Peptide Modification

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Stereoselective Syntheses and Reactions of Stannylated Peptides**

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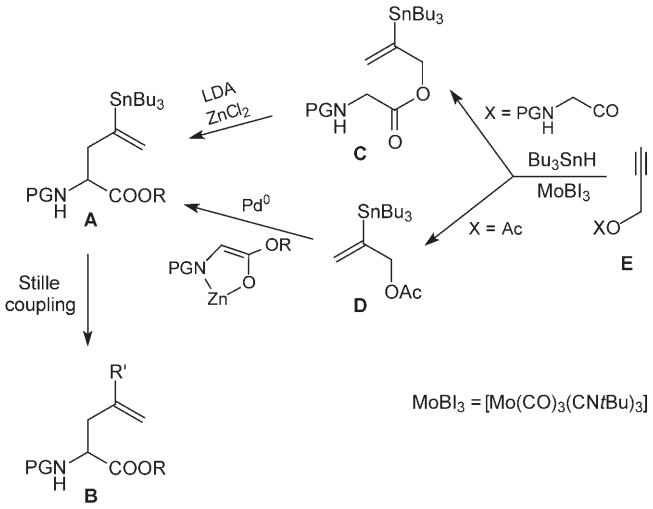
Dedicated to Professor Peter Hofmann on the occasion of his 60th birthday

Peptide metabolites produced by marine or terrestrial "lower" organisms differ significantly from those of eukaryotes. The non-ribosomal peptide synthesis[1] allows the prokaryotes to incorporate N-alkylated and D-amino acids, as well as "exotic side chains" into their peptides.[2] These peptides are in general resistant towards proteolytic cleavage, and therefore they are highly interesting from a pharmaceutical point of view.

For the development of peptide-based drugs, not only the synthesis of a natural product itself, but also a flexible strategy towards its analogues is important to prove and improve the structure—activity relationship (SAR). In this respect, peptide modifications for the structural variation of a given peptide are an extremely valuable tool.[3] The modifications can occur either in suitably functionalized side chains or directly at the peptide backbone (backbone modification). While side-chain modifications are in general relatively uncritical,[4] stereoselective backbone modifications are not a trivial issue. In principle, peptide radicals,[5] cations,[6] and anions can be used as reactive intermediates in the modification step. The last approach in particular, the application of peptide enolates, was intensively investigated by Seebach et al.[7] While linear peptides generally give diastereomeric mixtures with moderate selectivity (if at all), much better results can be obtained for modifications of cyclic peptides.[8]

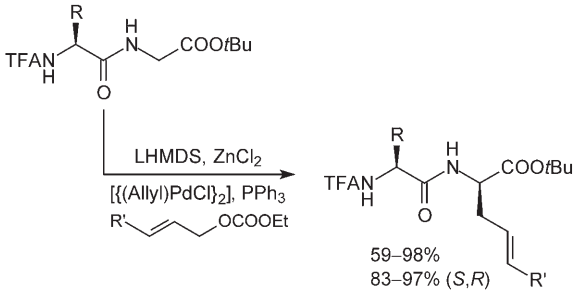
Stille couplings have been found to be well suited for side-chain modifications of amino acids. For example, protected amino acids (PG: protecting group) with a vinyl stannane side chain (**A**) can be coupled with a wide range of electrophiles giving rise to functionalized derivatives **B** (Scheme 1).[9] During the last years we have developed two independent approaches towards such stannylated amino acids **A**. They can either be obtained by the chelate–enolate Claisen rearrangement of stannylated allylic ester **C**, or by palladium-catalyzed allylic alkylation using stannylated allylic acetates **D**.[10] The stannylated esters can be obtained easily by a molybdenum-catalyzed regioselective hydrostannation of the corresponding propargylic ester **E**.[11]

In other projects we are developing new protocols for peptide modification, especially focussing on stereoselective



Scheme 1. Syntheses and modifications of stannylated amino acids

reactions.[12] We found that besides the chelate–enolate Claisen rearrangement[13] the palladium-catalyzed allylation of peptides also gives high yields and selectivities (Scheme 2).



Scheme 2. Modifications of peptides by palladium-catalyzed allylic alkylation. LHMDS = lithium hexymethyldisilazide, TFA = trifluoroacetate.

This protocol shows broad applicability, and even with the smallest amino acid alanine ($R = CH_3$) an acceptable selectivity (83:17) was observed. All other amino acids gave better results, and various side chains, also highly functionalized ones, were incorporated with selectivities $> 90\%$.[14] In all examples investigated so far, an *S* amino acid generated an *R* amino acid ("unlike" product) and vice versa.[15] This observation might be explained by the multiple coordination of the peptide chain on the chelating metal ion. In such a complex one face of the enolate is most likely shielded by the side chain R of the adjacent amino acid, resulting in an attack

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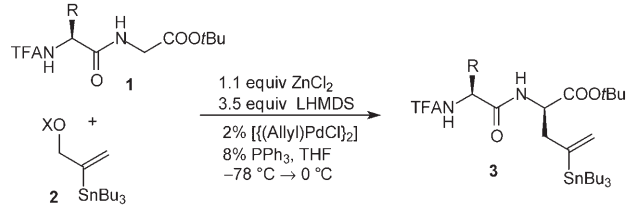
of the electrophile from the opposite face and generation of the "unlike" product (*S*,*R*).

Herein we report on a successful combination of these two concepts: The stereoselective syntheses of stannylated peptides by palladium-catalyzed stannaallylation and subsequent side-chain modifications. This approach allows the synthesis of a wide range of new peptides in a maximum of three steps via one common intermediate, which is formed in a single stereocontrolled step.

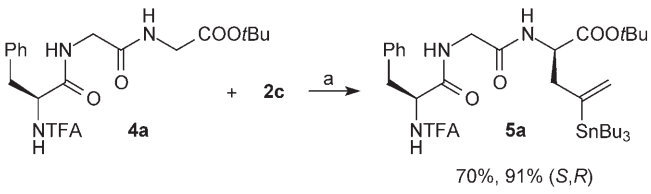
We chose phenylalanine dipeptide **1a**, which gave good results in the allylation with "normal" allyl substrates, as the nucleophile in optimizing the reaction conditions (Table 1).

Table 1: Stereoselective stannaallylation of dipeptides.[a][16]

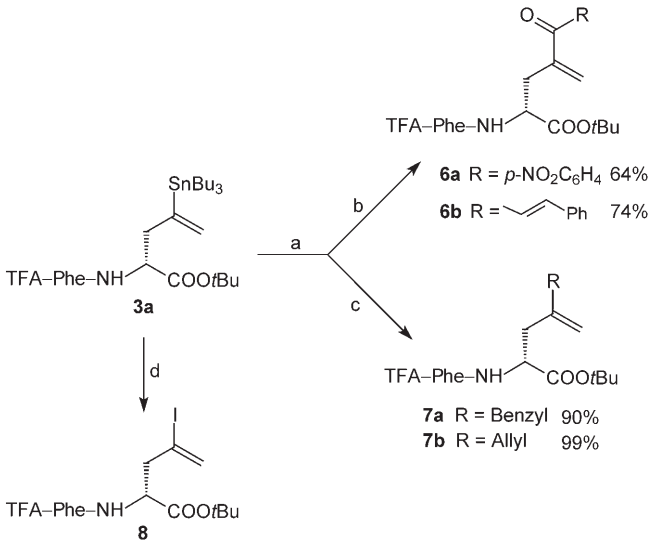


Peptide	R	Allyl	X	**1**/**2**	Prod.	Yield [%]	d.r.[b]
1a	Bn	**2a**	Ac	1.5:1	**3a**	48	99:1
1a	Bn	**2b**	COOMe	1.5:1	**3a**	56	98:2
1a	Bn	**2c**	COOEt	1.5:1	**3a**	65	98:2
1a	Bn	**2c**	COOEt	1:1.1	**3a**	73	98:2
1b	*i*Bu	**2c**	COOEt	1:1.1	**3b**	69	97:3
1c	CH_2OR'[c]	**2c**	COOEt	1:1.1	**3c**	81	95:5
1d	Me	**2c**	COOEt	1:1.1	**3d**	51	92:8

[a] Bn = benzyl, Ac = acetyl. [b] Diastereomeric ratio *S*,*R*/*S*,*S*. [c] R′ = TBDPS (*tert*-butyldimethylsilyl).



Scheme 3. Stereoselective allylation of tripeptide **4a**: a) 1.5 equiv $ZnCl_2$, 5.5 equiv LHMDS, 2 mol% [{(allyl)PdCl}$_2$], 8 mol% PPh_3, THF, −78 °C→0 °C.



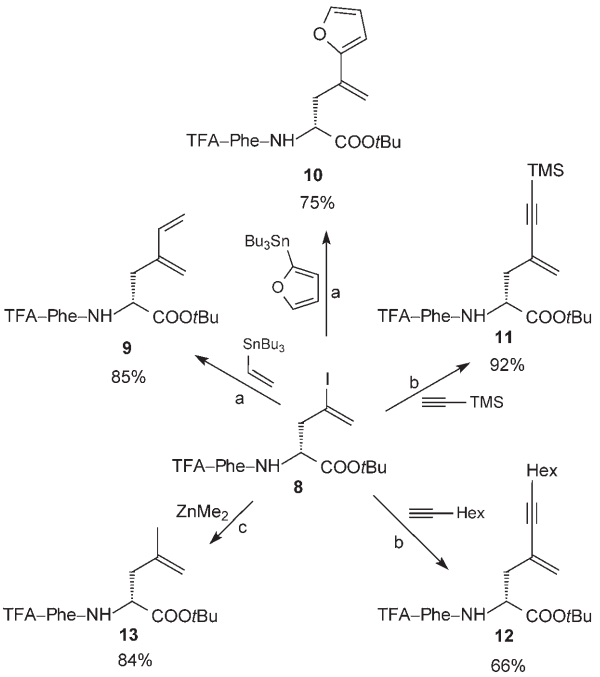
Scheme 4. Modifications of stannylated dipeptide **3a**: a) 1 mol% [{(allyl)PdCl}$_2$], 2 mol% PPh_3, b) 1.2 equiv RCOCl, THF, 50 °C; c) 2 equiv RBr, THF, 60 °C, 24 h; d) 2 equiv I_2, Et_2O, RT.

Using a slight excess of the peptide nucleophile, excellent selectivities could be obtained with all leaving groups, while the carbonates (**2b,c**) gave better yields than the acetate **2a**. The yield could further be increased by using allyl substrate **2c** in slight excess. Under these optimized conditions several other peptides (Table 1, **1b–d**) were subjected to allylation. The selectivities were generally high, nearly independent of the directing amino acid. Even the alanine peptide **1d** showed a diastereoselectivity of 92%, although in this case the yield was a little lower. The highest yield was obtained with serine derivative **1c**.[16]

As discussed earlier, the "unlike" product is thought to result from the multiple coordination of the peptide chain and a one-sided shielding of the enolate. If this assumption is correct, one might expect also some stereocontrol in reactions of larger peptides. Therefore, we subjected tripeptide **4a** to our reaction conditions, and indeed, the substituted tripeptide **5a** was obtained with > 90% selectivity (Scheme 3). This is an excellent result when one considers that this is a rare case of 1,7-induction.

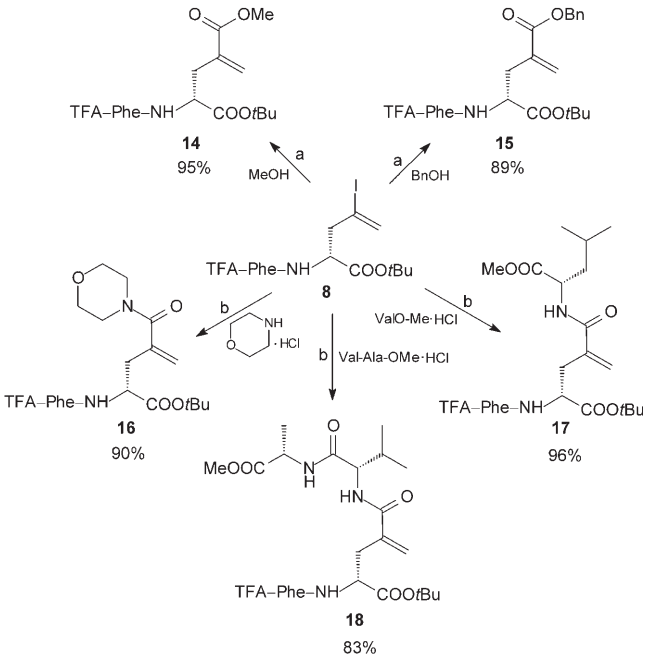
With the stannylated peptides in hand we next investigated the possibilities for side-chain modifications. Stille couplings of stannylated amino acids are already well-documented, and therefore we tested only two couplings each with allyl and acyl halides (Scheme 4). The reactions with acyl chlorides give rise to peptides with a vinyl ketone side chain (**6**), which can be further modified, for example, by Michael additions. In the coupling with cinnamoyl chloride a double Michael-acceptor system (**6b**) is formed, which can be converted into a heterocyclic side chain, for example, by amine addition.[17] While the acyl chlorides react rapidly at 50 °C, nearly no reaction was observed under these conditions with allyl and benzyl bromide. However, increasing the temperature to 60 °C provided the coupling products **7** in almost quantitative yield. No epimerization occurred under the reaction conditions used, as determined by HPLC.

The synthetic potential of the stannylated peptides can easily be expanded (Scheme 5). Metal–halogen exchange converted peptide **3a** in quantitative yield into the iodinated derivative **8**, which can be used in cross-coupling reactions as an electrophilic component (umpolung). Reaction with vinylstannane gave rise to peptide **9** with a diene side chain. Also heterocyclic ring systems (**10**) can be coupled using the Stille approach.[18] The Sonogashira reaction resulted in the generation of enyne side chains (**11**, **12**), while the Negishi coupling allowed the introduction of alkyl groups.[19] The methylated peptide **13** was used to determine the absolute configuration of the newly formed stereogenic center. The "unlike" product was confirmed by simple hydrogenation of **13** and HPLC analysis of the corresponding leucine peptide obtained.



Scheme 5. Cross-coupling reactions of iodinated peptide **8**: a) 1 mol% [{(allyl)PdCl}$_2$], 2 mol% PPh_3, THF, 60 °C; b) 3 mol% [Pd(PPh_3)$_4$], 10 mol% CuI, NEt_3, THF, 50 °C; c) 2 mol% [{(allyl)PdCl}$_2$], 4 mol% PPh_3, THF, 0 °C→RT.

Peptides with a vinyl iodide side chain are interesting substrates not only for cross-couplings, but also for carbonylation reactions (Scheme 6).[20] This allows the formation of glutamic acid derivatives. For example, if this, also palladium-catalyzed reaction is carried out in alcohol as the solvent, the corresponding ester (**14**, **15**) is formed directly. Switching to other, non-nucleophilic solvents allows the trapping of the in situ formed acyl–Pd complex with other nucleophiles such as amines (→**16**) and amino acids (→**17**) in nearly quantitative yield. Reaction with peptides allows a straightforward incorporation of the side chain into a peptide (**18**).



Scheme 6. Coupling of iodinated **8** with CO insertion: a) 3 mol% [Pd(PPh_3)$_4$], 1 atm CO, 3 equiv NEt_3, RT; b) 5 mol% [Pd(PPh_3)$_4$], 1 atm CO, 4 equiv NEt_3, THF, RT.

In conclusion, the palladium-catalyzed allylic alkylation is an excellent tool for the stereoselective synthesis of stannylated peptides. These can be subjected to a wide range of further modifications, which allows the generation of peptides with structurally diverse, unusual side chains. Attempts to obtain the corresponding "like" products (*S*,*S* or *R*,*R*) as well as synthetic applications of this protocol are currently under investigation.

Experimental Section

Synthesis of **3a**: Hexamethyldisilazane (936 mg, 5.8 mmol) was dissolved in an oven-dried Schlenk flask in abs. THF (6 mL) before *n*BuLi (1.6 M in hexane, 3.3 mL, 5.3 mmol) was added slowly at −78 °C. The cooling bath was removed and the colorless solution was stirred at room temperature for 10 min, before it was cooled again to −78 °C. In a second Schlenk tube $ZnCl_2$ (245 mg, 1.8 mmol) was dried with a heat gun in high vacuum. After cooling to room temperature (*S*)-TFA-Phe-Gly-O*t*Bu (562 mg, 1.5 mmol) was added in THF (3 mL). This solution was added slowly to the LHMDS solution at −78 °C, and stirring was continued for 30 min. In a third Schenk tube [{(allyl)PdCl}$_2$] (5.5 mg, 15 μmol) and PPh_3 (15.7 mg, 60 μmol) were stirred in THF (0.5 mL) for 5 min, before **2c** (755 mg, 1.8 mmol) was added. This solution was added dropwise to the cold zinc enolate solution. The excess dry ice was removed from the cooling bath, and the reaction mixture was allowed to warm to 0 °C. After dilution with ether, the reaction was quenched with NH_4OAc/HOAc buffer, and the aqueous layer was extracted with ether. After the combined organic layers had been dried (Na_2SO_4) and the solvents removed by evaporation in vacuo, the crude product was purified by flash chromatography (silica, hexanes/EtOAc/NEt_3 95:4:1). Yield: 765 mg (1.09 mmol, 73%) **3a** as colorless crystals; m.p. (hexanes/Et_2O) 55–56 °C. $[\alpha]_D^{20} = -6.3$ ($c = 1.0$, $CHCl_3$, 98% ds). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.84$ (t, $J = 7.3$ Hz, 9H), 0.89 (dt, $J = 50.8$, 8.1 Hz, 6H), 1.27 (tq, $J = 7.3$, 7.3 Hz, 6H), 1.35 (s, 9H), 1.40–1.54 (m, 6H), 2.27 (dd, $J = 14.1$, 8.1 Hz, 1H), 2.49 (dd, $J = 14.1$, 6.2 Hz, 1H),), 2.97 (dd, $J = 13.8$, 7.9 Hz, 1H), 3.06 (dd, $J = 13.8$, 5.8 Hz, 1H), 4.49 (ddd, $J = 7.7$, 7.7, 5.5 Hz, 1H), 4.58 (ddd, $J = 7.5$, 7.5, 6.2 Hz, 1H), 5.12 (dd, $J = 59.5$, 1.3 Hz, 1H), 5.53 (dd, $J = 128.0$, 1.1 Hz, 1H), 5.77 (d, $J = 7.6$ Hz, 1H), 7.11–7.25 ppm (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 9.6$ (d, $J = 328$ Hz), 13.7, 27.4 (d, $J = 57.4$ Hz), 27.9, 29.0 (d, $J = 19.7$ Hz), 38.5, 44.1 (d, $J = 40.3$ Hz), 52.6 (d, $J = 12.4$ Hz), 54.5, 82.5, 115.6 (q, $J = 288$ Hz), 127.5, 128.3 (d, $J = 23.6$ Hz), 128.9, 129.2, 135.3, 149.6, 156.6 (q, $J = 37.6$ Hz), 168.4, 170.5 ppm. ^{119}Sn NMR (149 MHz, $CDCl_3$): $\delta = -43.7$ ppm. Elemental analysis (%) 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.

Synthesis of **8**: Iodine (195 mg, 0.77 mmol) was added in portions to a solution of **3a** (270 mg, 0.38 mmol) in Et_2O (10 mL) at room temperature, and the solution was stirred for 30 min. After the solution had been washed three times with 10% $Na_2S_2O_3$ and brine and then dried (Na_2SO_4), the solvent was removed in vacuo and the crude product was purified by flash chromatography (silica, hexanes/EtOAc, 1. 95:5; 2. 85:15). Yield: 204 mg (0.377 mmol, 99%) **8** as colorless crystals, m.p. (hexane/Et_2O): 119–120 °C. $[\alpha]_D^{20} = -4.6$ ($c = 1.0$, $CHCl_3$, 99% ds). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.37$ (s, 9H), 2.59 (dd, $J = 14.8$, 7.4 Hz, 1H), 2.67 (dd, $J = 14.8$, 6.2 Hz, 1H), 3.03 (dd, $J = 13.8$, 7.7 Hz, 1H), 3.08 (dd, $J = 13.8$, 6.3 Hz, 1H), 4.53 (ddd, $J = 7.7$, 7.7, 6.2 Hz, 1H), 4.66 (ddd, $J = 7.6$, 7.6, 6.5 Hz, 1H), 5.69 (s, 1H), 5.93 (s, 1H), 6.14 (d, $J = 7.7$ Hz, 1H), 7.13–7.30 ppm (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 27.9$, 38.5, 47.1, 52.4, 54.6, 83.3, 103.4, 115.6 (q, $J = 288$ Hz), 127.5, 128.5, 129.3, 135.2, 156.6 (q, $J = 37.7$ Hz), 168.9, 169.1 ppm. Elemental analysis (%) calcd for $C_{20}H_{24}F_3IN_2O_4$ (540.07): C 44.46, H 4.48, N 5.18; found: C 44.68, H 4.33, N 5.24. HPLC (Reprosil 100 Chiral-NR 8 μm, hexane/*i*PrOH 99:1, 2.0 mL min^{-1}, 209 nm): $t_{(S,S)} = 9.15$ min, $t_{(S,R)} = 12.03$ min.

Synthesis of **13**: Dimethylzinc (2 M in toluene, 0.23 mL, 0.46 mmol) was added to a solution of **8** (81 mg, 0.15 mmol), [{(allyl)PdCl}$_2$] (1.1 mg, 3.0 μmol) and PPh_3 (1.6 mg, 6.0 μmol) in abs. THF (3 mL) at 0 °C. After the reaction mixture had been stirred for 24 h at room temperature, *t*BuOH (0.5 mL) was added and the solvents were removed in vacuo. The crude product was purified by flash chromatography (hexanes/CH_2Cl_2 6:4) giving **13** (54 mg, 0.126 mmol, 84 %) as colorless crystals, m.p. (hexane/Et_2O): 114 °C. $[\alpha]_D^{20} = +3.5$ ($c = 1.0$, 98 % ds, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.35$ (s, 9H), 1.63 (s, 3H), 2.20 (dd, $J = 14.0$, 7.8 Hz, 1H), 2.28 (dd, $J = 14.1$, 6.3 Hz, 1H), 3.03 (dd, $J = 13.8$, 7.5 Hz, 1H), 3.08 (dd, $J = 13.8$, 6.8 Hz, 1H), 4.41 (ddd, $J = 7.7$, 7.7, 6.3 Hz, 1H), 4.56 (s, 1H), 4.64 (ddd, $J = 7.7$, 7.7, 6.9 Hz, 1H), 4.71 (s, 1H), 6.33 (d, $J = 7.7$ Hz, 1H), 7.11–7.25 (m, 5H), 7.51 ppm (d, $J = 7.7$ Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 21.7$, 27.9, 38.6, 40.6, 51.1, 54.7, 82.6, 114.6, 115.8 (q, $J = 286$ Hz), 127.4, 128.8, 129.3, 135.3, 140.3, 156.6 (q, $J = 37.2$ Hz), 168.8, 170.5 ppm. Elemental analysis (%) calcd for $C_{21}H_{27}F_3N_2O_4$ (428.46): C 58.87, H 6.35, N 6.54; found: C 59.02, H 6.30, N 6.54. HRMS (CI) calcd for $C_{21}H_{28}F_3N_2O_4$ $[M+H]^+$: 429.2001; found: 429.2041. HPLC (Reprosil 100 Chiral-NR 8 μm, hexane/*i*PrOH 99.5/0.5, 1.5 mL min^{-1}, 209 nm): $t_{(S,S)} = 16.65$ min, $t_{(S,R)} = 22.07$ min.

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