Stereoselective palladium-catalyzed allylic alkylations of peptide amide enolates†

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Pd-catalyzed allylations are an excellent tool for stereoselective peptide modifications, being clearly superior to normal alkylations. The reactions proceed not only in high yield, 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.

Introduction

Peptides and especially cyclopeptides with unusual amino acids are widespread found in nature, mainly produced by bacteria or marine organisms.[1] In most cases, these secondary metabolites show interesting biological properties, and many of these peptide-based structures have either directly found applications as drugs or at least as lead structures for the development of new drug candidates.[2] For the target screening or the optimization of lead structures, where libraries of similar but slightly modified peptides are required, flexible and modular concepts are desired.[3] In addition, the targeted modification of biologically active peptides is a promising tool for the elucidation of structure–activity-relationships.[4] Therefore, the direct introduction or manipulation of a side chain onto a given peptide represents a powerful alternative to classical peptide synthesis.[5]

While the modification of a functionalized side chain in general is not a big problem,[6] the direct introduction of a side chain into a peptide is not a trivial issue, especially with respect to the stereochemical outcome of the reaction. In principle, peptide-incorporated glycine cations,[7] radicals[8] or anions are suitable reactive intermediates for further modifications. The last approach was investigated intensively by Seebach *et al.*[9] Probably the most spectacular success was the regio- as well as stereoselective alkylation of the sarcosin (sar) subunit in cyclosporin (Fig. 1).[10]

At this position, the secondary amide allowed the formation of an amide enolate, which could be reacted with electrophiles. In this case, one face of the enolate is shielded by the deprotonated peptide ring, and therefore the attack of the electrophile occurs preferentially from the opposite face. In comparison, modifications of linear peptides generally proceed unselectively, giving rise to diastereomeric mixtures.[11] 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.[10]

Studies of O'Donnell *et al.* have shown that alkylations of imine-activated dipeptides can be achieved under phase-transfer conditions [12] or by using non-ionic phosphazene bases.[13] Stereoselective

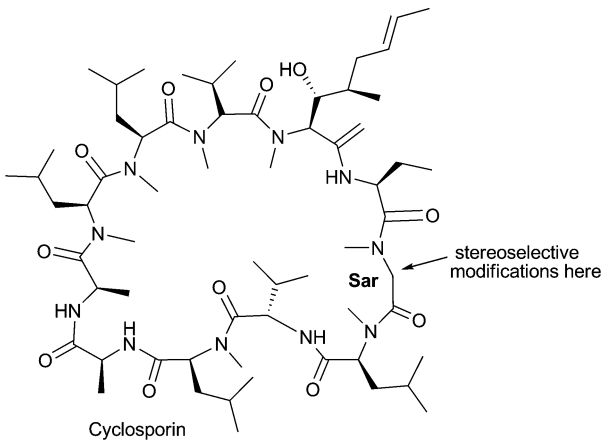
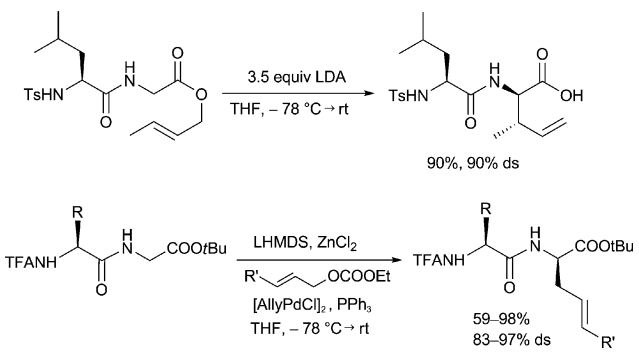


Fig. 1 Modification of cyclosporine according to Seebach *et al.*

modifications could only be obtained so far by either using chiral imines[14] or chiral phase transfer catalysts.[15]

For some time, our group has also been involved in stereoselective peptide modifications. Our primary aim is to transfer the chiral information of a given peptide chain *via* metal peptide complexes to the newly formed stereogenic centre. We observed that besides chelate–enolate Claisen rearrangements,[16] palladium-catalyzed allylations of peptides also provide high yields and selectivities (Scheme 1).[17] These protocols show a broad applicability, and in general selectivities >90% are obtained.[18] In all examples investigated so far, an (*S*)-amino acid generated an (*R*)-amino acid and *vice versa*. This might be explained by a multifold coordination of the peptide chain towards the chelating metal ion.



Scheme 1 Stereoselective peptide ester modifications.

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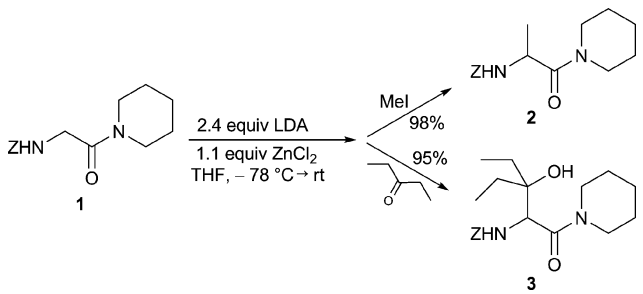
In such a complex, one face of the enolate is probably shielded by the side chain of the adjacent amino acid, resulting in an attack of the electrophile from the opposite face, giving rise to the unlikely product (*S*,*R*).[19]

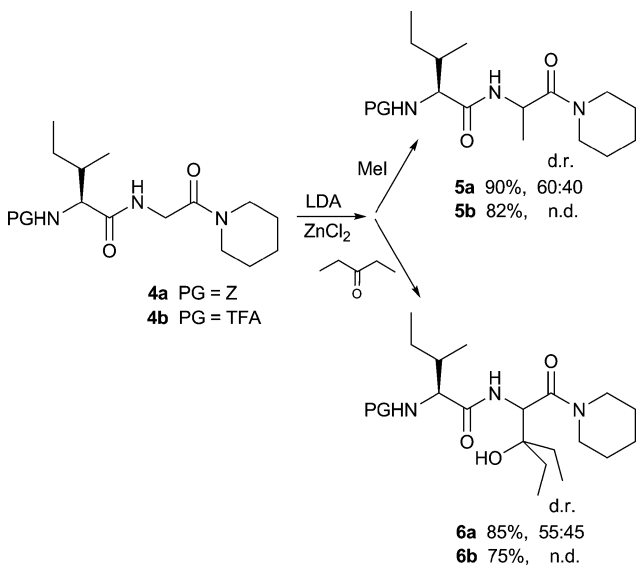
Results and discussion

Based on the good results obtained with chelated ester enolates, we were interested to see if analogue reactions can also be carried out with amide enolates, an important precondition for internal peptide modifications. As a first example, we subjected protected glycine piperidide **1** to methylation and an aldol reaction under the same reaction conditions generally used for ester-enolate reactions (Scheme 2). We were very pleased to see, that both reactions proceeded cleanly in almost quantitative yield.



Scheme 2 Reactions of chelated glycine amide enolates.

Therefore, we switched directly to dipeptides **4** as nucleophiles (Scheme 3). With the Z-protected dipeptide (**4a**) an excellent yield was also obtained, but unfortunately without any selectivity. The TFA-protected derivative (**4b**) caused severe analytical problems and we were unable to determine the diastereomeric ratio exactly. The products were not volatile enough for GC separation, and HPLC-analyses failed because of a missing chromophor. Determination of the diastereomeric ratio *via* NMR was hampered by the formation of rotamers, but a doubled set of signals indicated a ratio close 1 : 1.



Scheme 3 Reactions of chelated peptide amide enolates.

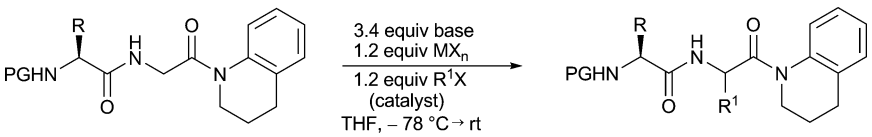
To solve this problem we decided to replace the piperidide by the tetrahydroquinolide **7** (Table 1). The yields obtained were absolutely identical to those obtained by the simpler amides **4** (entries 1–3). In this case, the diastereomers could easily be separated by HPLC, confirming the unselective reaction of the TFA derivatives **7b**. Similar results were also obtained with the phenylalanine peptide **8**, a substrate which was also used to investigate the influence of the *N*-protecting group (entries 4–7).

In principle, all standard protecting groups can be used with similar success, while the best yields were obtained with the tosyl protecting group (entry 7). A similar behavior we also observed during our initial investigations of peptide modifications based on Claisen-rearrangements.[20] This forced us to investigate the effect of additional metal salts on the stereochemical outcome of the methylation. While no tremendous effect was observed in the presence of $CuBr_2$ (entry 8) and $NiCl_2$ (entry 9), in the presence of $Ti(OiPr)_4$ the alkylation product could be obtained as a 3 : 1 diastereomeric mixture in good yield (entry 10). Although this effect is significant, the selectivity observed is not satisfying from a synthetic point of view. Therefore, we switched from simple alkylations to palladium-catalyzed allylic alkylations, which showed a higher efficiency in reactions of peptide ester enolates.[21] With methallyl carbonate as substrate the selectivity of the titanium-enolate was unchanged, but the yield dropped dramatically to 35% (entry 11). It should be mentioned that with other metal salts (*e.g.* $NiCl_2$) or in the absence of chelating metal ions (reaction of the lithium peptide enolate) no reaction was observed at all. By far the best result was obtained in the presence of $ZnCl_2$ giving rise to the allylation product in a very clean reaction in 90% yield (entry 12). The selectivity was unchanged compared to the titanium-enolate and still moderate. In addition, the tosyl-protecting group is not an ideal candidate, because in general it cannot be removed from the peptide without affecting the peptide chain. Therefore, we focused again on the TFA-protected peptide **8b**. The TFA-protecting group can easily be removed by saponification[22] or with mild reducing agents such as $NaBH_4$,[23] which do not affect the peptide. In addition, the TFA-group was the protecting group of choice in allylic alkylations of ester enolates of amino acids[24] and peptides as well.[25] An indeed, also here the selectivity could be improved to 6 : 1 (entry 13), and if the peptide enolate was used in slight excess (1.5 equiv.) even up to > 20 : 1 (entry 14).[26]

Peptide **10f** was also used to determine the absolute configuration of the allylation product. Catalytic hydrogenation provided the corresponding leucin-peptide which could be compared with a reference sample obtained *via* classical peptide coupling. This clearly indicates that the (*S*,*S*)-isomer is the minor product formed, and that a (*S*)-stereogenic centre in the peptide chain induces a (*R*)-configured amino acid. Probably, one face of the chelated amide enolate is shielded by the side chain of the adjacent amino acid, directing the electrophile to the opposite side. This is in perfect agreement with the results obtained with ester enolates.

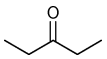
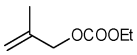
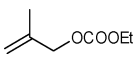
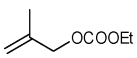
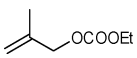
To prove the generality of this observation, we subjected a range of other allylic substrates to our optimized reaction conditions (Table 2). All examples investigated so far gave the allylation products in high yield and a diastereoselectivity of 83–94%. The linear, monosubstituted substrates gave rise to the linear substitution product exclusively, with clean *trans* olefin geometry, even if *cis*-configured substrates (entry 4) were used. This clearly indicates, that the amide enolates are (slightly) less reactive compared to

Table 1 Modifications of dipeptide amides **7** and **8**



7 R = *s*Bu
8 R = Bn

9 R = *s*Bu
10 R = Bn

Entry	Subs.	PG	Base	*R*	R^1X	Catalyst	MX_n	Product	Yield (%)	Diast. ratio[a]
1	**7a**	Z	LDA	*s*Bu	MeI		$ZnCl_2$	**9a**	90	40 : 60
2	**7b**	TFA	LDA	*s*Bu	MeI		$ZnCl_2$	**9b**	82	36 : 64
3	**7b**	TFA	LDA	*s*Bu			$ZnCl_2$	**9c**	65	62 : 38
4	**8a**	Z	LDA	Bn	MeI		$ZnCl_2$	**10a**	89	41 : 59
5	**8b**	TFA	LDA	Bn	MeI		$ZnCl_2$	**10b**	71	38 : 62
6	**8c**	Boc	LDA	Bn	MeI		$ZnCl_2$	**10c**	78	40 : 60
7	**8d**	Ts	LDA	Bn	MeI		$ZnCl_2$	**10d**	92	47 : 53
8	**8d**	Ts	LDA	Bn	MeI		$CuBr_2$	**10d**	90	42 : 58
9	**8d**	Ts	LDA	Bn	MeI		$NiCl_2$	**10d**	88	40 : 60
10	**8d**	Ts	LDA	Bn	MeI		$Ti(OiPr)_4$	**10d**	80	24 : 76
11	**8d**	Ts	LHMDS	Bn		2 mol% $[allylPdCl]_2$ 9 mol% PPh_3	$Ti(OiPr)_4$	**10e**	35[b]	24 : 76
12	**8d**	Ts	LHMDS	Bn		2 mol% $[allylPdCl]_2$ 9 mol% PPh_3	$ZnCl_2$	**10e**	90	24 : 76
13	**8b**	TFA	LHMDS	Bn		2 mol% $[allylPdCl]_2$ 9 mol% PPh_3	$ZnCl_2$	**10f**	87[c]	14 : 86
14	**8b**	TFA	LHMDS	Bn		2 mol% $[allylPdCl]_2$ 9 mol% PPh_3	$ZnCl_2$	**10f**	92[d]	4 : 96

[a] Determined by HPLC. [b] 40% starting material recovered. [c] 1.0 equiv R^1X used. [d] 0.7 equiv R^1X used.

ester enolates, which can react with *cis*-substrates under retention of the double bond geometry.[27] The amide enolates react at higher temperature, where the π–σ–π-isomerization obviously is faster than the nucleophilic attack. This is also illustrated in the reaction of a branched allylic substrate (entry 5). Not only that, here also the linear product is formed exclusively, the stereogenic centre of the leaving group (used as a 6 : 4 diastereomeric mixture) has no influence on the stereochemical outcome of the reaction.[28] This was solely controlled by the peptide chain like in all other reactions.

Interestingly, isoprenylcarbonate gave a mixture of two regiomers, with the branched product as the major one. Probably in this case the reaction proceeds in a S_N1-type fashion at the higher substituted position.[29] This would allow the introduction of sterically highly demanding β-quarternary amino acids into a given peptide chain. Surprisingly, this effect could not be verified with other 3,3-disubstituted substrates such as geranylcarbonate (entry 7) and may be limited to small methyl substituents, probably for steric reasons. So far, the best stereoselectivities were obtained with 2-substituted allyl carbonates (entries 8 and 9), and the excellent yield and selectivity obtained with the stannylated substrate (entry 9) are extremely promising, because the stannylated peptides obtained can be further modified, *e.g.* by Stille coupling.[30]

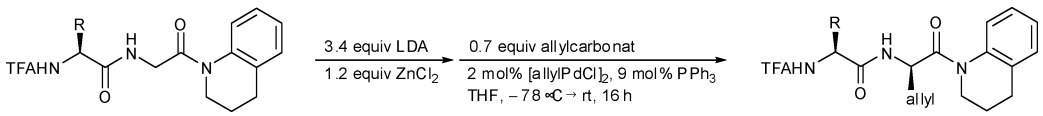
To prove the generality of this protocol we also investigated some other dipeptides (entries 10–12). The yields and selectivities were comparable to the phenylalanine dipeptide, although the induction of amino acids with aliphatic side chains seems to be slightly lower. The selectivity increases with the sterical demand of the inducing amino acid (entries 10 and 11).

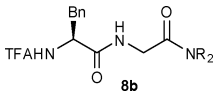
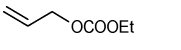
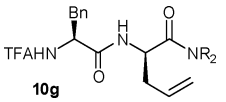
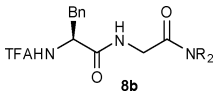
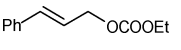
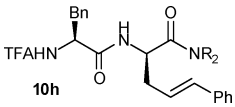
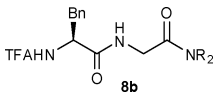
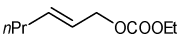
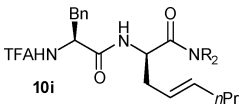
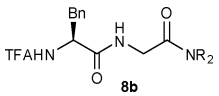
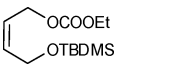
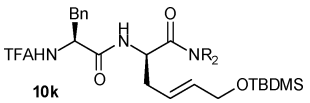
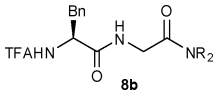
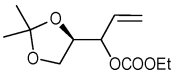
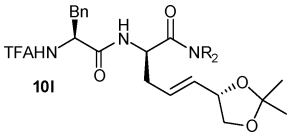
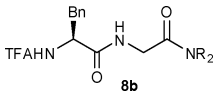
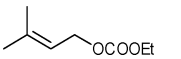
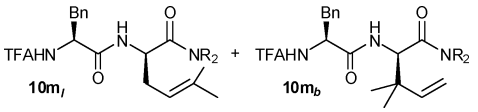
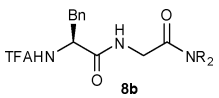
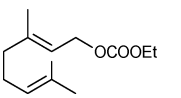
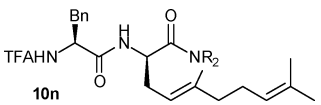
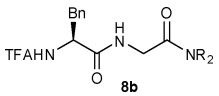
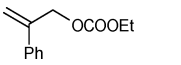
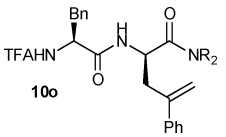
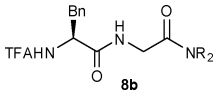
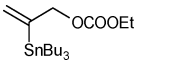
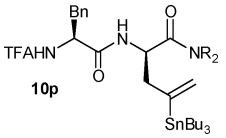
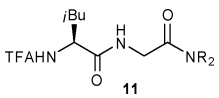
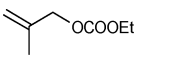
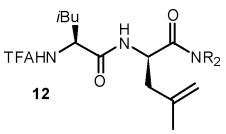
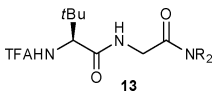
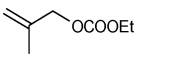
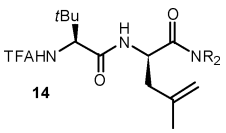
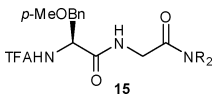
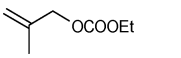
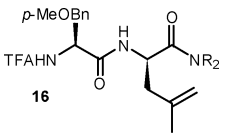
As mentioned earlier, the stannylated dipeptide **10p** is an ideal candidate for further modifications *via* cross coupling (Scheme 4). For example, Stille coupling with benzyl bromide gives rise to benzylated peptide **10q**, while the coupling with benzoyl chloride provides an amino acid with a vinylketone in the side chain (**10r**), which should be a good acceptor for subsequent Michael additions. Tin-iodine exchange results in an "umpolung" of the side chain, and the iodinated peptide is a nice substrate for cross couplings with a wide range of other organometallics. Based on the mild, neutral reaction conditions of the Stille coupling, all reactions proceed epimerization-free, allowing to transfer the excellent stereoselectivity of the allylic alkylation to a wide range of modified peptides.

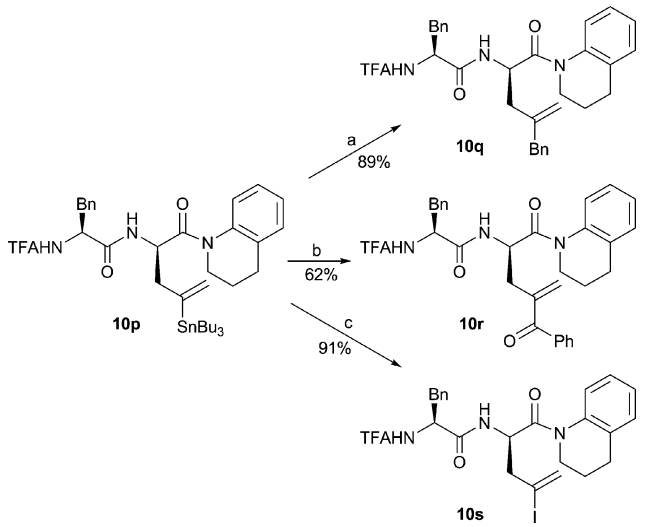
Conclusion

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 yield, but also with high regio- and diastereoselectivities, and *trans*-products are formed exclusively. Therefore, this is

Table 2 Allylic alkylations of TFA-protected dipeptide amides



Entry	Substrate	Allylcarbonat	Product	Yield (%)	ds
1	 **8b**		 **10g**	72	85
2	 **8b**		 **10h**	84	86
3	 **8b**		 **10i**	85	91
4	 **8b**		 **10k**	81	83
5	 **8b**		 **10l**	89	90
6	 **8b**		 **10m$_l$** **10m$_b$**	27 (**10m$_l$**) 58 (**10m$_b$**)	85 (**10m$_l$**) 90 (**10m$_b$**)
7	 **8b**		 **10n**	83 92	92
8	 **8b**		 **10o**	76	94
9	 **8b**		 **10p**	92	94
10	 **11**		 **12**	90	86
11	 **13**		 **14**	85	91
12	 **15**		 **16**	92	92



Scheme 4 Modification of stannylated peptides. Reagents and reaction conditions: a) 2.0 equiv benzyl bromide, 1 mol% [allylPdCl]2, 2 mol% PPh3, THF, 60 °C, 24h; b) 1.05 equiv benzoyl chloride, 2.5 mol% $[allylPdCl]_2$, CH_3CN, 50 °C, 4h; c) 1.2 equiv I2, Et_2O, r.t., 30 min.

a powerful synthetic tool for natural product and drug synthesis. Further investigations using even larger peptides are currently in progress.

Experimental

General remarks

All reactions were carried out in oven-dried glassware (70 °C) under an atmosphere of nitrogen. THF and Et_2O were dried with sodium and benzophenone and distilled before use. The products were purified by column chromatography on silica gel columns (Macherey–Nagel 60, 0.063–0.2 mm). Mixtures of ethyl acetate and hexanes were generally used as eluents. Analytical TLC was performed on precoated silica gel plates (Macherey–Nagel, Polygram® SIL G/UV254). Visualization was accomplished with UV-light, $KMnO_4$ solution or iodine. ^1H and ^{13}C NMR spectra were recorded with a Bruker AC-400 [400 MHz (^1H) and 100 MHz (^{13}C)] spectrometer in $CDCl_3$. Compound which shows mixture of rotamers at room temperature NMR analysis, spectra were recorded with Bruker DRX-500 [500 MHz (^1H) and 125 MHz (^{13}C)] spectrometer at 80 °C (353 K) in DMSO-d_6. Mass spectra were recorded with a Finnigan MAT 95 spectrometer using the CI technique. Elemental analyses were performed at the Saarland University.

General procedure for methylation of dipeptide amides

n-BuLi (1.6 M, 0.47 mL, 0.81 mmol) was added to a solution of diisopropyl amine (0.10 mL, 0.78 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 further 10 min before the mixture was cooled 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). This solution was added to the LDA solution at –78 °C and stirring was continued for 30 min at –78 °C before the addition of methyl iodide (39.3 mg, 0.28 mmol). 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.

(2*S*)-2-(2,2,2-Trifluoroacetamido)-*N*-[1-(3,4-dihydroquinolin-1(2*H*)-yl)-1-oxopropan-2-yl]-3-phenylpropanamide (10b). Following the general procedure for methylation of dipeptides, the desired product **10b** was obtained from **8b** (100 mg, 0.23 mmol) in 94% yield (73.2 mg, 0.16 mmol after column chromatography (hexanes/EtOAc 4 : 1) as a mixture of diastereomers. HPLC (Silicagel, hexanes/EtOAc 70 : 30, 1 mL min^{-1}): t_R (38%) = 12.12 min, t_R (62%) = 14.87 min. Major diastereomer: $[\alpha]_D^{20}$ = +30.2° (c 1.0, $CHCl_3$); m.p. 74–76 °C; ^1H-NMR (500 MHz, DMSO-d_6, 353 K): δ 9.15 (d, J = 7.5 Hz, 1H, TFANH), 8.24 (d, J = 7.0 Hz, 1H, NH), 7.48 (d, J = 7.0 Hz, 1H, ArH), 7.28–7.24 (m, 4H, ArH), 7.21–7.18 (m, 3H, ArH), 7.14–7.11 (m, 1H, ArH), 4.98–4.96 (m, 1H, $CHCH_3$), 4.66–4.62 (m, 1H, TFANHCH), 3.86–3.81 (m, 1H, NCH_2), 3.59–3.54 (m, 1H, NCH_2), 3.12 (dd, J = 14.0, 4.5 Hz, 1H, $PhCH_2$), 2.93 (dd, J = 14.0, 10.5 Hz, 1H, $PhCH_2$), 2.79–2.71 (m, 1H, $NCH_2CH_2CH_2$), 2.68–2.65 (m, 1H, $NCH_2CH_2CH_2$), 1.99–1.85 (m, 2H, NCH_2CH_2), 1.21 (d, J = 7.0 Hz, 3H, CH_3); ^{13}C-NMR (125 MHz, DMSO-d_6, 353 K): δ 171.2 (CO), 168.5 (CO), 155.5 (q, $^2J_{C,F}$ = 36.8 Hz, CF_3CO), 138.2 (ArC), 136.7 (ArC), 132.3 (ArC), 128.4 (2 ArCH), 127.9 (ArCH), 127.4 (2 ArCH), 125.8 (ArCH), 125.3 (ArCH), 124.5 (ArCH), 123.7 (ArCH), 115.2 (q, $^1J_{C,F}$ = 286.5 Hz, CF_3), 53.9 (TFANHCH), 45.4 ($CHCH_3$), 42.7 (NCH_2), 36.3 ($PhCH_2$), 25.4 ($NCH_2CH_2CH_2$), 23.0 (NCH_2CH_2), 17.0 (CH_3). HRMS (CI) m/z calcd for $C_{23}H_{25}F_3N_3O_3$ $[M+H]^+$: 448.1848, found 448.1824. Minor diastereomer: $[\alpha]_D^{20}$ = +34.2° (c 1.0, $CHCl_3$); m.p. 129–131 °C; ^1H-NMR (500 MHz, DMSO-d_6, 353 K): δ 9.16 (d, J = 8.0 Hz, 1H, TFANH), 8.21(d, J = 7.0 Hz, 1H, NH), 7.50 (d, J = 8.0 Hz, 1H, ArH), 7.26–7.25 (m, 4H, ArH), 7.24–7.21 (m, 3H, ArH), 7.14–7.10 (m, 1H, ArH), 4.95 (quintet, J = 7.0 Hz, 1H, $CHCH_3$), 4.69–4.64 (m, 1H, TFANHCH), 3.90–3.85 (m, 1H, NCH_2), 3.54–3.49 (m, 1H, NCH_2), 3.09 (dd, J = 14.0 Hz, J = 5.0 Hz, 1H, $PhCH_2$), 2.96 (dd, J = 14.0, 10.0 Hz, 1H, $PhCH_2$), 2.78–2.72 (m, 1H, $NCH_2CH_2CH_2$), 2.70–2.64 (m, 1H, $NCH_2CH_2CH_2$), 1.99–1.92 (m, 1H, NCH_2CH_2), 1.91–1.83 (m, 1H, NCH_2CH_2), 1.13 (d, J = 6.5 Hz, 3H, CH_3); ^{13}C-NMR (125 MHz, DMSO-d_6, 353 K): δ 171.3 (CO), 168.4 (CO), 155.4 (q, $^2J_{C,F}$ = 36.2 Hz, CF_3CO), 138.2 (ArC), 136.5 (ArC), 132.2 (ArC), 128.5 (2 ArCH), 127.9 ArCH), 127.4 (2 ArCH), 125.8 (ArCH), 125.3 (ArCH), 124.5 (ArCH), 123.7 (ArCH), 54.0 (TFANHCH), 45.3 ($CHCH_3$), 42.7 (NCH_2), 36.6 ($PhCH_2$), 25.3 ($NCH_2CH_2CH_2$), 22.9 (NCH_2CH_2), 17.0 (CH_3). HRMS (CI) m/z calcd for $C_{23}H_{25}F_3N_3O_3$ $[M+H]^+$: 448.1848. Found 448.1800.

General procedure for aldol reactions of dipeptide amides

n-BuLi (1.6 M, 0.47 mL, 0.81 mmol) was added to a solution of diisopropyl amine (0.10 mL, 0.78 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 further 10 min before the mixture was cooled 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). This solution was added to the LDA solution at –78 °C and

stirring was continued for 30 min at −78 °C before the addition of 3-pentanone (25.8 mg, 0.30 mmol). 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.

(2*S*,3*S*)-2-(2,2,2-Trifluoroacetamido)-*N*-[3-ethyl-1-(3,4-dihydroquinolin-1(2H)-yl)-3-hydroxy-1-oxopentan-2-yl]-3-methylpentanamide (9c). Following the general procedure for aldol reaction of dipeptide, the desired product **9c** was obtained from **7b** (100 mg, 0.25 mmol) in 65% yield (79.0 mg, 0.16 mmol) as a mixture of two diastereomers after column chromatography (hexanes/EtOAc 4 : 1). HPLC (Silicagel, hexanes/EtOAc 7 : 3, 1 mL min^{-1}): t_R (62%) = 53.21 min, t_R (38%) = 61.11 min. Major diastereomer: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.56 (d, J = 9.5 Hz, 1H, Ar*H*), 7.33–7.28 (m, 1H, Ar*H*), 7.23–7.17 (m, 3H, 2 Ar*H*, TFAN*H*), 6.88 (d, J = 8.8 Hz, 1H, N*H*), 5.27 (d, J = 8.8 Hz, 1H, C*H*), 4.49 (dd, J = 10.0, 7.5 Hz, 1H, TFANHC*H*), 4.38–4.26 (m, 1H, NCH_2), 3.54 (s, 1H, O*H*), 3.41–3.35 (m, 1H, NCH_2), 2.80–2.71 (m, 1H, $NCH_2CH_2CH_2$), 2.63–2.54 (m, 1H, $NCH_2CH_2CH_2$), 2.21–2.11 (m, 1H, NCH_2CH_2), 1.99–1.91 (m, 1H, $CH(CH_3)CH_2CH_3$), 1.88–1.79 (m, 1H, NCH_2CH_2), 1.63–1.03 (m, 5H, 2 CH_2CH_3, $CHHCH_3$), 0.99–0.87 (m, 7H, 2 CH_2CH_3, $CHHCH_3$), 0.64 (t, J = 7.2 Hz, 3H, CH_2CH_3), 0.57 (t, J = 7.6 Hz, 3H, CH_2CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.6 (*C*O), 169.1 (*C*O), 156.7 (q, $^2J_{C,F}$ = 36.8 Hz, CF_3CO), 137.6 (Ar*C*), 134.3 (Ar*C*), 128.5 (Ar*C*H), 126.8 (Ar*C*H), 126.6 (Ar*C*H), 124.8 (Ar*C*H), 115.7 (q, $^1J_{C,F}$ = 287.5 Hz, CF_3), 77.2 (*C*–OH), 57.6 (TFANH*C*H), 52.6 (C*H*), 43.2 (NCH_2), 38.3 ($CH(CH_3)CH_2CH_3$), 27.9 ($CH(CH_3)CH_2CH_3$), 26.6 ($NCH_2CH_2CH_2$), 25.5 (CH_2CH_3), 25.1 (CH_2CH_3), 23.7 (NCH_2CH_2), 15.0 ($CHCH_3$), 11.4 ($CH(CH_3)CH_2CH_3$), 7.2 (CH_2CH_3), 7.0 (CH_2CH_3). Minor diastereomer (selected signals): ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.57 (d, J = 9.0 Hz, 1H, Ar*H*), 6.94 (d, J = 9.2 Hz, 1H, N*H*), 5.35 (d, J = 9.2 Hz, 1H, C*H*), 4.57 (dd, J = 8.4, 4.8 Hz, 1H, TFANHC*H*), 3.56 (s, 1H, O*H*), 2.08–2.03 (m, 1H, NCH_2CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.4 (*C*O), 168.9 (*C*O), 156.7 (q, $^2J_{C,F}$ = 37.3 Hz, CF_3CO), 137.6 (Ar*C*), 134.5 (Ar*C*), 128.4 (Ar*C*H), 126.8 (Ar*C*H), 126.7 (Ar*C*H), 125.1 (Ar*C*H), 57.8 (TFANH*C*H), 52.4 (C*H*), 43.1 (NCH_2), 38.7 ($CH(CH_3)CH_2CH_3$), 27.6 ($CH(CH_3)CH_2CH_3$), 26.5 ($NCH_2CH_2CH_2$), 25.6 (CH_2CH_3), 24.4 (CH_2CH_3), 15.4 ($CHCH_3$), 7.0 (CH_2CH_3). HRMS (CI) m/z calcd for $C_{24}H_{35}F_3N_3O_4$ $[M+H]^+$ 486.2580. Found 486.2561. Analysis calcd for $C_{24}H_{34}F_3N_3O_4$ (485.55): C 59.34, H 7.06, N 5.65. Found: C 59.85 H 6.94, N 8.28.

General procedure for palladium-catalyzed allylic alkylations of dipeptide amides

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 further 10 min before the mixture was cooled 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 reaction mixture 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.

(2*S*)-2-(2,2,2-Trifluoroacetamido)-*N*-[1-(3,4-dihydroquinolin-1(2*H*)-yl)-4-methyl-1-oxopent-4-en-2-yl]-3-phenylpropanamide (10f). Following the general procedure for palladium-catalyzed allylic alkylations of dipeptides, the desired product **10f** was obtained from **8b** (100 mg, 0.23 mmol), in 92% yield (102.3 mg, 0.21 mmol) as a mixture of diastereomers (96 : 4) after column chromatography (hexanes/EtOAc 4 : 1). HPLC (Reprosil, hexanes/*i*PrOH 95 : 5, 1 mL min^{-1}): t_R (4%) = 10.56 min, t_R (96%) = 13.34 min. Major diastereomer: ^{1}H-NMR (500 MHz, DMSO-d_6, 353 K): δ 9.11 (d, J = 8.0 Hz, 1H, TFAN*H*), 8.11 (d, J = 8.0 Hz, 1H, N*H*), 7.43 (d, J = 8.0 Hz, 1H, Ar*H*), 7.24–7.11 (m, 8H, Ar*H*), 5.13 (q, J = 8.0 Hz, 1H, C*H*), 4.68–4.63 (m, 1H, TFANHC*H*), 4.66 (s, 1H, C=CH_2), 4.59 (s, 1H, C=CH_2), 3.99–3.94 (m, 1H, NCH_2), 3.42–3.35 (m, 1H, NCH_2), 3.08 (dd, J = 14.0, 5.0 Hz, 1H, PhCH_2), 2.92 (dd, J = 14.0, 10.0 Hz, 1H, PhCH_2), 2.71 (dt, J = 16.0, 6.5 Hz, 1H, $NCH_2CH_2CH_2$), 2.59 (dt, J = 16.0, 6.5 Hz, 1H, $NCH_2CH_2CH_2$), 2.24 (dd, J = 14.0, 1.5 Hz, 1H, $CH_2C(CH_3)=CH_2$), 2.15 (dd, J = 14.0, 8.5 Hz, 1H, $CH_2C(CH_3)=CH_2$), 1.99–1.92 (m, 1H, NCH_2CH_2), 1.83–1.76 (m, 1H, NCH_2CH_2), 1.40 (s, 3H, CH_3); ^{13}C-NMR (125 MHz, DMSO-d_6, 353 K): δ 170.2 (*C*O), 169.2 (*C*O), 156.1 (q, $^2J_{C,F}$ = 36.5 Hz, CF_3CO), 140.5 (*C*=CH_2), 138.3 (Ar*C*), 136.7 (Ar*C*), 133.2 (Ar*C*), 128.9 (2 Ar*C*H), 128.3 (Ar*C*H), 127.9 (2 Ar*C*H), 126.4 (Ar*C*H), 125.8 (Ar*C*H), 125.4 (Ar*C*H), 124.3 (Ar*C*H), 115.6 (q, $^1J_{C,F}$ = 286.4 Hz, CF_3), 113.2 (C=*C*H_2), 54.6 (TFANH*C*H), 48.4 (C*H*), 43.1 (NCH_2), 40.2 ($CH_2C(CH_3)=CH_2$), 37.1 (PhCH_2), 25.7 ($NCH_2CH_2CH_2$), 23.3 (NCH_2CH_2), 21.2 (CH_3). Minor diastereomer (selected signals): ^{1}H-NMR (500 MHz, DMSO-d_6, 353 K): δ 8.02 (d, J = 7.5 Hz, 1H, N*H*), 7.40 (d, J = 7.5 Hz, 1H, Ar*H*), 1.42 (s, 3H, CH_3); ^{13}C-NMR (125 MHz, DMSO-d_6, 353 K): δ 140.5 (*C*=CH$_2$), 136.8 (Ar*C*), 124.2 (Ar*C*H), 113.1 (C=*C*H_2), 54.4 (TFANH*C*H), 48.5 (C*H*), 40.1 ($CH_2C(CH_3)=CH_2$), 36.5 (PhCH_2), 21.3 (CH_3). HRMS (CI) m/z calcd for $C_{26}H_{29}F_3N_3O_3$ $[M+H]^+$: 488.2161. Found 488.2106.

(2*S*)-2-(2,2,2-Trifluoroacetamido)-*N*-[4-(tributylstannyl)-1-(3,4-dihydroquinolin-1(2*H*)-yl)-1-oxopent-4-en-2-yl]-3-phenylpropanamide (10p). Following the general procedure for palladium-catalyzed allylic alkylations of dipeptides, the stannylated peptide **10p** was obtained from **8b** (100 mg, 0.23 mmol), in 92% yield (102.3 mg, 0.21 mmol) as a mixture of diastereomers (94 : 6) after column chromatography (hexanes/EtOAc 4 : 1). HPLC (Reprosil, hexanes/*i*PrOH 95 : 5, 1 mL min^{-1}): t_R (6%) = 6.88 min, t_R (94%) = 8.07 min. Major diastereomer: ^{1}H-NMR (500 MHz, DMSO-d_6, 353 K): δ 9.19 (bs, 1H, TFAN*H*), 8.18 (d, J = 8.0 Hz, 1H, N*H*), 7.52 (dd, J = 8.0, 1.5 Hz, 1H, Ar*H*), 7.28–7.23 (m, 5H, Ar*H*), 7.20–7.17 (m, 2H, Ar*H*), 7.13 (dt, J = 7.0, 1.5 Hz, 1H, Ar*H*), 5.66 (dd, $J_{H,Sn}$ = 134.9 Hz, $J_{H,H}$ = 2.4 Hz, 1H, C=CH_2), 5.17 (dd, $J_{H,Sn}$ = 63.9 Hz, $J_{H,H}$ = 2.4 Hz, 1H, C=CH_2), 5.06–5.02 (m, 1H, C*H*), 4.73–4.71 (m, 1H, TFANHC*H*), 4.10–4.03 (m, 1H, NCH_2), 3.34–3.30 (m, 1H, NCH_2), 3.09 (dd, J = 14.0, 5.0 Hz,

1H, PhCH_2), 2.96 (dd, J = 14.0, 10.0 Hz, 1H, PhCH_2), 2.76 (dt, J = 16.0, 6.5 Hz, 1H, NCH$_2$CH$_2$CH_2), 2.64–2.56 (m, 2H, NCH$_2$CH$_2$CH_2, CH_2C═CH$_2$), 2.38 (dd, J = 13.7, 7.6 Hz, 1H, CH_2C═CH$_2$), 2.02–1.94 (m, 1H, NCH$_2$CH_2), 1.84–1.77 (m, 1H, NCH$_2$CH_2), 1.45–1.39 (m, 6H, 3 SnCH$_2$CH_2), 1.29–1.22 (m, 6H, 3 SnCH$_2$CH$_2$CH_2), 0.87–0.75 (m, 15H, 3 SnCH_2CH$_2$CH$_2$CH_3); ^{13}C-NMR (125 MHz, DMSO-d$_6$, 353 K): δ 170.3 (*C*O), 168.6 (*C*O), 155.5 (q, $^2J_{C,F}$ = 36.2 Hz, CF$_3$*C*O), 149.1 (*C*═CH$_2$), 138.1 (Ar*C*), 136.6 (Ar*C*), 132.2 (Ar*C*), 128.5 (2 Ar*C*H), 127.8 (Ar*C*H), 127.4 (2 Ar*C*H), 127.3 (C═*C*H$_2$), 125.8 (Ar*C*H), 125.4 (Ar*C*H), 124.6 (Ar*C*H), 123.8 (Ar*C*H), 115.2 (q, $^1J_{C,F}$ = 287.1 Hz, *C*F$_3$), 54.1 (TFANH*C*H), 48.8 (C*H*), 42.7 (N*C*H$_2$), 42.2 (*C*H$_2$C═CH$_2$), 36.7 (Ph*C*H$_2$), 27.8 ($J_{C,Sn}$ = 19.3 Hz, 3 SnCH$_2$*C*H$_2$), 25.9 ($J_{C,Sn}$ = 52.6 Hz, 3 SnCH$_2$CH$_2$*C*H$_2$), 25.4 (NCH$_2$CH$_2$*C*H$_2$), 23.0 (NCH$_2$*C*H$_2$), 12.6 (3 SnCH$_2$CH$_2$CH$_2$*C*H$_3$), 8.6 ($J_{C,Sn}$ = 324.5 Hz, 3 Sn*C*H$_2$). Minor diastereomer (selected peaks): ^{1}H-NMR (500 MHz, DMSO-d$_6$, 353 K): δ 9.05 (bs, 1H, TFANH), 8.13 (d, J = 8.0 Hz, 1H, NH), 7.46 (dd, J = 8.0, 1.0 Hz, 1H, ArH), 4.03–3.99 (m, 1H, NCH_2); ^{13}C-NMR (125 MHz, DMSO-d$_6$, 353 K): δ 168.7 (*C*O), 149.2 (*C*═CH$_2$), 128.4 (2 Ar*C*H), 123.6 (Ar*C*H), 53.8 (TFANH*C*H), 49.2 (C*H*), 23.1 (NCH$_2$*C*H$_2$), 12.7 (3 SnCH$_2$CH$_2$CH$_2$*C*H$_3$). HRMS (CI) m/z calcd for $C_{33}H_{43}F_3N_3O_3Sn$ [M-C_4H_9]$^+$ 706.2279. Found 706.2268.

Procedure for Stille couplings reactions

(2*S*)-2-(2,2,2-Trifluoroacetamido)-*N*-[(*R*)-4-benzyl-1-(3,4-dihydroquinolin-1(2*H*)-yl)-1-oxopent-4-en-2-yl]-3-phenylpropanamide (10q). Benzyl bromide (44.6 gm, 0.26 mmol) was added to a THF (2.0 mL) solution of stannylated dipeptide **10p** (100 mg, 0.13 mmol, 91% ds) in a Schlenk tube under nitrogen. To this solution a THF solution (1 mL) of [AllylPdCl]$_2$ (0.5 mg, 1.3 μmol) and triphenylphosphine (0.64 mg, 2.6 μmol) was added before it was heated to 60 °C for 24 h. The reaction mixture was cooled to room temperature before a saturated solution of KF in H$_2$O (2 mL) was added. After stirring overnight the solution was extracted twice with diethyl ether and the combined organic layers were washed with H$_2$O. After drying (Na$_2$SO$_4$) and evaporation of the solvent, the crude product was dissolved in ethyl acetate. The precipitated tin fluoride was filtered off and the residue obtained after evaporation of the solvent was purified by column chromatography (hexanes/EtOAc 3 : 1) to provide **10q** in 89% yield (65.1 mg, 0.11 mmol, 90% ds). HPLC (Reprosil, hexanes/*i*PrOH 95 : 5, 1 mL min^{-1}): t$_R$ (10%) = 13.50 min, t$_R$ (90%) = 18.41 min. Major diastereomer: ^{1}H-NMR (500 MHz, DMSO-d$_6$, 353 K): δ 9.22 (d, J = 8.5 Hz, 1H, TFANH), 8.32 (d, J = 8.5 Hz, 1H, NH), 7.50 (d, J = 7.5 Hz, 1H, ArH), 7.28–7.15 (m, 11H, ArH), 6.97 (d, J = 7.0 Hz, 2H, ArH), 5.27–5.22 (m, 1H, CH), 4.78 (s, 1H, C═CH$_2$), 4.73–4.68 (m, 1H, TFANHCH), 4.70 (s, 1H, C═CH$_2$), 4.02–3.97 (m, 1H, NCH_2), 3.35–3.30 (m, 1H, NCH_2), 3.12–3.08 (m, 3H, PhCH_2C═CH$_2$, PhCH_2), 2.95 (dd, J = 14.0, 10.0 Hz, 1H, PhCH_2), 2.72 (dt, J = 16.0, 6.5 Hz, 1H, NCH$_2$CH$_2$CH_2), 2.56 (dt, J = 16.0, 7.0 Hz, 1H, NCH$_2$CH$_2$CH_2), 2.24 (dd, J = 14.0, 5.5 Hz, 1H, CHCH_2C═CH$_2$), 2.16 (dd, J = 14.0, 8.5 Hz, 1H, CHCH_2C═CH$_2$), 1.97–1.89 (m, 1H, NCH$_2$CH_2), 1.82–1.74 (m, 1H, NCH$_2$CH_2); ^{13}C-NMR (125 MHz, DMSO-d$_6$, 353 K): δ 170.3 (*C*O), 168.8 (*C*O), 156.6 (q, $^2J_{C,F}$ = 36.3 Hz, CF$_3$*C*O), 143.7 (*C*═CH$_2$), 138.3 (Ar*C*), 138.0 (Ar*C*), 136.6 (Ar*C*), 132.5 (Ar*C*), 128.5 (2 Ar*C*H), 128.1 (2 Ar*C*H), 127.9 (Ar*C*H), 127.6 (2 Ar*C*H), 127.4 (2 Ar*C*H), 125.8 (Ar*C*H), 125.5 (Ar*C*H), 125.4 (Ar*C*H), 124.7 (Ar*C*H), 123.9 (Ar*C*H), 115.3 (q, $^1J_{C,F}$ = 287.4 Hz, *C*F$_3$), 113.6 (C═*C*H$_2$), 54.2 (TFANH*C*H), 47.9 (*C*H), 42.7 (N*C*H$_2$), 41.0 (Ph*C*H$_2$C═CH$_2$), 37.7 (CH*C*H$_2$C═CH$_2$), 36.7 (Ph*C*H$_2$), 25.4 (NCH$_2$CH$_2$*C*H$_2$), 22.9 (NCH$_2$*C*H$_2$). Minor diastereomer (selected peaks); ^{1}H-NMR (500 MHz, DMSO-d$_6$, 353 K): δ 9.16 (d, J = 8.5 Hz, 1H, TFANH), 8.21 (d, J = 7.5 Hz, 1H, NH), 7.46 (d, J = 7.5 Hz, 1H, ArH), 3.96–3.92 (m, 1H, NCH_2), 3.48–3.41 (m, 1H, NCH_2); ^{13}C-NMR (125 MHz, DMSO-d$_6$, 353 K): δ 138.1 (Ar*C*), 128.2 (Ar*C*H), 54.1 (TFANH*C*H), 25.4 (NCH$_2$CH$_2$*C*H$_2$). HRMS (CI) m/z calcd for $C_{32}H_{33}F_3N_3O_3$ [M+H]$^+$ 564.2475: Found 56.2475.

(2*S*)-2-(2,2,2-Trifluoroacetamido)-*N*-[(*R*)-1-(3,4-dihydroquinolin-1(2*H*)-yl)-4-methylene-1,5-dioxo-5-phenylpentan-2-yl]-3-phenylpropanamide (10r). Benzoyl chloride (20.2 mg, 0.14 mmol) was added to a solution of stannylated dipeptide **10p** (100 mg, 0.13 mmol, 91% ds) in acetonitrile (2.0 mL) in a Schlenk tube under nitrogen. To this solution was added an acetonitrile solution (1 mL) of [allylPdCl]$_2$ (1.16 mg, 3.2 μmol) before it was heated to 50 °C for 4 h. The reaction mixture was cooled to room temperature before a saturated solution of KF in H$_2$O (2 mL) was added. After stirring overnight the solution was extracted twice with diethyl ether and the combined organic layers were washed with H$_2$O. After drying (Na$_2$SO$_4$) and evaporation of the solvent, the crude product was dissolved in ethyl acetate. The precipitated tin fluoride was filtered off and the residue obtained after evaporation of the solvent was purified by column chromatography (hexanes/ethyl acetate 7 : 3) to give rise to **10r** in 62% yield (46.5 mg, 0.08 mmol, 90% ds). HPLC (Reprosil, hexanes/*i*PrOH 95 : 5, 1 mL min^{-1}): t$_R$ (10%) = 25.61 min, t$_R$ (90%) = 40.81 min. Major diastereomer: ^{1}H-NMR (500 MHz, DMSO-d$_6$, 353 K): δ 9.27 (d, J = 8.5 Hz, 1H, TFANH), 8.35 (d, J = 8.5 Hz, 1H, NH), 7.59–7.56 (m, 3H, ArH), 7.50 (d, J = 7.5 Hz, 1H, ArH), 7.45 (d, J = 7.5 Hz, 2H, ArH), 7.27–7.23 (m, 4H, ArH), 7.19–7.16 (m, 2H, ArH), 7.15–7.08 (m, 2H, ArH), 5.88 (s, 1H, C═CH$_2$), 5.58 (s, 1H, C═CH$_2$), 5.21–5.17 (m, 1H, CH), 4.71–4.66 (m, 1H, TFANHCH), 3.91–3.86 (m, 1H, NCH_2), 3.61–3.56 (m, 1H, NCH_2), 3.08 (dd, J = 14.0, 5.0 Hz, 1H, PhCH_2), 2.93 (dd, J = 14.0, 10.5 Hz, 1H, PhCH_2), 2.85 (dd, J = 14.0, 4.5 Hz, 1H, CH_2C═CH$_2$), 2.77–2.66 (m, 2H, CH_2C═CH$_2$, NCH$_2$CH$_2$CH_2), 2.63 (dd, J = 14.0, 8.5 Hz, 1H, NCH$_2$CH$_2$CH_2), 2.00–1.92 (m, 1H, NCH$_2$CH_2), 1.91–1.85 (m, 1H, NCH$_2$CH_2); ^{13}C-NMR (125 MHz, DMSO-d$_6$, 353 K): δ 196.0(*C*OPh), 169.7(*C*O), 168.7 (*C*O), 156.5 (q, $^2J_{C,F}$ = 35.6 Hz, CF$_3$*C*O), 142.5 (*C*═CH$_2$), 137.8 (Ar*C*), 136.7 (Ar*C*), 136.6 (Ar*C*), 131.9 (Ar*C*), 131.4 (Ar*C*H), 128.5 (C═*C*H$_2$), 128.5 (2 Ar*C*H), 128.4 (2 Ar*C*H), 127.9 (Ar*C*H), 127.5 (2 Ar*C*H), 127.4 (2 Ar*C*H), 125.8 (Ar*C*H), 125.2 (Ar*C*H), 124.5 (Ar*C*H), 123.8 (Ar*C*H), 115.2 (q, $^1J_{C,F}$ = 287.3 Hz, *C*F$_3$), 54.2 (TFANH*C*H), 48.4 (C*H*), 43.0 (N*C*H$_2$), 36.5 (Ph*C*H$_2$), 34.0 (*C*H$_2$C═CH$_2$), 25.4 (NCH$_2$CH$_2$*C*H$_2$), 22.9 (NCH$_2$*C*H$_2$). Minor diastereomer (selected peaks): ^{1}H-NMR (500 MHz, DMSO-d$_6$, 353 K): δ 9.19 (d, J = 8.5 Hz, 1H, TFANH), 5.95 (s, 1H, C═CH$_2$), 5.59 (s, 1H, C═CH$_2$), 3.85–3.80 (m, 1H, NCH_2), 3.66–3.61 (m, 1H, NCH_2); ^{13}C-NMR (125 MHz, DMSO-d$_6$, 353 K): δ 142.4 (*C*═CH$_2$), 136.6 (Ar*C*), 128.5 (2 Ar*C*H), 128.4 (2 Ar*C*H), 125.2 (Ar*C*H), 43.1 (N*C*H$_2$), 36.5 (Ph*C*H$_2$), 34.0 (*C*H$_2$C═CH$_2$), 23.0 (NCH$_2$*C*H$_2$). HRMS (CI) m/z calcd for $C_{32}H_{31}F_3N_3O_4$ [M+H]$^+$ 578.2267: Found 578.2288.

(2*S*)-2-(2,2,2-Trifluoroacetamido)-*N*-[1-(3,4-dihydroquinolin-1(2*H*)-yl)-4-iodo-1-oxopent-4-en-2-yl]-3-phenylpropanamide (10s). Iodine (66.2 mg, 0.26 mmol) dissolved in Et_2O (1 mL) was added to a solution of **10p** (100 mg, 0.13 mmol, 91% ds) in Et_2O (2 mL). After stirring for 30 min a saturated KF solution (2 mL) and ethyl acetate (5 mL) were added. After vigorous stirring for 2 h the aqueous layer was removed and the organic layer was filtrated and dried (Na_2SO_4). After evaporation of the solvent, the crude product was purified by flash chromatography (hexanes/ethyl acetate 3 : 1) to yield **10s** (70.9 mg, 0.12 mmol, 91%, 91% ds). HPLC (Reprosil, hexanes/*i*PrOH 95 : 5, 1 mL min^{-1}): t_R (9%) = 11.45 min, t_R (91%) = 13.55 min. Major diastereomer; ^{1}H-NMR (500 MHz, DMSO-d_6, 353 K): δ 9.15 (d, J = 8.5 Hz, 1H, TFAN*H*), 8.55 (d, J = 8.0 Hz, 1H, N*H*), 7.49 (d, J = 7.5 Hz, 1H, Ar*H*), 7.26–7.25 (m, 4H, Ar*H*), 7.21–7.16 (m, 3H, Ar*H*), 7.13 (td, J = 7.5, 1.5 Hz, 1H, Ar*H*), 6.11 (d, J = 1.0 Hz, 1H, C=CH_2), 5.71 (d, J = 1.0 Hz, 1H, C=CH_2), 5.24–5.19 (m, 1H, C*H*), 4.71–4.66 (m, 1H, TFANHC*H*), 4.00–3.95 (m, 1H, NCH_2), 3.51–3.45 (m, 1H, NCH_2), 3.10 (dd, J = 14.0, 5.0 Hz, 1H, PhCH_2), 2.96 (dd, J = 14.0, 10.0 Hz, 1H, PhCH_2), 2.77–2.72 (m, 2H, CH_2C=CH_2, NCH_2CH_2CH_2), 2.69–2.60 (m, 2H, CH_2C=CH_2, NCH_2CH_2CH_2)), 2.02–1.94 (m, 1H, NCH_2CH_2), 1.89–1.81 (m, 1H, NCH_2CH_2); ^{13}C-NMR (125 MHz, DMSO-d_6, 353 K): δ 169.2 (*C*O), 168.8 (*C*O), 155.6 (q, $^2J_{C,F}$ = 36.4 Hz, CF_3*C*O), 137.9 (Ar*C*), 136.5 (Ar*C*), 132.5 (Ar*C*), 128.6 (2 Ar*C*H), 128.4 (C=*C*H_2), 127.9 (Ar*C*H), 127.5 (2 Ar*C*H), 125.9 (Ar*C*H), 125.5 (Ar*C*H), 124.8 (Ar*C*H), 123.9 (Ar*C*H), 115.3 (q, $^1J_{C,F}$ = 286.5 Hz, *C*F_3), 104.2 (*C*=CH_2), 54.2 (TFANH*C*H), 48.9 (C*H*), 47.1 (*C*H_2C=CH_2), 42.9 (N*C*H_2), 36.7 (Ph*C*H_2), 25.5 (NCH_2CH_2*C*H_2), 23.0 (NCH_2*C*H_2). Minor diastereomer (selected peaks); ^{1}H-NMR (500 MHz, DMSO-d_6, 353 K): δ 8.25 (d, J = 7.0 Hz, 1H, N*H*), 7.44 (d, J = 7.5 Hz, 1H, Ar*H*), 6.12 (d, J = 1.0 Hz, 1H, C=CH_2), 5.73 (d, J = 1.0 Hz, 1H, C=CH_2); ^{13}C-NMR (125 MHz, DMSO-d_6, 353 K): δ 128.5 (2 Ar*C*H), 53.9 (TFANH*C*H), 49.2 (C*H*), 36.3 (Ph*C*H_2), 25.5 (NCH_2CH_2*C*H_2). HRMS (CI) m/z calcd for $C_{25}H_{26}F_3N_3O_3I$ $[M+H]^+$ 600.0971. Found 600.0990.

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