 (C(CH$_3$)$_3$), 24.4 (CH$_2$), 21.8 (CH$_3$). HRMS (CI) *m/z* calcd for $C_{25}H_{34}F_3N_4O_4$ [M + H]$^+$ 511.2532; found 511.2483. $C_{25}H_{33}F_3N_4O_4$ (510.56) calcd C 58.81, H 6.51, N 10.97; found: C 58.41, H 6.48, N 10.68. Minor diastereomer (4%); $[\alpha]_D^{20}$ = −52.5° (*c* = 0.5, $CHCl_3$). M.p. 89–91 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.06 (s, 1 H, NH), 8.03 (d, *J* = 8.8 Hz, 1 H, NH), 7.68 (d, *J* = 7.6 Hz, 2 H, ArH), 7.26 (t, *J* = 7.6 Hz, 2 H, ArH), 7.19 (d, *J* = 9.4 Hz, 1 H, NH), 7.04 (t, *J* = 7.6 Hz, 1 H, ArH), 5.03 (ddd, *J* = 9.6, 8.8, 4.0 Hz, 1 H, NHCH), 4.94 (dd, *J* = 8.4, 2.4 Hz, 1 H, NCH), 4.64 (d, *J* = 9.4 Hz, 1 H, NHCH), 4.45 (s, 1 H, C=CH$_2$), 4.42 (s, 1 H, C=CH$_2$), 3.85 (m, 1 H, NCH$_2$), 3.76 (m, 1 H, NCH$_2$), 2.49 (dd, *J* = 13.6 Hz, *J* = 4.0 Hz, 1 H, CH$_2$C=CH$_2$), 2.30–2.25 (m, 2 H, CH$_2$), 2.19 (dd, *J* = 13.6, 9.6 Hz, 1 H, CH$_2$C=CH$_2$), 2.12–2.06 (m, 2 H, CH$_2$), 1.65 (s, 3 H, C=CCH$_3$), 0.94 (s, 9 H, C(CH$_3$)$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0 (C=O), 169.5 (C=O), 169.0 (C=O), 156.9 (q, $^2J_{C,F}$ = 37.2 Hz, CF$_3$CO), 139.8 (C=CH$_2$), 138.0 (ArC), 128.7 (ArC), 123.9 (ArC), 119.5 (ArC), 115.9 (q, $^1J_{C,F}$ = 285.9 Hz, CF$_3$), 115.0 (C=CH$_2$), 60.8 (NCHCO), 60.3 (NHCHCO), 49.3 (NHCHCO), 47.3 (NCH$_2$), 41.9 (CH$_2$C=CH$_2$), 35.2 (C(CH$_3$)$_3$), 28.6 (CH$_2$), 26.5 (C(CH$_3$)$_3$), 24.5 (CH$_2$), 21.7 (CH$_3$). HRMS (CI) *m/z* calcd for $C_{25}H_{34}F_3N_4O_4$ [M + H]$^+$ 511.2532; found 511.2528. $C_{25}H_{33}F_3N_4O_4$ (510.56) calcd C 58.81, H 6.51, N 10.97; found C 58.91, H 6.54, N 10.45. HPLC (silica, hexane–EtOAc = 70 : 30, 1 mL min^{-1}, 254 nm): t_R (4%) = 7.77 min, t_R (96%) = 8.61 min.

***N*-Trifluoroacetyl-(*S*)-phenylalanyl-(*R*)-(2-methylallyl)-glycyl-(*S*)-*N*-methylleucineanilide (16a).** According to the general procedure for palladium-catalyzed allylic alkylations of tripeptides **16a** was obtained from **11** (208 mg, 0.400 mmol) in 80% yield (183 mg, 0.310 mmol). Major diastereomer (97%): $[\alpha]_D^{20}$ = −128.0° (*c* = 1.0, $CHCl_3$). M.p. 112–113 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (s, 1 H, ArNH), 7.59 (d, *J* = 7.6 Hz, 2 H, ArH), 7.35–7.25 (m, 6 H, ArH, NH), 7.17 (m, 2 H, ArH), 7.08 (t, *J* = 7.4 Hz, 1 H, ArH), 6.46 (d, *J* = 5.6 Hz, 1 H, NH), 5.30 (dd, *J* = 10.0, 5.4 Hz, 1 H, NCHCO), 4.86 (m, 1 H, C=CH$_2$), 4.82–4.70 (m, 3 H, C=CH$_2$, NHCHCO), 3.13–3.09 (m, 2 H, ArCH$_2$), 3.07 (s, 3 H, NCH$_3$), 2.33 (dd, *J* = 14.0, 5.7 Hz, 1 H, CH$_2$C=CH$_2$), 2.23 (dd, *J* = 13.9, 9.1 Hz, 1 H, CH$_2$C=CH$_2$), 1.98–1.88 (m, 2 H, NCHCH$_2$), 1.73 (s, 3 H, CH$_3$C=CH$_2$), 1.67 (m, 1 H, CHCH$_3$), 0.96 (d, *J* = 6.6 Hz, 3 H, CHCH$_3$), 0.90 (d, *J* = 6.6 Hz, 3 H, CHCH$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9 (C=O), 169.6 (C=O), 168.3 (C=O), 156.7 (q, $^2J_{C,F}$ = 37.6 Hz, CF$_3$C=O), 139.2 (C=CH$_2$), 137.9 (ArC), 135.2 (ArC), 129.1 (ArC), 128.9 (ArC), 128.8 (ArC), 127.5 (ArC), 124.3 (ArC), 120.0 (ArC), 115.7 (C=CH$_2$), 115.5 (q, $^1J_{C,F}$ = 287.4 Hz, CF$_3$), 56.1 (NCHCO), 54.3 (NHCHCO), 48.3 (NHCHCO), 39.8 (CH$_2$C=CH$_2$), 38.3 (ArCH$_2$), 36.1 (NCHCH$_2$), 31.0 (NCH$_3$), 24.9 (CHCH$_3$), 23.2 (CHCH$_3$), 21.9 (CHCH$_3$), 21.7 (CH$_3$C=CH$_2$). HRMS (CI) *m/z* calcd for $C_{30}H_{37}F_3N_4O_4$ [M + H]$^+$ 575.2840; found: 575.2798. $C_{30}H_{37}F_3N_4O_4$ (574.63) calcd C 62.70, H 6.49, N 9.75; found C 62.78, H 6.79, N 9.33. HPLC (Reprosil, hexane–*i*PrOH = 9 : 1 to 7 : 3, 40 min, 1 mL min^{-1}, 252 nm): t_R (3%) = 16.16 min, t_R (97%) = 20.48 min.

***N*-Trifluoroacetyl-(*S*)-phenylalanyl-(*R*/*S*)-(2-methylallyl)-glycyl-(*R*)-*N*-methylleucineanilide (17).** According to the general procedure for palladium-catalyzed allylic alkylations of tripeptides **17** was obtained from **12** (208 mg, 0.400 mmol) in 78% yield (180 mg, 0.310 mmol) as a mixture of diastereomers (dr = 51 : 49): ^{1}H NMR (500 MHz, d_6-DMSO, 373 K): δ 9.34/9.17 (bs, 1 H, NH), 9.02/8.96 (d, *J* = 7.3 Hz, 1 H, NH), 8.07 (bs, 1 H, NH), 7.57 (m, 2 H, ArH), 7.31–7.10 (m, 7 H, ArH), 7.05 (m, 1 H, ArH), 5.14 (m, 1 H, NCHCO), 4.97 (m, 1 H, NHCHCO), 4.78 (m, 2 H, C=CH$_2$), 4.67 (m, 1 H, NHCHCO), 3.20–2.95 (m, 2 H, ArCH$_2$), 3.05 (s, 3 H, NCH$_3$), 2.44 (m, 1 H, CH$_2$C=CH$_2$), 2.32 (m, 1 H, CH$_2$C=CH$_2$), 1.82–1.60 (m, 2 H,

NCHCH_2), 1.76/1.73 (s, 3 H, CH_3C═CH$_2$), 1.56 (m, 1 H, CHCH$_3$), 1.00–0.89 (m, 6 H, CHCH_3). ^{13}C NMR (125 MHz, d$_6$-DMSO, 373 K): δ 171.3 (*C*═O), 168.7 (*C*═O), 168.6 (*C*═O), 155.4/155.3 (q, $^2J_{C,F}$ = 36.6 Hz, CF$_3$*C*═O), 140.3/140.1 (*C*═CH$_2$), 138.0 (Ar*C*), 136.4/136.3 (Ar*C*), 128.3/128.2 (Ar*C*), 127.7/127.6 (Ar*C*), 127.3 (Ar*C*), 125.7/125.6 (Ar*C*), 122.9/122.8 (Ar*C*), 119.6/119.5 (Ar*C*), 115.1 (q, $^1J_{C,F}$ = 288.4 Hz, *C*F$_3$), 112.5/112.4 (C═*C*H$_2$), 54.1 (N*C*HCO), 53.8 (NH*C*HCO), 47.9 (NH*C*HCO), 47.2 (*C*H$_2$C═CH$_2$), 36.6 (ArCH$_2$), 36.0 (NCH*C*H$_2$), 24.0(N*C*H$_3$), 23.9 (*C*HCH$_3$), 22.2/22.0 (CH*C*H$_3$), 21.5/21.4 (CH*C*H$_3$), 20.9 (*C*H$_3$C═CH$_2$). HRMS (CI) *m*/*z* calcd for $C_{30}H_{37}F_3N_4O_4$ [M + H]$^+$ 575.2840; found: 575.2881. HPLC (Reprosil, hexane–*i*PrOH = 9 : 1 to 7 : 3, 40 min, 1 mL min^{-1}, 252 nm): t_R (51%) = 15.67 min, t_R (49%) = 20.33 min.

***N*-Trifluoroacetyl-(*S*)-phenylalanyl-(*R*)-(2-methylallyl)-glycyl-(*S*)-*N*-benzylleucineanilide (18).** According to the general procedure for palladium-catalyzed allylic alkylations of tripeptides **18** was obtained from **13** (239 mg, 0.400 mmol) in 66% yield (172 mg, 0.260 mmol). Major diastereomer (94%): $[\alpha]_D^{20}$ = −121.7° (*c* = 1.0, CHCl$_3$). M.p. 74–75 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.56 (s, 1 H, ArN*H*), 7.55 (d, *J* = 7.6 Hz, 2 H, Ar*H*), 7.36–7.21 (m, 10 H, Ar*H*), 7.18 (d, *J* = 7.6 Hz, 1 H, N*H*), 7.12–7.06 (m, 3 H, Ar*H*), 6.16 (d, *J* = 4.8 Hz, 1 H, N*H*), 5.35 (t, *J* = 6.9 Hz, 1 H, NC*H*CO), 4.94 (d, *J* = 17.4 Hz, 1 H, ArCH_2N), 4.72–4.60 (m, 3 H, C═CH_2, NHC*H*CO), 4.57 (d, *J* = 17.4 Hz, 1 H, ArCH_2N), 4.35 (dt, *J* = 10.6, 4.2 Hz, 1 H, NHC*H*CO), 3.08–3.04 (m, 2 H, ArCH_2CH), 2.25–2.10 (m, 2 H, CH_2C═CH$_2$), 1.95 (dd, *J* = 13.9, 3.5 Hz, 1 H, NCHCH_2), 1.71 (m, 1 H, NCHCH_2), 1.57 (m, 1 H, CHCH$_3$), 1.13 (s, 3 H, CH_3C═CH$_2$), 0.99 (d, *J* = 3.9 Hz, 3 H, CHCH_3), 0.98 (d, *J* = 4.1 Hz, 3 H, CHCH_3). ^{13}C NMR (100 MHz, CDCl$_3$): δ 174.5 (*C*═O), 169.4 (*C*═O), 168.3 (*C*═O), 156.6 (q, $^2J_{C,F}$ = 37.9 Hz, CF$_3$*C*═O), 139.6 (*C*═CH$_2$), 138.0 (Ar*C*), 137.0 (Ar*C*), 135.0 (Ar*C*), 129.1 (Ar*C*), 129.0 (Ar*C*), 128.9 (Ar*C*), 128.8 (Ar*C*), 128.0 (Ar*C*), 127.5 (Ar*C*), 126.5 (Ar*C*), 124.3 (Ar*C*), 120.1 (Ar*C*), 115.5 (q, $^1J_{C,F}$ = 287.7 Hz, *C*F$_3$), 115.6 (C═CH_2), 57.7 (N*C*HCO), 54.2 (NH*C*HCO), 49.7 (NH*C*HCO), 48.5 (ArCH_2N), 39.9 (*C*H$_2$C═CH$_2$), 38.2 (ArCH_2CH), 37.0 (NCH*C*H$_2$), 25.4 (*C*HCH$_3$), 22.7 (CH*C*H$_3$), 22.3 (CH*C*H$_3$), 20.7 (*C*H$_3$C═CH$_2$). HRMS (CI) *m*/*z* calcd for $C_{36}H_{41}F_3N_4O_4$ [M + H]$^+$ 651.3153; found: 651.3149. $C_{36}H_{41}F_3N_4O_4$ (650.73) calcd C 66.45, H 6.35, N 8.61; found C 66.55, H 6.68, N 8.27. HPLC (Reprosil, hexane–*i*PrOH = 9 : 1 to 7 : 3, 40 min, 1 mL min^{-1}, 252 nm): t_R (6%) = 15.13 min, t_R (94%) = 18.87 min.

***N*-Trifluoroacetyl-(*S*)-valyl-(*R*)-(2-methylallyl)-glycyl-(*S*)-*N*-methylleucineanilide (20).** According to the general procedure for palladium-catalyzed allylic alkylations of tripeptides **20** was obtained from **15** (189 mg, 0.400 mmol) in 71% yield (150 mg, 0.285 mmol). Major diastereomer (>98%): $[\alpha]_D^{20}$ = −162.6° (*c* = 1.0, CHCl$_3$). M.p. 141–143 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.22 (s, 1 H, ArN*H*), 7.56 (d, *J* = 7.6 Hz, 2 H, Ar*H*), 7.32–7.26 (m, 2 H, Ar*H*, N*H*), 7.15–7.05 (m, 2 H, Ar*H*), 6.67 (d, *J* = 6.4 Hz, 1 H, N*H*), 5.27 (dd, *J* = 9.8, 5.8 Hz, 1 H, NC*H*CO), 4.98–4.90 (m, 2 H, NHC*H*CO, C═CH_2), 4.85 (s, 1 H, C═CH_2), 4.44 (dd, *J* = 8.3, 5.3 Hz, 1 H, NHC*H*CO), 3.09 (s, 3 H, NCH_3), 2.48–2.32 (m, 2 H, CH_2C═CH$_2$), 2.19 (m, 1 H, NHCHC*H*), 1.91 (ddd, *J* = 14.7, 9.2, 5.8 Hz, 1 H, NCHCH_2), 1.80 (s, 3 H, CH_3C═CH$_2$), 1.69 (ddd, *J* = 14.1, 9.7, 5.0 Hz, 1 H, NCHCH_2), 1.47 (m, 1 H, CHCH$_3$), 0.98 (d, *J* = 3.2 Hz, 3 H, CHCH_3), 0.96 (d, *J* = 3.3 Hz, 3 H, CHCH_3), 0.94 (d, *J* = 6.9 Hz, 3 H, CHCH_3), 0.91 (d, *J* = 6.6 Hz, 3 H, CHCH_3). ^{13}C NMR (100 MHz, CDCl$_3$): δ 173.1 (*C*═O), 169.5 (*C*═O), 168.2 (*C*═O), 157.0 (q, $^2J_{C,F}$ = 37.5 Hz, CF$_3$*C*═O), 139.5 (*C*═CH$_2$), 137.8 (Ar*C*), 128.8 (Ar*C*), 124.3 (Ar*C*), 119.9 (Ar*C*), 115.7 (q, $^1J_{C,F}$ = 287.8 Hz, *C*F$_3$), 115.6 (C═CH_2), 58.2 (N*C*HCO), 56.0 (NH*C*HCO), 48.3 (NH*C*HCO), 40.4 (*C*H$_2$C═CH$_2$), 36.1 (NCH*C*H$_2$), 31.7 (N*C*H$_3$), 30.9 (*C*HCH$_3$), 24.9 (*C*HCH$_3$), 23.2 (CH*C*H$_3$), 21.8 (*C*H$_3$C═CH$_2$, CH*C*H$_3$), 18.8 (CH*C*H$_3$), 17.6 (CH*C*H$_3$). HRMS (CI) *m*/*z* calcd for $C_{26}H_{37}F_3N_4O_4$ [M + H]$^+$ 527.2767; found: 527.2861. $C_{26}H_{37}F_3N_4O_4$ (526.59) calcd C 59.30, H 7.08, N 10.64; found C 58.92, H 7.00, N 10.48. HPLC (Reprosil, hexane–*i*PrOH = 9 : 1 → 7 : 3, 40 min, 1 mL min^{-1}, 252 nm): t_R (>99%) = 23.93 min.

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