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Highly Stereoselective Peptide Modifications through Pd-Catalyzed Allylic Alkylations of Chelated Peptide Enolates

Jan Deska and Uli Kazmaier*[a]

Dedicated to Professor Lutz Tietze on the occasion of his 65th birthday

Abstract: Deprotonation of peptides in the presence of zinc chloride gives rise to highly reactive nucleophiles that can be subjected to palladium-catalyzed allylic alkylation reactions. Excellent diastereoselectivities are obtained that are nearly independent of the allylic substrate used. By using this protocol, highly functionalized side chains can also be incorporated in excellent yields and selectivities. The stereochemical outcome of the reaction is exclusively controlled by the peptide chain as long as terminal π-allyl–palladium complexes are involved. Probably, there is a threefold coordination, at least, of the deprotonated peptide chain to the chelating zinc ion. In such metal peptide complexes, one face of the generated enolate is shielded by the side chain of the adjacent amino acid, thus directing the electrophilic attack onto the opposite face. This behavior explains why an *S* amino acid always generates an *R* amino acid (and the other way round).

Keywords: allylic alkylation · asymmetric synthesis · chelates · palladium · peptide modification · peptides

Introduction

Small peptides, linear as well as cyclic, are found as metabolites in a wide range of microorganisms, sponges, and fungi. Many of these peptides show highly interesting biological properties[1] and are therefore suitable candidates as lead structures for the synthesis of drugs.[2] On the basis of their non-ribosomal peptide synthesis (NRPS),[3] these "lower organisms" can incorporate unusual amino acids with "exotic" side chains and *N*-methylated or D-amino acids into their metabolites.[4] In addition, cyclic structures have been found. In most cases, the unusual amino acids participate significantly in binding towards an enzyme or receptor and are therefore (at least in part) responsible for the biological activity.

For synthetic and medicinal chemists, this behavior leads to the challenge of developing synthetic strategies towards these unusual peptides that are as flexible as possible to generate libraries of structurally related derivatives for structure–activity studies.[5] An alternative to the classical approach, the stepwise coupling of commercially available or separately synthesized amino acids, is the incorporation of a (unusual) side chain into a given peptide, a so-called backbone modification. This route has the advantage that a wide range of derivatives can readily be prepared from a single peptide without repetition of the peptide synthesis for each modification. In principle, various types of intermediates can be involved in the C–C coupling step, such as glycine cations,[6] radicals,[7] or anions.[8] The major problem of this efficient process is control of the stereochemical outcome of the C–C bond formation, especially in the modification of linear peptides. For cyclic peptides, the selectivities are generally better, because one face of the reaction intermediate can be shielded by the peptide ring.[9] The most spectacular example reported so far was the modification of cyclosporine, as reported by Seebach et al.[10] In this case, a single sarcosine subunit was alkylated stereoselectively. Recently, Maruoka and co-workers[11] reported the stereoselective functionalization of peptide Schiff bases[12] by chiral phase-transfer catalysis. The fine tuning of the catalyst allowed the introduction of various substituents at the N-terminus of the peptide chain with remarkable selectivity.

Our group has been involved in peptide modifications for some time,[13] and our aim is to use the chiral information of

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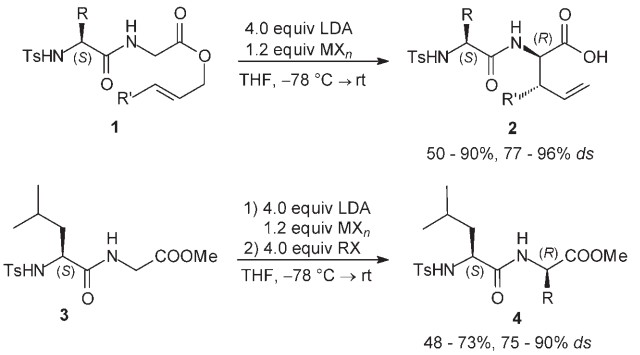
the peptide chain to control the stereochemical outcome of the modification step by taking advantage of metal–peptide complexes.[8d] In the case of peptide Claisen rearrangements, good results were obtained with tosyl-protected peptides, such as **1**.[14] Although the yields and selectivities varied depending on the chelating metal salt (MX_n) used, the *S,R* diastereomer was always formed preferentially (Scheme 1). This behavior can be explained by a multifold

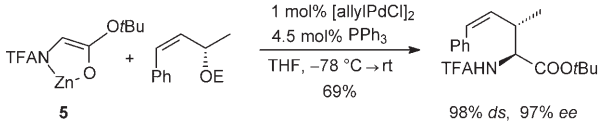


Scheme 1. Stereoselective modifications of peptides. LDA = lithium diisopropylamide, M = metal, Ts = tosyl.

coordination of the peptide chain to the metal ion,[8d] and the shielding of one face of the enolate by the side chain of the neighboring amino acid. The highly ordered transition state of the Claisen rearrangement might also favor the transfer of chirality.

Very recently, we showed that tosyl-protected peptides **3** also undergo diastereoselective modifications in an intermolecular fashion, for example, through alkylation or aldol reactions.[15] Unfortunately, the tosyl protecting group is difficult to remove, which results in a serious limitation of this protocol and the need to find other protecting groups that give good yields and selectivities.

Independent of this consideration, we were able to develop new protocols towards unsaturated amino acids through Pd- or Rh-catalyzed allylic alkylations[16,17] of chelated glycine ester enolates **5**. These enolates are much more reactive relative to the generally used stabilized enolates and undergo allylation already at −78 °C.[18] With these enolates, therefore, isomerization processes (e.g., of the double bond) can be suppressed completely, a precondition for highly selective reactions (Scheme 2).[19]

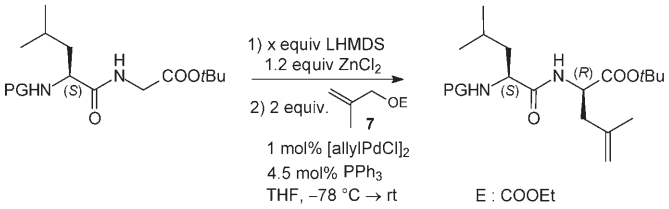


Scheme 2. Isomerization-free allylation of chelated glycine ester **5**. TFA = trifluoroacetyl.

Results and Discussion

Herein, we report the transfer of this protocol from amino acids to peptides and its application to highly stereoselective peptide modifications. We began our investigations with the protected leucine dipeptides **6** and methallyl carbonate **7** under the reaction conditions shown (Table 1). The *tert*-butyl ester was chosen to avoid side reactions, such as transesterifications with the ethylate moiety liberated from **7** (which is a serious problem if the corresponding methyl esters are used). Zinc chloride was superior to other metal salts with respect to a clean conversion, which is in good agreement with observations made from other alkylations of chelated enolates. LHMDS was preferred as the base (instead of LDA) to avoid epimerization of the newly formed stereogenic center. To obtain complete conversion of the peptide, we used an excess of **7**. Interestingly, the results obtained were comparable to those of the Claisen rearrangement and the alkylation reactions. The carbamate-protected peptides **6a** and **6b** gave the best yields (Table 1, entries 1 and 2), whereas the tosyl derivative **6c** showed the highest selectivity (Table 1, entry 3). Based on our positive experiences with TFA protecting groups in the allylic alkylation of glycine enolates, we subjected the TFA-protected peptide **9a** to our reaction conditions, and indeed, the yield could be increased relatively to **6c**, whereas the selectivity was unchanged. Regarding the amount of base used, 3.5 equivalents of LHMDS seemed to be a good compromise with respect to yield and selectivity (Table 1, entry 5).

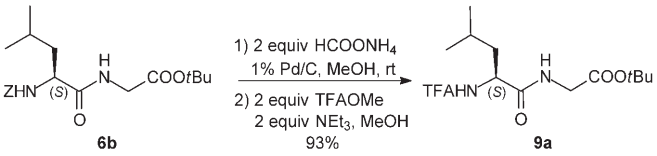
Table 1. Allylic alkylations of leucine dipeptides.



Entry	Peptide	Protecting group	Equiv LHMDS	Product	Yield [%]	d.r. (*S,S*)/(*S,R*)
1	**6a**	Boc	4	**8a**	67	30:70
2	**6b**	Z	4	**8b**	67	37:64
3	**6c**	Ts	4	**8c**	40	14:86
4	**9a**	TFA	4	**10a**	63	13:87
5	**9a**	TFA	3.5	**10a**	74	16:84
6	**9a**	TFA	3.2	**10a**	63	17:83

Under these optimized conditions, we investigated the allylation of a range of different TFA-protected dipeptides. Unfortunately, these peptides can not be directly obtained by simple peptide coupling of TFA-protected amino acids because of their configurational lability. In some cases, nearly complete racemization was observed,[20] probably through the formation of azlactone intermediates.[21] Therefore, the required dipeptides were prepared from the corresponding Z-protected derivatives, for example, the synthesis

of **9a** (Scheme 3). For the introduction of the TFA group, methyl trifluoroacetate proved superior to the generally used trifluoroacetic anhydride, which showed side reactions



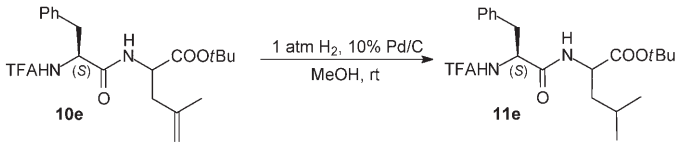
6b 9a

Scheme 3. Preparation of TFA-protected dipeptides. Z = BnOCO.

with several substrates. But with the methyl ester, the required peptides were obtained in 71–99% yield.

The results obtained with the different TFA-protected peptides **9** are summarized in Table 2. As expected, the selectivity increased with increasing steric demand of the inducing amino acid. The alanine peptide **9b** gave the worst result, whereas the *tert*-leucine derivative **9f** gave the best, although in this case the yield was lower. Surprisingly, with some substrates, such as **9d**, the yields varied dramatically and it was difficult to get reproducible results (Table 2, entry 4). Therefore we had a closer look at the reaction conditions with our model peptide **9a**. We found, that the reaction proceeded under very mild conditions, and **10a** was obtained in 50% yield if the temperature was kept at −78°C overnight (Table 2, entry 7). But in general, the yield was higher if the reaction mixture was warmed to −20°C overnight in the presence of 4 mol% Pd^0 (Table 2, entries 8–10).

Interestingly, the selectivity was nearly unchanged under the different reaction conditions. The selectivity was determined by HPLC using the chiral column Reprosil Chiral NR. In all the cases investigated so far, the minor diastereomer was eluted first. To determine the absolute configuration of the allylation product, the peptides **10** were subjected to catalytic hydrogenation (Scheme 4), and the HPLC chromatograms were compared with those of the corresponding



10e 11e

	ret. time	Conf.
minor isomer:	13.97 min	(*S*,*S*)
major isomer:	19.62 min	(*S*,*R*)

Scheme 4. Determination of configuration.

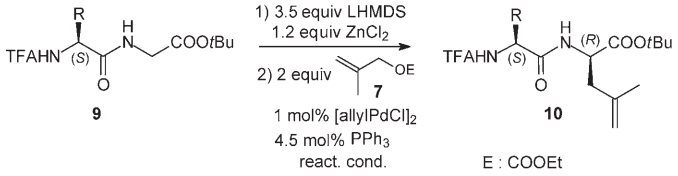
peptides **11** containing (*S*)-leucine, as illustrated with peptide **10e**. We found that the reference *S*,*S* peptides correspond to the minor isomer, so obviously the *S*,*R* stereoisomer is formed preferentially, which is in good agreement with results obtained earlier, for example, in the peptide Claisen rearrangements.[14,22]

In case of methallyl carbonate **7**, the use of an excess of allylating agent caused no problems as the reagent is inexpensive. But bearing in mind that this protocol might be applied to drug synthesis, in which more complicated and synthetically valuable side chains could be incorporated, a twofold excess is not really attractive, especially if the substrate cannot be recovered. Therefore, we were interested in whether it is possible to change the ratio and use the peptide in excess to get a clean conversion of the allylating reagent (Table 3; the yields are calculated relative to the allyl substrate).

Surprisingly, the yield could be increased with an excess of enolate, and even more interestingly, the selectivity also increased. For reactions with valuable allylic substrates, the optimal conditions seem to be a 1.5-fold excess of the peptide enolate (Table 3, entry 4). As long as only proteinogenic amino acids are incorporated, such an excess can be tolerated, especially because the excess peptide can be recovered relatively easily by chromatography.[22]

Therefore, the allylation of our TFA-protected peptides **9** was reinvestigated again under these "optimized" conditions (Table 4). Indeed, both the yield and the selectivity increased in most cases. Even with **9b**, the peptide with the "smallest" amino acid alanine, the selectivity could be increased to 83% (Table 4, entry 1). All other peptides gave

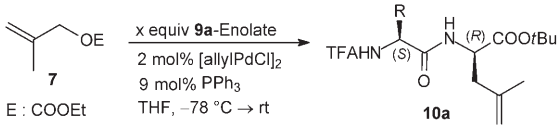
Table 2. Allylic alkylations of various dipeptides **9**.



9 10

Entry	Peptide	R	Reaction conditions	Product	Yield [%]	d.r. (*S*,*S*)/(*S*,*R*)
1	**9a**	*i*Bu	−78°C to rt, overnight	**10a**	74	16:84
2	**9b**	Me	−78°C to rt, overnight	**10b**	52	29:71
3	**9c**	CH_2OMOM	−78°C to rt, overnight	**10c**	61	24:76
4	**9d**	CH_2CH_2SMe	−78°C to rt, overnight	**10d**	30–70	11:89
5	**9a**	*i*Bu	−78°C, 17 h	**10a**	50	16:84
6	**9a**	*i*Bu	−78→−20°C, 4.5 h, 2 mol% [{allylPdCl}$_2$]	**10a**	81	16:84
7	**9e**	Bn	−78→−20°C, 4.5 h, 2 mol% [{allylPdCl}$_2$]	**10e**	82	11:89
8	**9f**	*t*Bu	−78°C to −20°C, 4.5 h, 2 mol% [{allylPdCl}$_2$]	**10f**	59	9:91

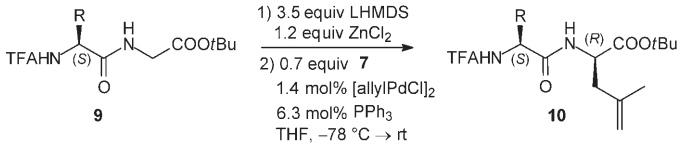
Table 3. Inversion of the reagent excess.



Entry	Equiv **9a**	Yield [%]	d.r. (*S*,*S*)/(*S*,*R*)
1	0.5	81[a]	16:84
2	1.0	60	12:88
3	1.2	77[b]	10:90
4	1.5	90[b]	8:92
5	2.0	91[b]	10:90

[a] Calculated relative to the peptide enolate. [b] Calculated relative to the allyl carbonate.

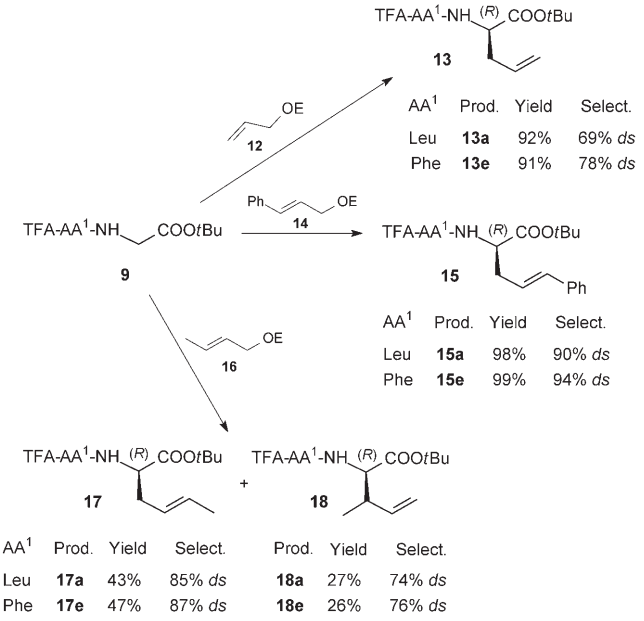
Table 4. Allylic alkylations of various dipeptides **9** revisited.



Entry	Peptide	R	Product	Yield [%]	d.r. (*S*,*S*)/(*S*,*R*)
1	**9b**	Me	**10b**	85	17:83
2	**9c**	CH_2OMOM	**10c**	72	25:75
3	**9d**	CH_2CH_2SMe	**10d**	89	10:90
4	**9e**	Bn	**10e**	92	7:93
5	**9f**	*t*Bu	**10f**	73	7:93
6	**9g**	*p*-MeOBn	**10g**	93	8:92
7	**9h**	$CH_2OTBDPS$	**10h**	98	8:92

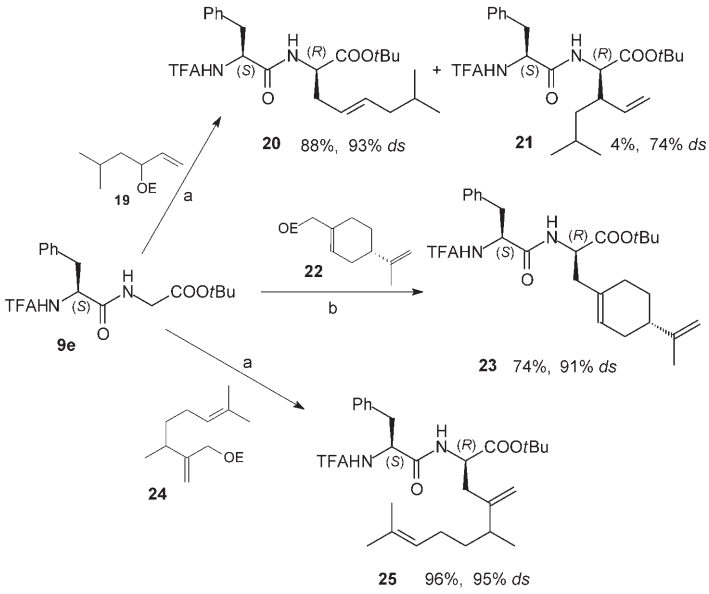
selectivities of $\geq 90\%$, except the MOM-protected serine peptide **9c** (Table 4, entry 2), which gave the worst result. But this problem could be readily solved by introduction of the more sterically demanding, and therefore stronger directing, TBDPS protecting group (**9h**; Table 4, entry 7).

To assess out the scope and limitations of this protocol, we varied the allylating reagents (Scheme 5). The simple allyl carbonate **12** seems to be the worst-case scenario. Independent of the peptide used, the diastereomers of **13** are only formed in a ratio of 2:1–3:1. But the selectivities were much better with all other substrates. For example, the cinnamyl derivative **14** gave the allylation products **15** in quantitative yield and excellent diastereoselectivities (*ds*). Although an unsymmetrical π-allyl complex was formed as an intermediate, only attack of the peptide enolate at the terminal position of the allyl complex was observed, thus giving rise to the product with the linear side chain as the sole regioisomer. The situation with crotyl carbonate **16** is slightly different: As expected, the regioisomeric branched product **18** was formed in a comparable yield; however, a second set of diastereomers was formed, which makes substrates of this type less attractive. But this problem is not a result of the peptide allylation but of the allylic alkylation itself.



Scheme 5. Introduction of several unfunctionalized side chains. Reaction conditions: allylic substrate (0.7 equiv), [{allylPdCl}$_2$] (1.4 mol%), PPh_3 (6.3 mol%), LHMDS (3.5 equiv), $ZnCl_2$ (1.2 equiv), THF, −78→−55°C. AA = amino acid, E = electrophile.

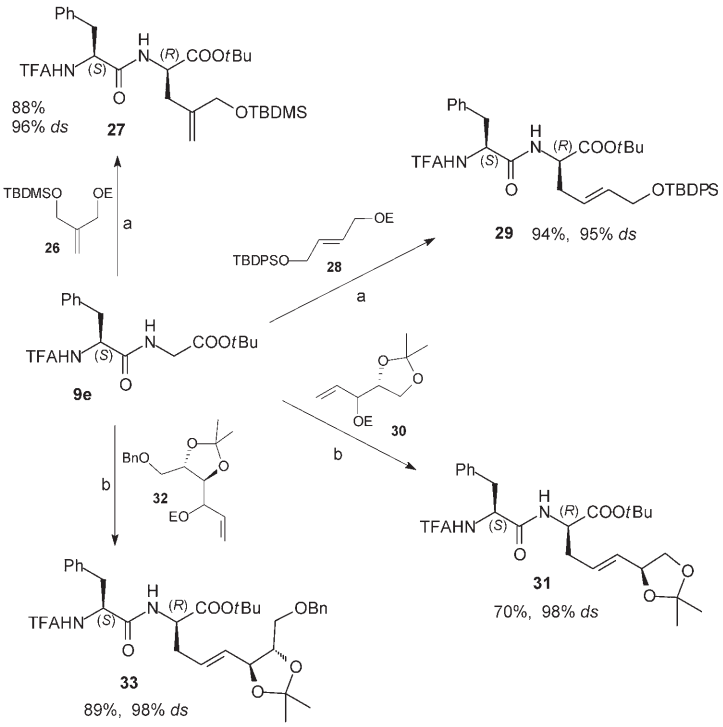
The formation of the branched product is by far less dramatic if allylic substrates with more sterically demanding substituents are used (Scheme 6). For example, with carbonate **19**, the linear product **20** was the major product and formed with excellent diastereo- and regioselectivity. Using the terpenoid substrate **22**, no reaction was observed on



Scheme 6. Regioselective introduction of several aliphatic side chains. Reaction conditions: a) allylic substrate (0.7 equiv), [{allylPdCl}$_2$] (1.4 mol%), PPh_3 (6.3 mol%), LHMDS (3.5 equiv), $ZnCl_2$ (1.2 equiv), THF, −78→−55°C; b) **22** (0.5 equiv), [{allylPdCl}$_2$] (1 mol%), PPh_3 (4.5 mol%), LHMDS (3.5 equiv), $ZnCl_2$ (1.2 equiv), THF, −78→55°C.

warming the reaction mixture to room temperature. In this special case, heating to 55 °C was required to get consumption of the carbonate, and allylation product **23** was obtained as the only regioisomer in good yield. This case impressively demonstrates the extraordinary thermal stability of the chelated peptide enolates. Substrate **24**, readily prepared from citronellal, opens up access to another terpene-type side chain in both excellent yield and selectivity.

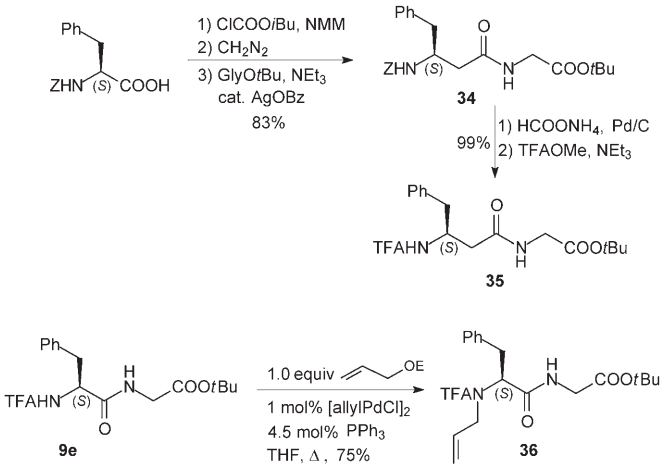
For drug syntheses, it might be also interesting to incorporate side chains bearing functional groups. A few examples of peptides with oxygenated side chains are shown in Scheme 7. The oxygenated allylic substrates seem to be



Scheme 7. Regioselective introduction of several functionalized side chains. Reaction conditions: a) allylic substrate (0.7 equiv), [{allylPdCl}$_2$] (1.4 mol%), PPh_3 (6.3 mol%), LHMDS (3.5 equiv), $ZnCl_2$ (1.2 equiv), THF, −78→−55 °C; b) the same as (a), but warming to 0 °C was required. TBDMS = *tert*-butyldimethylsilyl, TBDPS = tert-butyldiphenylsilyl ether.

even more suitable than the unfunctionalized side chains. In all the examples investigated so far, the selectivities were 95% or higher and the yields were very high. These findings allowed the direct incorporation of sugar-type side chains into a given peptide. Substrates **30** and **32** could readily be obtained by addition of a vinyl Grignard reagent to the corresponding aldehyde. In this case, the configuration of the leaving group had no influence as terminal π-allyl complexes isomerize readily and the stereochemical outcome of the allylation reaction is solely controlled by the peptide.

To explain the stereochemical outcome of the reaction, one might assume a threefold coordination of the peptide chain towards the chelating zinc ion, as proposed earlier for the peptide Claisen rearrangement.[13,14] In such complexes, one face of the enolate should be shielded by the side chain of the adjacent amino acids. It is known from X-ray analysis of metal–peptide complexes that the phenyl rings of aromatic side chains can especially interact with the chelating metal center,[23] which would explain why these peptides show the highest selectivities. If this assumption is correct, one might expect that the selectivity would fall if the phenylalanine is replaced by a more flexible β amino acid. In addition, alkylation of the TFA–amide functionality should suppress the proposed threefold coordination completely, thus resulting in a loss of stereoselectivity. To prove this prediction, the required substrates were prepared according to Scheme 8. For the preparation of a prolonged phenylalanine



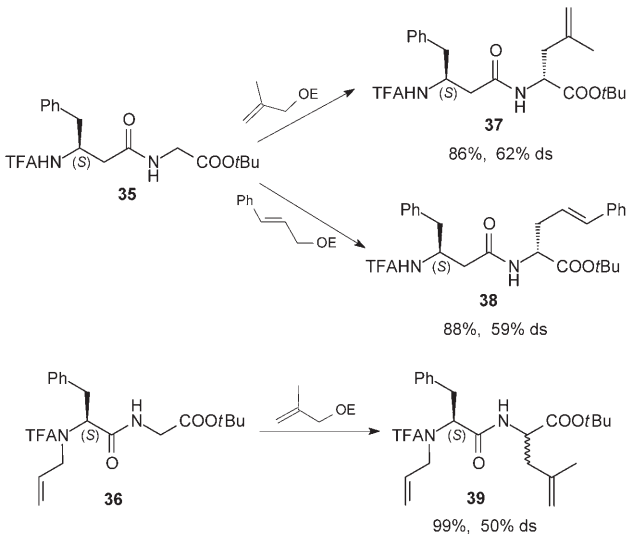
Scheme 8. Preparation of modified dipeptides. NMM = *N*-methylmorpholine.

derivative **35**, a Z-protected phenylalanine was subjected to an Arndt–Eistert homologation. Decomposition of the intermediate diazoketone was accomplished directly in the presence of *tert*-butyl glycinate, thus giving rise to the Z-protected β-dipeptide **34**.[24] Replacing the protecting group with TFA was carried out analogously to the dipeptide prepared previously. TFA-protected peptides can be readily *N*-allylated under neutral conditions by using palladium catalysis.[25] Using this protocol, peptide **36** was obtained directly from **9e**.

And indeed, allylation of these two peptides gave exactly the expected results (Scheme 9). With the prolonged peptide **35**, the selectivities dropped dramatically, and the *N*-alkylated derivative gave a 1:1 diastereomeric mixture of **39** in quantitative yield. These results support the theory of multifold coordination of the peptide chain.

Conclusion

In conclusion, we have shown that chelated peptide enolates are excellent nucleophiles for stereoselective palladium-catalyzed allylic alkylations. All the results indicate that a



Scheme 9. Allylic alkylations of modified dipeptides. Reaction conditions: allylic substrate (0.7 equiv), [{allylPdCl}$_2$] (1.4 mol%), PPh_3 (6.3 mol%), LHMDS (3.5 equiv), $ZnCl_2$ (1.2 equiv), THF, $-78\rightarrow-55\,^{\circ}C$.

threefold coordination of the peptide chain is the reason for the high selectivities obtained. Even highly functionalized and complex side chains can be introduced in excellent yields and selectivities. Applications of this protocol towards natural product synthesis and investigations of chiral π-allyl complexes are currently in progress.

Experimental Section

General remarks: All the reactions were carried out in oven-dried glassware (100 °C) under argon. All the solvents were dried before use: THF was distilled from $LiAlH_4$ and CH_2Cl_2 from CaH_2 and stored over molecular sieves. The products were purified by flash chromatography on silica gel (32–63 μm). Mixtures of ethyl acetate and hexanes were generally used as the eluents. Analysis by TLC was carried out on commercially precoated Polygram SIL-G/UV 254 plates (Machery—Nagel, Dueren). Visualization was accomplished with UV light, $KMnO_4$ solution, or iodine. Melting points were determined on a Büchi melting-point apparatus and are uncorrected. ^1H and ^{13}C NMR spectroscopic analysis was performed on Bruker AC-500 or Bruker DRX-500 spectrometers. Selected signals for the minor diastereomers are extracted from the spectra of the diastereomeric mixture. The values for diastereomeric excess were determined on by analytical HPLC using a Trentec Reprosil-100 Chiral-NR 8 μm-column and a Shimadzu UV detector. Optical rotations were measured on a Perkin–Elmer polarimeter PE 241. Chemical ionization (CI) mass-spectrometric analysis was performed on a Finnigan MAT 95 machine. Elemental analyses were carried out at the Department of Chemistry, University of Saarland (Germany).

General procedure for the synthesis of TFA-protected peptides: *N*-methylmorpholine (1.05 equiv) and isobutyl chloroformate (1.0 equiv) were added to a solution of the Z-protected amino acid (1.0 equiv) in dry THF (2 mL mmol^{-1}) at −20 °C, and reaction mixture was stirred for 5 min followed by addition of *tert*-butyl glycinate (1.0 equiv). The reaction mixture was diluted with diethyl ether after stirring at room temperature overnight, washed with 1 N HCl, sat. $NaHCO_3$ solution, and brine. The organic layer was dried over Na_2SO_4 and the solvent was evaporated in vacuo. The crude Z dipeptide was dissolved in methanol (1 mL mmol^{-1}), ammonium formate (2–3 equiv) and palladium on charcoal were added at room temperature and the reaction mixture was stirred until analysis by TLC showed complete conversion (20–90 min). After addition of diethyl ether (2 mL mmol^{-1}), the reaction mixture was filtered through celite and concentrated in vacuo. The free amine was redissolved in methanol (2 mL mmol^{-1}), triethylamine (2 equiv) and methyl trifluoroacetate (2 equiv) were added at 0 °C and the reaction mixture was stirred overnight at room temperature. The solvent was evaporated and the residue was partitioned between diethyl ether and 1 N HCl. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The title compound was purified by column chromatography or recrystallization.

***tert*-Butyl (*N*-trifluoroacetyl-(*S*)-leucyl)glycinate (9a)**: According to the general procedure for peptide coupling, starting from Z-(*S*)-leucine, **9a** was obtained after recrystallization (hexane, dichloromethane) as a colorless solid in a yield of 8.06 g (23.7 mmol, 90%). M.p. 113–115 °C; $[\alpha]_D^{20}=-25.6$ ($c=1.0$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta=7.50$ (d, $J=8.5$ Hz, 1H; NH), 6.71 (t, $J=5.1$ Hz, 1H; NH), 4.58 (dt, $J=8.5$, 5.7 Hz, 1H; NCH), 3.84 (dd, $J=18.0$, 5.4 Hz, 1H; NCH_2), 3.86 (dd, $J=18.3$, 5.1 Hz, 1H; NCH_2), 1.66 (m, 3H; $CH(CH_3)_2$, $CHCH_2CH$), 1.44 (s, 9H; $C(CH_3)_3$), 0.92 (d, $J=3.5$ Hz, 3H; $CH(CH_3)_2$), 0.91 ppm (d, $J=3.8$ Hz, 3H; $CH(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=168.4$, 170.7 (CON, COO), 157.0 (q, $J=37.2$ Hz; CF_3CO), 115.7 (q, $J=286$ Hz; CF_3), 82.7 ($C(CH_3)_3$), 52.0 (NCH), 42.1 (NCH_2), 41.5 ($CHCH_2CH$), 28.0 ($C(CH_3)_3$), 24.7 ($CH(CH_3)_2$), 22.7 ($CH(CH_3)_2$), 21.9 ppm ($CH(CH_3)_2$); HRMS (CI) calcd for $C_{10}H_{16}F_3N_2O_4$ $[M-C_4H_8]^+$: 285.1017; found: 285.1033; elemental analysis calcd (%) for $C_{14}H_{23}F_3N_2O_4$ (340.36): C 49.41, H 6.81, N 8.23; found: C 49.30, H 6.64, N 8.25.

(*S*)-*tert*-Butyl (*N*-trifluoroacetyl-(*S*)-phenylalanyl)glycinate (9e): According to the general procedure for peptide coupling, starting from Z-(*S*)-phenylalanine, **9e** was obtained after recrystallization (hexane, dichloromethane) as a colorless solid in a yield of 1.45 g (3.87 mmol, 95%). M.p. 134 °C; $[\alpha]_D^{20}=+19.5$ ($c=1.0$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta=7.38$ (d, $J=7.5$ Hz, 1H; NH), 7.17–7.30 (m, 5H; C_6H_5), 6.18 (t, $J=4.5$ Hz, 1H; NH), 4.71 (dt, $J=7.5$, 6.5 Hz, 1H; NCH), 3.88 (dd, $J=18.2$, 5.1 Hz, 1H; NCH_2), 3.81 (dd, $J=18.2$, 5.0 Hz, 1H; NCH_2), 3.13 (dd, $J=13.8$, 6.4 Hz, 1H; $C_6H_5CH_2$), 3.08 (dd, $J=13.7$, 7.5 Hz, 1H; $C_6H_5CH_2$), 1.43 ppm (s, 9H; $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=168.0$, 169.2 (CON, COO), 156.7 (q, $J=37.2$ Hz; CF_3CO), 127.5, 128.8, 129.2, 135.3 (C_6H_5), 115.6 (q, $J=286$ Hz; CF_3), 82.8 ($C(CH_3)_3$), 54.7 (NCH), 42.0 (NCH_2), 38.5 ($C_6H_5CH_2$), 28.0 ppm ($C(CH_3)_3$); HRMS (CI) calcd for $C_{17}H_{21}F_3N_2O_4$ $[M]^+$: 374.1453; found: 374.1464; elemental analysis calcd (%) for $C_{17}H_{21}F_3N_2O_4$ (374.39): C 54.54, H 5.65, N 7.48; found: C 54.53, H 5.58, N 7.46.

General procedure for allylic alkylations of peptides: *n*-Butyllithium (1.6 M in hexanes, 0.82 mL, 1.31 mmol) was added dropwise to a solution of hexamethyldisilazane (233 mg, 1.44 mmol) in dry THF (2 mL) at −78 °C. The cooling bath was removed, and the solution was allowed to warm up to room temperature. In a second flask, $ZnCl_2$ (57 mg, 0.42 mmol) was carefully dried in vacuo with a heat gun. After the mixture was cooled to room temperature, the corresponding dipeptide (0.375 mmol) was added dissolved in dry THF (2 mL). The freshly prepared LHMDS solution was cooled to −78 °C and the $ZnCl_2$/peptide solution was slowly added by syringe. In a third flask, [{allylPdCl}$_2$] (1.8 mg, 5.0 μmol) and PPh_3 (5.9 mg, 22.5 μmol) were dissolved in dry THF (0.5 mL), allylic carbonate (0.25 mmol) was added, and the catalyst/carbonate solution was transferred to the cold solution of the zinc enolate by syringe. The excess dry ice was removed from the cooling bath, and the reaction mixture was allowed to warm up. After diluting with diethyl ether, the mixture was quenched by the addition of 1 N HCl (sat. NH_4Cl was added if substrates with acid labile groups were used). The aqueous layer was extracted twice with diethyl ether and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography (silica gel, hexane/ethyl acetate).

***tert*-Butyl (*N*-trifluoroacetyl-(*S*)-leucyl)-(*R*)-4,5-didehydroleucinate (10a)**: Following the general procedure, peptide **9a** (128 mg, 0.375 mmol) and carbonate **7** (36 mg, 0.25 mmol) were subjected to the peptide allylation. After column chromatography (silica gel, hexane/ethyl acetate 92:8) peptide **10a** (88 mg, 0.223 mmol; 89%) was obtained as a colorless oil. $[\alpha]_D^{20}=-30.7$ ($c=1.0$, $CHCl_3$, 92% *ds*). Major diastereomer: ^1H NMR

(500 MHz, $CDCl_3$): $\delta = 7.42$ (d, $J = 7.1$ Hz, 1H; NH), 6.49 (d, $J = 7.3$ Hz, 1H; NH), 4.81 (s, 1H; C=CH_2), 4.72 (s, 1H; C=CH_2), 4.50–4.56 (m, 2H; NCH), 2.51 (dd, $J = 14.0$, 5.6 Hz, 1H; H_2C=CCH_2), 2.36 (dd, $J = 14.0$, 8.3 Hz, 1H; H_2C=CCH_2), 1.72 (s, 3H; CCH_3), 1.51–1.68 (m, 3H; CH-$(CH_3)_2$, CHCH_2CH), 1.42 (s, 9H; $C(CH_3)_3$), 0.90 ppm (d, $J = 4.8$ Hz, 6H; CH(CH_3)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 170.1$, 170.7 (CON, COO), 156.9 (q, $J = 37.2$ Hz; CF_3CO), 140.5 (C=CH_2), 115.8 (q, $J = 285$ Hz; CF_3), 114.6 (C=CH_2), 82.6 ($C(CH_3)_3$), 52.1 (NCH), 51.1 (NCH), 41.7 (CHCHCH), 40.8 (H_2C=CCH_2), 27.9 (C(CH_3)$_3$), 24.7 ($CH(CH_3)_2$), 22.7 (CH(CH_3)$_2$), 22.1 (CH(CH_3)$_2$), 21.7 ppm (CCH_3). Minor diastereomer (selected signals): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.42$ (d, $J = 7.4$ Hz, 1H; NH), 4.80 (s, 1H; C=CH_2), 4.70 (s, 1H; C=CH_2), 1.70 (s, 3H; CCH_3), 1.43 ppm (s, 9H; $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 140.2 (C=CH_2), 82.5 ($C(CH_3)_3$), 41.2 (CHCH_2CH), 40.6 (H_2C=CCH_2), 27.7 ppm ($C(CH_3)_3$); HPLC (Reprosil 100 Chiral-NR 8 μm, hexane/*i*PrOH 98:2, 1.0 mL min^{-1}, 219 nm): $t_{R(S,S)} = 5.79$ min, $t_{R(S,R)} = 7.55$ min; HRMS (CI) calcd for $C_{18}H_{30}F_3N_2O_4$ $[M+H]^+$: 395.2113; found: 395.2119; elemental analysis calcd (%) for $C_{18}H_{29}F_3N_2O_4$ (394.44): C 54.81, H 7.41, N 7.10; found: C 54.97, H 7.26, N 6.94.

***tert*-Butyl (*N*-trifluoroacetyl-(*S*)-phenylalanyl)-(*R*)-4,5-didehydroleucinate (10e)**: Following the general procedure, peptide **9e** (140 mg, 0.375 mmol) and carbonate **7** (36 mg, 0.25 mmol) were subjected to the peptide allylation. After column chromatography (silica gel, hexane/ethyl acetate 92:8) peptide **10e** (99 mg, 0.231 mmol; 92%) was obtained as a colorless solid. M.p. 112–114 °C; $[\alpha]_D^{20} = +3.8$ ($c = 1.0$, $CHCl_3$, 93% *ds*). Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.51$ (d, $J = 7.7$ Hz, 1H; NH), 7.11–7.25 (m, 5H; C_6H_5), 6.33 (d, $J = 7.7$ Hz, 1H; NH), 4.71 (s, 1H; C=CH_2), 4.64 (dt, $J = 7.7$, 7.0 Hz, 1H; NCH), 4.56 (s, 1H; C=CH_2), 4.41 (dt, $J = 7.7$, 6.3 Hz, 1H; NCH), 3.08 (dd, $J = 13.8$, 6.3 Hz, 1H; $C_6H_5CH_2$), 3.03 (dd, $J = 13.7$, 7.5 Hz, 1H; $C_6H_5CH_2$), 2.28 (dd, $J = 14.1$, 6.3 Hz, 1H; H_2C=CCH_2), 2.20 (dd, $J = 14.0$, 7.8 Hz, 1H; H_2C=CCH_2), 1.63 (s, 3H; CCH_3), 1.35 ppm (s, 9H; $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 168.8$, 170.5 (CON, COO), 156.6 (q, $J = 37.2$ Hz; CF_3CON), 140.3 (C=CH_2), 127.4, 128.8, 129.3, 135.3, (C_6H_5), 115.8 (q, $J = 236$ Hz; CF_3), 114.6 (C=CH_2), 82.6 ($C(CH_3)_3$), 54.7 (NCH), 51.1 (NCH), 40.6 (H_2C=CCH_2), 38.6, ($C_6H_5CH_2$), 27.9 (C(CH_3)$_3$), 21.7 ppm (CCH_3). Minor diastereomer (selected signals): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.15$ (d, $J = 7.4$ Hz, 1H; NH), 4.53 (s, 1H; C=CH_2), 3.06 (d, $J = 6.3$ Hz, 1H; $C_6H_5CH_2$), 2.39 (dd, $J = 14.0$, 6.1 Hz, 1H; H_2C=CCH_2), 1.62 (s, 3H; CCH_3), 1.39 (s, 9H; $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 140.3$ (C=CH_2), 82.4 ($C(CH_3)_3$), 40.5 (H_2C=CCH_2), 28.0 ppm (s, $C(CH_3)_3$); HPLC (Reprosil 100 Chiral-NR 8 μm, hexane/*i*PrOH 99.5:0.5, 1.5 mL min^{-1}, 209 nm): $t_{R(S,S)} = 16.65$ min, $t_{R(S,R)} = 22.07$ min; HRMS (CI) calcd for $C_{21}H_{28}F_3N_2O_4$ $[M+H]^+$: 429.2001; found: 429.2041; 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.

Determination of the absolute configuration: For the determination of the absolute configuration of the allylation products, the dehydroleucine derivatives were hydrogenated to the corresponding (*S*,*S*/*R*)-AA-Leu dipeptides, which could be compared with their *S*,*S* analogues (e.g., phenylalanine–leucine dipeptide **11e**).

***tert*-Butyl (*N*-trifluoroacetyl-(*S*)-phenylalanyl)-(*R*)-leucinate ((*S*,*R*)-11e)**: Pd/C (20 mg) was added to peptide **10e** (43 mg, 0.10 mmol) in methanol (2 mL). The reaction mixture was stirred in an atmosphere of H_2 for 30 min. After filtration over silica, **11e** (43 mg, 0.10 mmol, 100%) was obtained as a colorless solid. M.p. 101–102 °C; $[\alpha]_D^{20} = +3.3$ ($c = 1.0$, $CHCl_3$, 93% *ds*). Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.55$ (d, $J = 7.6$ Hz, 1H; NH), 7.12–7.24 (m, 5H; C_6H_5), 6.28 (d, $J = 8.0$ Hz, 1H; NH), 4.67 (dt, $J = 7.4$, 6.7 Hz, 1H; NCH), 4.35 (dt, $J = 8.2$, 5.5 Hz, 1H; NCH), 3.07 (dd, $J = 13.8$, 6.4 Hz, 1H; $C_6H_5CH_2$), 3.03 (dd, $J = 13.8$, 6.4 Hz, 1H; $C_6H_5CH_2$), 1.37–1.54 (m, 3H; CH(CH$_3$)$_2$, CHCH_2CH), 1.40 (s, 9H; $C(CH_3)_3$), 0.83 (d, $J = 6.0$ Hz, 3H; CH(CH_3)$_2$), 0.82 ppm (d, $J =$ 6.0 Hz, 3H; CH(CH_3)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 168.8$, 171.3 (CON, COO), 156.7 (q, $J = 37.8$ Hz; CF_3CON), 127.4, 129.3, 129.7, 135.2 (C_6H_5), 115.6 (q, $J = 287$ Hz; CF_3), 82.2 ($C(CH_3)_3$), 54.6 (NCH), 51.8 (NCH), 41.6 (CHCH_2CH), 38.3, ($C_6H_5CH_2$), 27.9 (C(CH_3)$_3$), 24.8 (CH(CH$_3$)$_2$), 22.5 (CH(CH_3)$_2$), 22.0 ppm (CH(CH_3)$_2$); HPLC (Reprosil 100 Chiral-NR 8 μm, hexane/iPrOH 99.5/0.5, 1.5 mL min^{-1}, 206 nm): $t_{R(S,S)} =$ 13.97 min, $t_{R(S,R)} = 19.62$ min; HRMS (CI) calcd for $C_{21}H_{30}F_3N_2O_4$ $[M+H]^+$: 431.2158; found: 431.2177; elemental analysis calcd (%) for $C_{21}H_{29}F_3N_2O_4$ (430.47): C 58.59, H 6.79, N 6.51; found: C 59.05, H 6.76, N 6.26.

***tert*-Butyl (*N*-trifluoroacetyl-(*S*)-phenylalanyl)-(*S*)-leucinate ((S,S)-11e)**: (*S*)-Cbz-Phenylalanine (90 mg, 0.30 mmol) and (S)-*tert*-butyl leucinate hydrotosylate (108 mg, 0.30 mmol) were treated according to the general procedure for peptide coupling. Column chromatography (silica gel, hexane/ethyl acetate 85:15) yielded **11e** (108 mg, 0.25 mmol, 83%) as a colorless solid. M.p. 95–96 °C; $[\alpha]_D^{20} = +7.5$ ($c = 1.0$; $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.55$ (d, $J = 7.6$ Hz, 1H; NH), 7.12–7.24 (m, 5H; C_6H_5), 6.28 (d, $J = 8.0$ Hz, 1H; NH), 4.67 (dt, $J = 7.4$, 6.7 Hz, 1H; NCH), 4.35 (dt, $J = 8.2$, 5.5 Hz, 1H; NCH), 3.07 (dd, $J = 13.8$, 6.8 Hz, 1H; $C_6H_5CH_2$), 3.03 (dd, $J = 13.8$, 6.4 Hz, 1H; $C_6H_5CH_2$), 1.37–1.54 (m, 3H; CH(CH$_3$)$_2$, CHCH_2CH), 1.40 (s, 9H; $C(CH_3)_3$), 0.83 (d, $J = 6.0$ Hz, 3H; CH(CH_3)$_2$), 0.82 ppm (d, $J = 6.0$ Hz, 3H; CH(CH_3)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 168.8$, 171.3 (CON, COO), 156.7 (q, $J = 37.8$ Hz; CF_3CON), 127.4, 129.3, 129.7, 135.2 (C_6H_5), 115.6 (q, $J = 287$ Hz; CF_3), 82.2 ($C(CH_3)_3$), 54.6 (NCH), 51.8 (NCH), 41.6 (CHCH_2CH), 38.3, ($C_6H_5CH_2$), 27.9 (C(CH_3)$_3$), 24.8 (CH(CH$_3$)$_2$), 22.5 (CH(CH_3)$_2$), 22.0 (CH(CH_3)$_2$); HPLC (Reprosil 100 Chiral-NR 8 μm, hexane/*i*PrOH 99.5:0.5, 1.5 mL min^{-1}, 206 nm): $t_{R(S,S)} = 13.94$ min.

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