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Selective Peptide Modifications via Ruthenium-Catalyzed Allylic Alkylations

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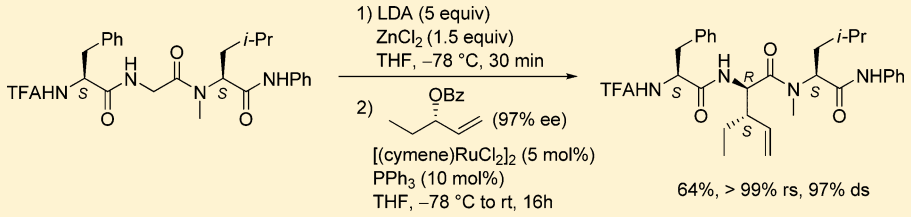
Supporting Information



ABSTRACT: Ruthenium-catalyzed allylic alkylations are an interesting alternative to palladium-catalyzed processes, since they can provide products which are not accessible under Pd-catalysis. Chiral terminal allylic substrates can be reacted with perfect stereo- and regioretention, and also (*Z*)-configured allylic substrates can be converted isomerization-free. This allows highly stereoselective modifications of peptides at glycine subunits. The configuration at the α-position of the new generated α-amino acid can be controlled by the chiral peptide chain, and at the β-position by using chiral allylic substrates.

Microorganisms are highly productive producers of natural products, and a wide range of their secondary metabolites became lead structures for the development of drugs.[1] Peptides and cyclo(depsi)peptides formed by non-ribosomal peptide synthetases (NRPS) are especially interesting from a pharmaceutical point of view.[2] Many of these peptides contain not only (*S*)- and (*R*)-configured or *N*-methylated amino acids but also rather unusual side chains. In classical peptide syntheses, these unusual amino acids are synthesized separately, and are subsequently coupled using suitable coupling reagents. No question, this protocol is suitable for the synthesis of a single target molecule (natural product or drug) but is by far less suited for the synthesis of libraries of related peptidic structures, as required for SAR studies or lead structure optimizations. In these cases, a concept allowing modifications in a very late stage of the synthesis would be much more attractive. Selective peptide modifications are a suitable tool to address this issue, while one can differentiate between two diverse protocols.[3] The advantage of the rather simple side chain modifications results from the fact, that the stereogenic α-center can be transmitted from the parent amino acid,[4] but on the other hand one is limited to the possible modifications of a given functionalized side chain. A significantly higher structural variety can be generated via peptide-backbone modifications, where complete side chains can be introduced at glycine subunits.[3] According to this protocol reactive glycine intermediates are generated in a peptide chain and reacted selectively. These intermediates can be either cations,[5] anions,[6] or even radicals,[7] but the other amino acids in the peptide chain should not be affected under the reaction conditions used.

The control of the stereochemical outcome of this side chain introduction is found to be not a trivial issue. Due to the flexibility of a linear peptide chain, in general diastereomeric mixtures of substitution products are formed.[5−8] The situation is better in the case of cyclic peptides, where one face of the glycine intermediate is shielded by the peptide ring. In this case stereoselective modifications become possible.[9] Probably, the most spectacular natural product modification based on this concept was the stereo- and regioselective alkylation of cyclosporine, reported by Seebach et al.[10]

Since a couple of years our group is also involved in stereoselective peptide modifications, focusing on linear peptides. For example, peptide allylesters can be subjected to a stereoselective chelate enolate Claisen rearrangement, where the stereochemical outcome is controlled by the stereogenic centers in the peptide chain.[11] An (*S*)-amino acid generates an adjacent new (*R*)-amino acid and *vice versa*. In case of *trans*-substituted allylic esters the new β-branched amino acid is formed with *syn*-configuration. Alternatively, similar unsaturated side chains can also be introduced via Pd-catalyzed allylic alkylation, generating also the (*S*)/(*R*)-peptides.[12] This approach nicely complements the Claisen rearrangement, since the *anti*-configured amino acids can be obtained by this protocol. But in contrast to the chelate Claisen rerarrangement, the Pd-catalyzed version is not limited to *C*-terminal glycine units, but can also be applied in the middle of a peptide chain, as long as an amide enolate can be formed.[13] Excellent diastereoselectivities are obtained with sterically demanding allylic substrates (>95% ds) (Scheme 1).[12] Although this sounds pretty good, the Pd-catalyzed version has nevertheless some drawbacks.

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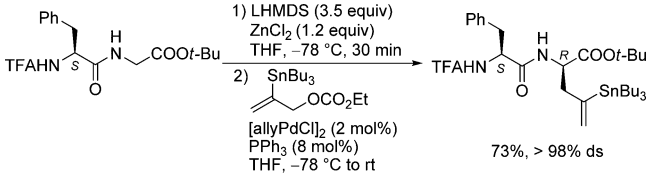
Scheme 1. Stereoselective Pd-Catalyzed Allylation of Peptides

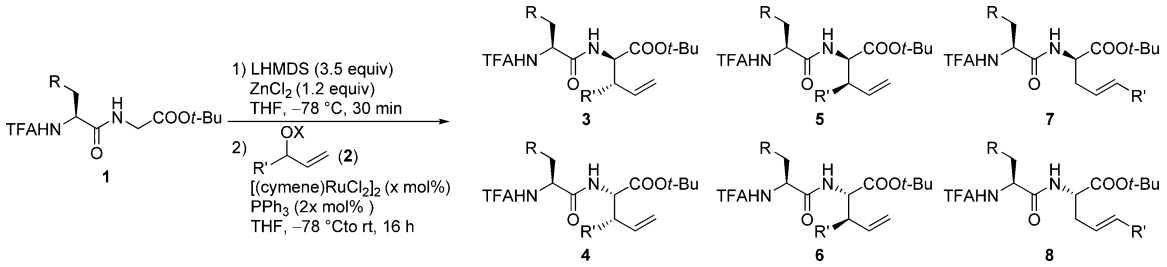


The reactions proceed via π-allyl complexes, generating regioisomeric mixtures if 1,3-disubstituted allylic substrates are used. If terminal π-allyl complexes are formed, the nucleophilic attack of the peptide enolate occurs preferentially at the sterically least hindered position, generating only linear side chains. In addition, terminal π-allyl Pd-complexes are highly sensitive to isomerization,[14] resulting in a racemization of chiral allylic substrates. With highly reactive chelated glycine ester enolates such isomerizations can be suppressed almost completely[15] but not with the less reactive peptide enolates.[16] A (*Z*/*E*)-isomerization is also observed if (*Z*)-configured allyl substrates are used. In these cases the thermodynamically more stable (*E*)-configured side chains are incorporated almost exclusively into the peptides.

This forced us to search for an alternative protocol. Although Pd is the by far most often used transition metal for allylic alkylations, several other metals such as Ir[17] or Ru[18] moved mainstream during the last years.[19] Recently, we reported Ru-catalyzed allylic alkylations of chelated glycine ester enolates, proceeding with excellent regioretention (>95% rs).[20] In addition, no isomerizations were observed if $[(\text{cymene})\text{RuCl}_2]_2$ was used as catalyst.[21] We assume that with this catalyst the allylations probably proceed via a (σ+π)-allyl complex (regioretention via double S_N'-reaction), as discussed also for Rh-catalyzed processes,[22] and not via a π-allyl complex as with the Pd catalysts. Other Ru complexes such as $[\text{Cp*Ru}(\text{MeCN})_3]\text{PF}_6$ seem to react via such π-allyl complexes, showing a significantly lower regioretention (75% rs).[23] The isomerization-free and highly regioselective allylations with $[(\text{cymene})\text{RuCl}_2]_2$ prompted us to investigate this catalyst also for peptide allylations, since this protocol should allow the stereoselective incorporation of β-branched amino acids into peptides. The configuration at the β-position should be transferred from a chiral allylic substrate (stereoretention), while the configuration at the α-position should be controlled by the peptide chain, in analogy to the Pd protocol.[12]

To prove the appropriations of peptide enolates in Ru-catalyzed allylic alkylations, we exemplarily investigated two peptides **1**, using the reaction conditions optimized in the Pd-catalyzed reactions. We used *N*-trifluoroacetylated *tert*-butyl esters, which in general give the best yields and selectivities. The nucleophile (deprotonated dipeptide) was used in a slight excess. In principle, six different products can be formed, which should be separable by chromatography (Table 1). Besides the four β-branched products **3**–**6**, the linear products **7** and **8** also might be formed, and the product ratio should depend on the configuration of the chiral allylic substrate used (matched/mismatched situation). To prove this option we used *rac*-butenyl acetate **2a** in our initial experiments (entry 1). In good yield a mixture of the four expected β-branched products (**3**–**6**) was obtained, while the linear products were not observed. This clearly indicates that peptide enolates also react with terminal allylic substrates with perfect regioretention. In addition, the adjacent chiral amino acid caused a high induced diastereoselectivity of 90% (**3** + **5**/**4** + **6**). The (*S*)-configured acetate reacts faster than the (*R*)-form, since 70% of the peptide shows a (3*S*)-configuration (**3** + **4**/**5** + **6**). To verify this observation and to assign the stereoisomers we also subjected *rac*-pentenyl acetate **2b** to the same reaction conditions (entry 2). In this case catalytic hydrogenation removes the stereogenic β-center, and the remaining stereoisomers are clearly the result of the induced distereoselectivity. In this case the yield was slightly lower as in the first example, but the selectivities observed were comparable. Also here the (3*S*)-isomer was

Table 1. Ru-Catalyzed Allylic Alkylations of Dipeptide Esters 1



											product ratio [%]					
entry	**1**	R	equiv **1**	**2**	R′	OX	conf.	ee	*x*	yield [%]	**3**	**4**	**5**	**6**	**7**	**8**
1	**1a**	Ph	1.5	**2a**	Me	OAc	(*R*/*S*)	–	2	74	63	7	27	3	0	0
2	**1a**	Ph	1.3	**2b**	Et	OBz	(*R*/*S*)	–	2	54	64	10	23	3	0	0
3	**1a**	Ph	1.3	**2b**	Et	OBz	(*S*)	97	2	54	83	14	3	0	0	0
4	**1a**	Ph	1.3	**2c**	Ph	OAc	(*R*/*S*)	–	2	34	49	6	26	3	14	2
5	**1a**	Ph	1.3	**2c**	Ph	OAc	(*R*)	99	2	43	67	9	7	1	14	2
6	**1b**	OTBDPS	1.3	**2c**	Ph	OAc	(*R*)	99	2	67	72	15	3	0	9	1
7	**1a**	Ph	1.3	**2c**	Ph	OAc	(*R*)	99	5	63	66	10	7	1	14	2
8	**1a**	Ph	2.0	**2c**	Ph	OAc	(*R*)	99	5	78	62	9	6	0	19	4
9	**1a**	Ph	2.0	**2c**	Ph	OAc	(*S*)	97	5	80	4	1	73	6	13	3
10	**1a**	Ph	2.0	**2d**	Me	OBz	(*S*)	97	5	99	74	20	3	0	3	0
11	**1a**	Ph	2.0	**2b**	Et	OBz	(*S*)	97	5	95	73	19	3	0	4	1

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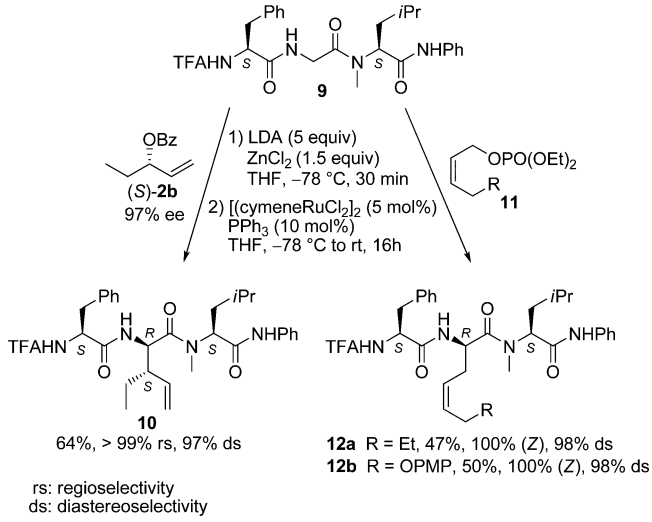
formed in excess (74%). Afterward, the same experiment was carried out with the almost enantiomerically pure (*S*)-**2b**, verifying the yields and selectivities. Reisolated allylic substrate and peptide had an unchanged ee of 97%, clearly indicating that under our reaction conditions neither the allylic substrate nor the peptides undergo epimerization.

Aryl-substituted allyl substrates often behave differently from the corresponding alkyl analogues.[24] Therefore, we also investigated the reaction of phenyl-substituted allyl acetate **2c** in racemic as well as enantiopure form (entries 4 and 5). Indeed, significant differences could be observed. Not only was the yield lower, in these cases also the linear product was formed as a side product (~15%). The induced diastereoselectivity (88−89% ds) was comparable to the results obtained with the Pd catalysts, although in this case only the linear product was formed.[12] Also here, one of the enantiomers of **2c** reacted preferentially (entry 4). Due to altered Cahn−Ingold−Prelog preferences,[25] the (3*R*)-isomer is incorporated preferentially (3*R*:3*S* = 65:35). The slower reacting (*S*)-**2c** was enriched in the recovered starting material (20% ee). Interestingly, even if enantiopure **2c** was used, a certain amount (8%) of the (3*S*)-isomers **5** and **6** were formed (entry 5), clearly indicating that either the allyl substrate **2c** or the allyl-ruthenium complex formed underwent isomerization during the reaction. To prove this option we isolated unreacted **2c** and recognized a drop of the ee value from 99% to 90%. Comparable isomerizations were observed by Kawatsura et al. in allylations of malonates with this catalyst.[26] To figure out if this is a general problem in Ru-catalyzed peptide allylations, we investigated several other peptides such as the *O*-protected serine derivative **1b**. In this case almost no isomerization was observed and the yield was also higher (entry 6). The moderate yields obtained with **2c** forced us to optimize the reaction conditions. An increase of the catalyst concentration to 5 mol % caused an increased yield, without significant influence on the product ratio (entry 7). A further improvement was observed by using the peptide enolate in excess (2 equiv) (entry 8). Interestingly, under competitive conditions the slower reacting (*S*)-**2c** gave the allylation product in almost the same yield and even slightly better selectivity, without significant isomerization (entry 9). By far the best results were obtained with the corresponding benzoates **2b** and **2d**. In an almost perfect yield and regioretention the reaction proceeded isomerization free with an induced diastereoselectivity of ~4:1 (entries 10 and 11).

To determine the configuration of the new products we synthesized reference samples via chelate Claisen rearrangement. In this case also the (*S*/*R*)-peptides are formed preferentially, while the new amino acid is obtained as the *syn*-isomer (90−95% *syn*).[11] This allows an easy assignment of the isomers via HPLC. To differentiate between the induced and the simple diastereoselectivity, we subjected the allylation products obtained from **2b** to catalytic hydrogenation providing only two isomers in the ratio of 6:1 (entry 3) or 4:1 (entry 11).

To illustrate that this protocol is not limited to terminal dipeptide esters but can also be applied to larger peptides and also in the middle of a peptide chain, we investigated allylations of tripeptide **9** (Scheme 2). In this case the valuable peptide and the allylic substrate were reacted in a stoichiometric 1:1 ratio. Under the reaction conditions used, the acidic NH bonds were deprotonated, protecting the adjacent stereogenic centers from epimerization.[6] Only the central glycine unit was able to form an amide enolate. Reaction with the almost enantiopure

Scheme 2. Ru-Catalyzed Allylic Alkylations of Tripeptide 9



benzoate (*S*)-**2b** gave access to the allylation product **10** with excellent regio- and diastereoselectivity and with perfect chirality transfer. Only traces of the other stereoisomers could be detected by HPLC.

Another great advantage of Ru-catalyzed allylations is the isomerization-free allylation using (*Z*)-allyl substrates, while in this case best results are obtained with allyl phosphates.[20] To depict that the good results obtained with glycine ester enolates can also be transferred to peptides, **9** was also reacted with two (*Z*)-allyl phosphates **11a** and **11b**. With perfect retention of the olefin geometry the desired products **12** were formed almost diastereomerically pure. The yields in both reactions were in the range of 50%, and unreacted dipeptide could be recovered almost completely (33−50%).

In conclusion, it was shown that the Ru-catalyzed allylic alkylation is an excellent tool to modify peptides not only at the *C*-terminus (via ester enolate) but also in the middle of a peptide chain (via amide enolate). The reactions proceed isomerization-free and in the case of alkyl-substituted allylic substrates with perfect regioretention. Therefore, the Ru-catalyzed reactions show a completely different reaction behavior compared to the Pd-catalyzed processes. The stereochemical outcome at the α-position of the newly formed amino acid is controlled by the peptide chain, while the configuration at the β-position can be transferred from the allylic substrate (stereoretention).

EXPERIMENTAL SECTION

General Remarks. All air- or moisture-sensitive reactions were carried out in dried glassware (>100 °C) under an atmosphere of nitrogen. THF was distilled from Na/benzophenone. The products were purified by flash chromatography on silica gel columns (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. Visualization was accomplished with UV-light and $KMnO_4$ solution. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded with a 400 MHz (^1H) and 100 MHz (^{13}C) spectrometer in $CDCl_3$. Chemical shifts are reported in ppm relative to TMS, and $CHCl_3$ was used as the internal standard. The correct assignment of signals was verified by *H*,*H*-COSY and *C*,*H*-COSY spectral data. Selected signals for the minor regio- and diastereomers are extracted from the spectra of the isomeric mixture. Regioisomeric and diastereomeric ratios were determined by HPLC equipped with a chiral ReproSil 100 Chiral-NR column (250 mm × 4.6 mm, 100 Å, 8

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μm). *n*-Hexane/isopropanol was used as eluent. In cases where separation on HPLC was not sufficient, integration of characteristic ^{1}H NMR signals was additionally used. Chirality transfer was determined by comparison of product mixtures received starting from racemic with those of enantiopure substrates. Absolute stereochemistry of the products **3a** and **5c** was assigned by comparison with products obtained by peptide ester enolate Claisen rearrangement of the corresponding crotyl or cinnnamyl esters.[27] Mass spectra were recorded with a high resolution quadrupole spectrometer (CI) and with an ion trap spectrometer (ESI).

Synthesis of Starting Materials. Allylic alcohols as precursors for **2a**, **2b**, **11a**, and **11b** were purchased from commercial suppliers. The racemic precursor for **2c** was prepared by addition of vinylmagnesium bromide to benzaldehyde. Enzymatic resolution of the resulting allylic alcohol with Novozyme 435 led to (*R*)-**2c** and after the acetylation of the remaining enantiomer with acetanhydride to (*S*)-**2c**.[28] **11a** and **11b** were prepared as described previously.[15b] (*S*)-**2a** and (*S*)-**2b** were obtained by the method described by Feringa et al.[29] The allylic alcohols were converted to benzoates, acetates, and phosphates by standard literature methods.[30]

The dipeptides **1a** and **1b** were obtained by standard peptide coupling respectively of *N*-Boc-protected phenylalanine and *O*-TBDPS-serine with *tert*-butyl glycinate using *iso*-butyrochloroformate (IBCF) and *N*-methyl morpholine (NMM) as base, followed by Boc-deprotection and Tfa-protection of the *N*-terminus.[12b] *N*,*N*-Boc-methyl leucine was obtained by *N*-methylation of Boc-leucine with methyl iodide and sodium hydride in THF.[31]

(*S*)-*N*,*N*-(*tert*-Butoxycarbonyl)methyl-leucine Anilide. To a stirred solution of *N*,*N*-Boc-methyl leucine (6.13 g, 25.0 mmol) and *N*-methyl morpholine (2.53 g, 25.0 mmol) in THF (75 mL) *iso*-butyrochloroformate (3.25 g, 23.8 mmol) was slowly added at −10 °C. After 15 min at this temperature a solution of aniline (2.33 g, 25.0 mmol) in THF (25 mL) was added, and the reaction mixture was stirred at rt for 16 h. The resulting solution was diluted with diethyl ether, washed with 1 M HCl, sat. $NaHCO_3$ solution, water, and brine. The organic layer was dried over Na_2SO_4, and the solvent was removed in vacuo. The residue was suspended twice in *n*-pentane and filtered, giving rise to the title compound (23.8 mmol, quant.) as a colorless solid, mp 87−88 °C; $[\alpha]^{20}_D$ = −65.7° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (d, *J* = 6.6 Hz, 3 H), 0.98 (d, *J* = 6.7 Hz, 3 H), 1.50 (s, 9 H), 1.52−1.63 (m, 1 H), 1.64−1.74 (m, 1 H), 1.75−1.95 (m, 1 H), 2.80 (s, 3 H), 4.76 (m, 1 H), 7.08 (m, 1 H), 7.30 (m, 2 H), 7.46−7.52 (m, 2 H), 7.62 and 8.33 (bs, 1 H, 2 rotamers); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.1, 23.1, 24.8, 28.4, 30.1, 36.1, 57.0, 80.9, 119.5, 119.6, 124.1, 129.0, 138.1, 157.4, 169.5; HRMS (CI) *m*/*z* calcd for $C_{18}H_{29}N_2O_3$ $[M + H]^+$: 321.2173, found: 321.2173; Analysis calcd for $C_{18}H_{28}N_2O_3$: C, 67.47, H, 8.81, N 8.74; found: C 67.84, H 8.98, N 8.72.

(*S*)-*N*-Methyl-leucine Anilide. To a stirred solution of (*S*)-*N*,*N*-Boc-methyl-leucine anilide (3.20 g, 10.0 mmol) in CH_2Cl_2 (6 mL) was slowly added trifluoroacetic acid (6 mL) at 0 °C. The reaction mixture was stirred at rt for 16 h. The solvent was removed in vacuo, the residue was dissolved in sat. $NaHCO_3$ solution (20 mL) and extracted twice with ethyl acetate (30 mL each). The combined organic layers were washed with water and brine and dried over Na_2SO_4, and the solvent was removed in vacuo. The title compound was obtained as colorless oil (2.20 g, quant.) which crystallized on standing. $[\alpha]^{20}_D$ = 36.1° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 6.4 Hz, 3 H), 0.98 (d, *J* = 6.4 Hz, 3 H), 1.45 (ddd, *J* = 13.6, 9.2, 5.4 Hz, 1 H), 1.50 (bs, 1 H), 1.63−1.79 (m, 2 H), 2.45 (s, 3 H), 3.09 (dd, *J* = 9.2, 4.5 Hz, 1 H), 7.09 (m, 1 H), 7.28−7.36 (m, 2 H), 7.60 (m, 2 H), 9.30 (bs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.0, 25.1, 34.9, 42.2, 63.8, 119.5, 124.1 (d, C-9), 128.9, 137.8, 171.9; HRMS (CI) *m*/*z* calcd for $C_{13}H_{21}N_2O$ $[M + H]^+$: 221.1648; found: 221.1652. Analysis calcd for $C_{13}H_{20}N_2O$: C, 70.87, H, 9.15, N, 12.72; found: C, 71.03, H, 9.15, N, 12.59.

(*S*)-*N*-Trifluoroacetyl-phenylalanyl-glycyl-(*S*)-*N*-methyl-leucine Anilide (9). To a solution of (*S*)-*N*-TFA-phenylalanyl-glycine (637 mg, 2.00 mmol) was added (*S*)-*N*-methyl-leucine anilide (441 mg, 2.00 mmol) and *N*-methyl-morpholine (242 mg 2.40 mmol) in CH_2Cl_2 (20 mL) propylphosphonic anhydride (T3P) (1.91 g 50% in ethyl acetate, 3.00 mmol). The reaction mixture was stirred for 16 h at rt. Water was added, and the aqueous solution was extracted with ethyl acetate. The combined organic phases were washed with sat. $NaHCO_3$ solution, water, and brine and were dried over Na_2SO_4. The solvent was removed in vacuo, and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 6:4), providing tripeptide **9** as a colorless foam (930 mg, 1.79 mmol, 89% yield). $[\alpha]^{20}_D$ = −110.3° (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 6.5 Hz, 3 H), 0.97 (d, *J* = 6.6 Hz, 3 H), 1.57−1.42 (m, 1 H), 1.70 (ddd, *J* = 14.2, 8.9, 5.6 Hz, 1 H), 1.82 (ddd, *J* = 14.6, 8.3, 6.6 Hz, 1 H), 2.96 (s, 3 H), 3.12 (m, 2 H), 4.06 (d, *J* = 4.1 Hz, 2 H), 4.94 (ddd, *J* = 8.0, 8.0, 8.0 Hz, 1 H), 5.18 (dd, *J* = 8.8, 6.6 Hz, 1 H), 7.06 (m, 1 H), 7.30−7.12 (m, 8 H), 7.40 (d, *J* = 8.0 Hz, 1 H), 7.46 (m, 2 H), 8.11 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.0, 22.9, 25.0, 29.9, 36.6, 38.6, 41.7, 54.4, 55.9, 115.6 (q, J_F = 288 Hz), 119.8, 124.5, 127.4, 128.7, 129.0, 129.1, 135.2, 137.6, 155.9 (q, J_F = 38.1 Hz), 168.2, 169.1, 169.4; Analysis calcd for $C_{26}H_{31}F_3N_4O_4$: C, 59.99, H, 6.00, N, 10.76; found: C, 59.94, H, 6.02, N, 10.50.

General Procedure. Ru-catalyzed allylic alkylations of dipeptide ester enolates were performed with 1 mmol of the allylic substrate in oven-dried glassware (>100 °C) under a nitrogen atmosphere.

Preparation of the des-Zn-Chelated Enolate. In a Schlenk tube was dissolved HMDS (1.14 g, 7.08 mmol, 3.5 equiv/peptide) in absolute THF (2 mL). After cooling to −20 °C a 1.6 M *n*-butyl lithium solution (3.9 mL, 6.23 mmol, 3.1 equiv/peptide) was slowly added. The cooling bath was removed, and the colorless solution was stirred for 15 min at rt. The LHMDS solution was cooled again to −78 °C, before the *N*-trifluoroacetyl-protected dipeptide *tert*-butyl ester **1** (2.00 mmol, 2 equiv) and dry zinc chloride (327 mg, 2.40 mmol, 1.2 equiv/peptide) (dried at 0.01 mbar, > 100 °C) in absolute THF (4 mL) were slowly added. For complete transmetalation the solution was stirred for 45 min at −78 °C.

Preparation of the Catalyst/Allylic Substrate Solution. In a second Schlenk tube di-μ-chlorobis-(*p*-cymene)chlororuthenium (30.6 mg, 50 μmol, 5 mol %) and triphenylphosphine (26.2 mg, 100 μmol, 10 mol %) were dissolved in absolute THF (2.0 mL). The deep-red solution was stirred for 5 min at rt, before the allylic substrate (1.00 mmol) was added.

The catalyst/allylic substrate solution was slowly added to the zinc enolate solution at −78 °C, and the mixture was warmed up to rt overnight. The reaction mixture was diluted with wet diethyl ether and hydrolyzed with 1 M $KHSO_4$ solution. The aqueous phase was three times extracted with ethyl acetate, and the combined organic phases were dried over sodium sulfate. After filtration the solution was concentrated in vacuo. An analytical sample was taken to determine the selectivities, before the crude product was purified by flash chromatography (hexanes/ethyl acetate).

General Procedure. Ru-catalyzed allylic alkylations of internal tripeptide amide enolates were performed with 0.4 mmol of the allylic substrate in oven-dried glassware (>100 °C) under a nitrogen atmosphere.

Preparation of the Zn-Chelated Enolate. *n*-BuLi (1.6 M, 0.51 mL, 0.81 mmol) was added to a solution of DIPA (0.11 mL, 0.84 mmol) in THF (4 mL) in a Schlenk flask at −20 °C. The cooling bath was removed, and stirring was continued for further 10 min before the mixture was cooled again to −78 °C. In a second Schlenk flask a mixture of *N*-protected tripeptide **8** (0.20 mmol) and $ZnCl_2$ (41.7 mg, 0.31 mmol) was dissolved in THF (3 mL). This solution was added to the LDA solution at −78 °C, and the mixture was warmed up to −40 °C within 30 min, before the solution was cooled again to −78 °C and stirred for further 15 min.

Preparation of the Catalyst/Allylic Substrate Solution. The ruthenium catalyst di-μ-chlorobis-(*p*-cymene)chlororuthenium (12.2 mg, 5 mol %) and triphenylphosphine (10.5 mg, 10 mol %) were dissolved in THF (2 mL). After stirring for 10 min at room temperature the allyl substrate (0.40 mmol) was added to the red solution formed.

The resulting mixture was added slowly to the chelated enolate at −78 °C. The solution was allowed to warm up to room temperature

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overnight, before it was diluted with ethyl acetate and 1 M $KHSO_4$ was added. After extraction with ethyl acetate, the organic layers were dried over Na_2SO_4 and concentrated *in vacuo*, and the crude product was purified by flash chromatography (hexanes/ethyl acetate).

***tert*-Butyl (*S*)-*N*-Trifluoroacetyl-phenylalanyl-(2*R*,3*S*)-(1-methylallyl)glycinate (3a).** By following the general procedure for Ru-catalyzed allylic alkylation of dipeptide ester enolates, **3a** (405 mg, 0.95 mmol, 95% yield) was obtained from allyl benzoate (*S*)-**2d** (176 mg, 1.00 mmol, 97% *ee*) and **1a** (749 mg, 2.00 mmol) as a colorless solid consisting of a mixture of mainly branched (97% rs), diastereomeric allylation products with a diastereomeric ratio of 74:20:3:0 in favor of the (*S*,2*R*,3*S*)-isomer. Mp 97−98 °C; $[\alpha]^{20}_D$ = −11.4° (*c* = 1.0, $CHCl_3$). Major diastereomer (*S*,2*R*,3*S*)-**3a** (74%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (d, *J* = 7.0 Hz, 3 H), 1.43 (s, 9 H), 2.49 (m, 1 H), 3.10 (m, 2 H), 4.43 (dd, *J* = 8.3, 4.6 Hz, 1 H), 4.73 (dt, *J* = 7.9, 6.0 Hz, 1 H), 4.92 (ddd, *J* = 17.1, 1.3, 1.3 Hz, 1 H), 5.01 (ddd, *J* = 10.3, 1.3, 1.3 Hz, 1 H), 5.55 (m, 1 H), 6.17 (d, *J* = 8.3 Hz, 1H), 7.29 (m, 5 H), 7.48 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.2, 28.0, 38.7, 40.4, 54.8, 56.6, 82.8, 115.6 (q, J_F = 288 Hz), 116.2, 127.5, 128.9, 129.2, 135.5, 138.2, 156.6 (d, J_F = 37 Hz), 169.0, 169.5. Minor diastereomer (*S*,2*S*,3*R*)-**4a** (20%): ^{1}H NMR (400 MHz, $CDCl_3$, selected signals): δ = 0.99 (d, *J* = 7.4 Hz, 1 H), 1.48 (s, 9 H), 2.69 (m, 1 H), 4.43 (dd, *J* = 8.3, 5.0 Hz, 1 H), 6.09 (d, *J* = 8.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, selected signals): δ = 15.8, 39.1, 40.2, 54.7, 56.9, 82.6, 115.6 (q, J_F = 288 Hz), 116.9, 128.8, 129.4, 135.2, 137.4, 169.0, 169.5; HPLC (Reprosil, *n*-hexane/*i*PrOH = 99:1, 1.0 mL/min, 210 nm): t_R [(*S*,2*S*,3*S*)-**4a**] = 14.64′ (21%), t_R [(*S*,2*R*,3*S*)-**3a**] = 21.61′ (79%); HRMS (CI) *m*/*z* calcd for $C_{21}H_{28}F_3N_2O_4$ [M + H]$^+$: 429.1996, found: 429.2007; Analysis calcd for $C_{21}H_{27}F_3N_2O_4$: C, 58.87, H, 6.35, N, 6.54; found: C, 59.25, H, 6.56, N, 6.33.

***tert*-Butyl (*S*)-*N*-Trifluoroacetyl-phenylalanyl-(2*R*,3*S*)-(1-ethylallyl)glycinate (3b).** By following the general procedure for Ru-catalyzed allylic alkylation of dipeptide ester enolates, **3b** (413 mg, 0.97 mmol, 97% yield) was obtained from allyl benzoate (*S*)-**2b** (190 mg, 1.00 mmol, 97% ee) and **1a** (749 mg of 2.00 mmol) as a colorless solid consisting of a mixture of mainly branched (95% rs), diastereomeric allylation products with a diastereomeric ratio of 73:19:3:0 in favor of the (*S*,2*R*,3*S*)-isomer. Mp 77−81 °C; $[\alpha]^{20}_D$ = −1.4° (*c* = 1.0, $CHCl_3$). Major diastereomer (*S*,2*R*,3*S*)-**3b**) (73%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 7.4 Hz, 3 H), 1.24 (m, 2 H), 1.44 (s, 9 H), 2.02 (tdd, *J* = 9.8, 5.8, 5.8, Hz, 1 H), 3.12 (m, 2 H), 4.42 (dd, *J* = 8.4, 5.2 Hz, 1 H), 4.74 (m, 1 H), 4.85 (ddd, *J* = 17.0, 1.1, 1.1 Hz, 1 H), 5.05 (ddd, *J* = 10.2, 1.7, 1.7 Hz, 1 H), 5.39 (m, 1 H), 6.28 (d, *J* = 8.7 Hz, 1 H), 7.27 (m, 5 H), 7.65 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.7, 23.6, 28.0, 38.7, 49.0, 54.9, 55.8, 82.9, 115.6 (q, J_F = 288 Hz), 118.4, 127.4, 128.9, 129.3, 135.4, 136.3, 156.7 (d, J_F = 38 Hz), 169.0, 169.6. Minor diastereomer (*S*,2*S*,3*S*)-**4b** (19%): ^{1}H NMR (400 MHz, $CDCl_3$, selected signals): δ = 0.99 (t, *J* = 7.4 Hz, 1 H), 1.48 (s, 9 H), 2.69 (m, 1 H), 4.43 (dd, *J* = 8.3, 5.0 Hz, 1 H), 6.09 (d, *J* = 8.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, selected signals): δ = 11.6, 23.5, 28.0, 38.1, 49.0, 54.9, 55.8, 82.6, 118.6, 127.4, 128.7, 129.3, 135.2, 135.8, 169.4, 170.0; HPLC (Reprosil, *n*-hexane/*i*PrOH = 99:1, 1.0 mL/min, 210 nm): t_R [(*S*,2*S*,3*S*)-**4b**] = 13.15′ (20%), tt_R [(*S*,2*R*,3*S*)-**3b**] = 20.48′ (74%), t_R [(*S*,2*R*,3*R*)-**5b**] = 22.61′ (3%); HRMS (CI) *m*/*z* calcd for $C_{22}H_{30}F_3N_2O_4$ [M + H]$^+$: 443.2152; found: 443.2150.

***tert*-Butyl (*S*)-*N*-Trifluoroacetyl-phenylalanyl-(2*R*,3*R*)-(1-phenylallyl)glycinate (3c).** By following the general procedure for Ru-catalyzed allylic alkylation of dipeptide ester enolates, **3c** (383 mg, 0.78 mmol, 78% yield) was obtained from allyl acetate (*R*)-**2c** (176 mg, 1.00 mmol, 99% ee) and **1a** (749 mg 2.00 mmol) as a colorless solid consisting of a mixture of mainly branched (77% rs), diastereomeric allylation products with a diastereomeric ratio of 62:9:6:0 in favor of the (*S*,2*R*,3*R*)-isomer. Mp 122−130 °C; $[\alpha]^{20}_D$ = +10.1° (*c* = 1.0, $CHCl_3$). Major diastereomer (*S*,2*R*,3*R*)-**3c** (62%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (s, 9 H), 2.93 (d, *J* = 6.8 Hz, 2 H), 3.71 (dd, *J* = 7.5, 7.5 Hz, 1H), 4.63 (dt, *J* = 7.4, 7.1 Hz, 1 H), 4.84 (dd, *J* = 8.7, 6.5 Hz, 1 H), 5.07 (ddd, *J* = 17.0, 1.1, 1.1 Hz, 1 H), 5.17 (ddd, *J* = 10.3, 1.1, 1.1 Hz, 1 H), 5.93 (ddd, *J* = 17.0, 10.3, 8.3 Hz, 1 H), 6.06 (d, *J* = 8.6 Hz, 1 H), 7.05−7.33 (m, 11 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.8, 38.4, 52.0, 54.8, 56.4, 82.9, 115.5 (q, J_F = 288 Hz), 118.1, 127.4, 127.5, 128.2, 128.7, 128.8, 129.3, 135.1, 136.0, 138.6, 156.6 (d, J_F = 38.0 Hz), 168.9, 169.2. Minor diastereomer (*S*,2*S*,2*R*)-**4c** (9%): ^{1}H NMR (400 MHz, $CDCl_3$, selected signals): δ = 1.22 (s, 9 H), 3.50 (dd, *J* = 8.7, 8.7 Hz, 1H). Minor diastereomer (*S*,2*R*,3*S*)-**5c** (6%): ^{1}H NMR (400 MHz, $CDCl_3$, selected signals): δ = 1.22 (s, 9 H), 3.56 (dd, *J* = 8.3, 8.3 Hz, 1H). The ^{1}H and ^{13}C NMR spectral data of the minor linear regioisomers **7c** and **8c** were in good agreement with the literature data.[13b] HPLC (Reprosil, *n*-hexane/*i*PrOH = 99:1, 1.0 mL/min, 210 nm): t_R [(*S*,2*S*,3*R*)-**4c**] = 8.85′ (9%), t_R [(*S*,2*S*,3*S*)-**6c**] = 10.04′ (0%), t_R [(*S*,2*R*,3*S*)- **5c**] = 13.44′ (6%), t_R [(*S*,2*R*,3*R*)-**3c**] = 15.49′ (62%), t_R [(*S*,*S*)-**8c**] = 18.76′ (4%), t_R [(*S*,*R*)-**7c**] = 23.68′ (19%); HRMS (CI) *m*/*z* calcd for $C_{26}H_{30}F_3N_2O_4$ [M + H]$^+$: 491.2152; found: 491.2148.

***tert*-Butyl (*S*)-*N*-trifluoroacetyl-phenylalanyl-(2*R*,3*S*)-(1-phenylallyl)glycinate (5c).** Following the general procedure for Ru-catalyzed allylic alkylation of dipeptide ester enolates **5c** (390 mg, 0.80 mmol, 80% yield) was obtained from allyl acetate (*S*)-**2c** (176 mg, 1.00 mmol, 97% ee) and **1a** (749 mg, 2.00 mmol) as a colorless solid consisting of a mixture of mainly branched (84% rs), diastereomeric allylation products with a diastereomeric ratio of 4:1:73:6 in favor of the (*S*,2*R*,3*S*)-isomer. $[\alpha]^{20}_D$ = −32.3° (*c* = 1.0, $CHCl_3$).

Major diastereomer (*S*,2*R*,3*S*)-**5c** (87%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 (s, 9 H, 11-H), 3.06 (d, *J* = 6.9 Hz, 2 H), 3.57 (dd, *J* = 8.4, 8.4 Hz, 1H), 4.73 (dt, *J* = 7.4, 7.4 Hz, 1 H), 4.75 (dd, *J* = 8.1, 8.1 Hz, 1 H), 5.11 (ddd, *J* = 16.8, 1.1, 1.1 Hz, 1 H), 5.12 (ddd, *J* = 9.5, 1.1, 1.1 Hz, 1 H), 5.84 (ddd, *J* = 16.8, 10.3, 8.8 Hz, 1 H), 6.25 (d, *J* = 7.1 Hz, 1 H), 7.06 (d, *J* = 7.7 Hz, 1 H), 7.28 (m, 10 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.6, 38.4, 53.0, 54.6, 56.7, 82.5, 115.6 (q, J_F = 288 Hz), 118.3, 127.4, 127.4, 128.3, 128.5, 128.8, 129.2, 135.2, 136.2, 138.7, 156.6 (d, J_F = 38.2 Hz), 169.1, 169.5. Minor diastereomer (*S*,2*S*,3*S*)-**6c** (6%): ^{1}H NMR (400 MHz, $CDCl_3$, selected signals): δ = 1.39 (s, 9 H), 3.69 (dd, *J* = 7.7, 7.7 Hz, 1H), 6.22 (d, *J* = 7.1 Hz, 1 H). Minor diastereomer (*S*,2*R*,3*R*)-**3c** (4%): ^{1}H NMR (400 MHz, $CDCl_3$, selected signals): δ = 1.36 (s, 9 H), 3.72 (dd, *J* = 7.8, 7.8 Hz, 1 H). The ^{1}H and ^{13}C NMR spectral data of the minor linear regioisomer **7c** and **8c** were in good agreement with the literature data.[13b] HPLC (Reprosil, *n*-hexane/*i*PrOH = 99:1, 1.0 mL/min, 210 nm): t_R [(*S*,2*S*,3*R*)-**4c**] = 8.85′ (1%), t_R [(*S*,2*S*,3*S*)-**6c**] = 10.04′ (6%), t_R [(*S*,2*R*,3*S*)-**5c**] = 13.44′ (73%), t_R [(*S*,2*R*,3*R*)-**3c**] = 15.49′ (4%), t_R [(*S*,*S*)-**8c**] = 18.76′ (3%), t_R [(*S*,*R*)-**7c**] = 23.68′ (13%); HRMS (CI) *m*/*z* calcd for $C_{26}H_{30}F_3N_2O_4$ [M + H]$^+$: 491.2152; found: 491.2153; Analysis calcd for $C_{26}H_{29}F_3N_2O_4$): C, 63.66, H, 5.96, N, 5.71; found: C, 63.79, H, 5.84, N, 5.76.

***tert*-Butyl (*S*)-*N*-trifluoroacetyl-*O*-(*tert*-butyldiphenylsilyl)-seryl-(2*R*,3*R*)-(1-phenylallyl)-glycinate (3d).** Following the general procedure for Ru-catalyzed allylic alkylation of dipeptide ester enolates **3d** (447 mg, 0.67 mmol, 67% yield) was obtained from allyl acetate (*R*)-**2c** (176 mg, 1.00 mmol, 98% ee) and **1b** (718 mg, 1.30 mmol) as a colorless solid consisting of a mixture of mainly branched (90% rs), diastereomeric allylation products with a diastereomeric ratio of 72:15:3:0 in favor of the (*S*,2*R*,3*R*)-isomer. Mp 48−50 °C; $[\alpha]^{20}_D$ = −6.3° (*c* = 1.0, $CHCl_3$).

Major diastereomer (*S*,2*R*,3*R*)-**3d** (72%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.09 (s, 9 H), 1.39 (s, 9 H), 3.56 (dd, *J* = 10.4, 6.0 Hz, 1 H), 3.76 (dd, *J* = 8.8, 6.2 Hz, 1 H), 3.89 (dd, *J* = 10.4, 4.3 Hz, 1 H), 4.45 (ddd, *J* = 6.3, 6.3, 4.3 Hz, 1 H), 4.92 (dd, *J* = 8.9, 6.8 Hz, 1 H), 5.08−5.15 (m, 2 H), 6.04 (ddd, *J* = 16.8, 10.4, 8.5 Hz, 1 H), 6.55 (d, *J* = 8.9 Hz, 1 H), 7.08−7.71 (m, 16 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2, 26.8, 27.9, 52.6, 54.6, 56.4, 63.3, 82.8, 118.1, 127.3, 127.9, 128.1, 128.5, 130.2, 132.0, 132.4, 135.4, 135.5, 135.6, 136.0, 138.7, 167.5, 169.2. The signals of C-12 and C-13 were not found. LC-MS (Luna C18(2) 5 cm, 3 μm, H_2O/ACN = 40:60 to 20:80, 1.0 mL/min, 254 nm, ESI$^-$): t_R = 9.00′ (19%, *m*/*z* 667); t_R = 9.97′ (81%, *m*/*z* 667); HRMS (CI) *m*/*z* calcd for $C_{36}H_{44}F_3N_2O_5Si$ [M + H]$^+$: 669.2966; found: 669.2967; Analysis calcd for $C_{36}H_{43}F_3N_2O_5Si$: C, 64.65, H, 6.48, N, 4.19; found C, 64.31, H, 6.23, N, 4.37.

(*S*)-*N*-Trifluoroacetyl-phenylalanyl-(2*R*,3*S*)-(1-ethylallyl)-glycyl-(*S*)-*N*-methyl-leucine Anilide (10). Following the general procedure for Ru-catalyzed allylic alkylation of tripeptide ester enolates

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10 (150 mg, 0.26 mmol, 64% yield) was obtained from allyl benzoate (*S*)-**2b** (58, 0.40 mmol, 97% ee) and tripeptide **9** (208 mg, 0.40 mmol) as a colorless solid consisting of a mixture of diastereomeric allylation products with a diastereomeric ratio of 97:3 in favor of the (*S*,2*R*,3*S*,*S*)-isomer. Mp 65−69 °C; $[\alpha]^{20}_{D} = -96.0°$ (*c* = 1.0, $CHCl_3$). Major diastereomer (*S*,2*R*,3*S*,*S*)-**10** (97%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79 (t, *J* = 7.4 Hz, 3 H), 0.89 (d, *J* = 6.5 Hz, 3 H), 0.96 (d, *J* = 6.7 Hz, 3 H), 1.22−1.52 (m, 3 H), 1.66 (ddd, *J* = 14.5, 10.1, 4.5 Hz, 1 H), 1.90 (ddd, *J* = 14.8, 9.8, 5.5 Hz, 1 H), 2.12 (dddd, *J* = 10.7, 8.3, 8.3, 3.0 Hz, 1 H), 3.08 (s, 3 H), 3.10−3.20 (m, 2 H), 4.63 (dd, *J* = 7.4, 7.4 Hz, 1 H), 4.77 (ddd, *J* = 7.8 Hz, 7.8, 6.0 Hz, 1 H), 5.01 (dd, *J* = 17.0, 1.2 Hz, 1 H), 5.11 (dd, *J* = 10.2, 1.5 Hz, 1 H), 5.27 (dd, *J* = 10.0, 5.4 Hz, 1 H), 5.47 (ddd, *J* = 17.0, 9.9, 9.9 Hz, 1 H), 6.71 (d, *J* = 6.9 Hz, 1 H), 7.08 (m, 1 H), 7.18 (m, 2 H), 7.25−7.33 (m, 5 H), 7.36 (d, *J* = 6.9 Hz, 1 H), 7.55 (m, 2 H), 8.28 (s, 1 H);^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.4, 21.5, 22.8, 23.3, 24.6, 31.4, 36.3, 38.4, 48.3, 53.2, 54.5, 56.2, 115.5 (q, J_F = 288 Hz), 119.3, 120.0, 124.3, 127.5, 128.8, 128.9, 129.1, 135.3, 135.7, 137.8, 156.7 (q, J_F = 38.1 Hz), 168.3, 170.0, 172.8;HPLC (Reprosil, *n*-hexane/*i*PrOH = 9:1 to 7:3, 40 min, 1 mL/min, 252 nm): t_R [(*S*,2*S*,3*S*,*S*)-**10**] = 13.03′ (3%), t_R [(*S*,2*R*,3*S*,*S*)-**10**] = 18.67′ (97%); HRMS (CI) *m*/*z* calcd for $C_{25}H_{33}F_3N_3O_4$ [M − $PhNH_2$]$^+$: 496.2423; found: 496.2412.

(*S*)-*N*-Trifluoroacetyl-phenylalanyl-(*R*)-(2-(*Z*)-hexenyl)-glycyl-(*S*)-*N*-methyl-leucine Anilide (12a). Following the general procedure for Ru-catalyzed allylic alkylation of tripeptide ester enolates **12a** (114 mg, 0.19 mmol, 47% yield) was obtained from allyl phosphate (*Z*)-**11a** (95 mg, 0.40 mmol) and tripeptide **9** (208 mg, 0.40 mmol) as a colorless solid consisting of a mixture of linear, diastereomeric allylation products with a diastereomeric ratio of 98:2 in favor of the (*S*,*R*,*S*)-isomer. $[\alpha]^{20}_{D} = -98.4°$ (*c* = 1.0, $CHCl_3$). Major diastereomer (*S*,*R*,*S*)-**12a** (98%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.6 Hz, 3 H), 0.91 (t, *J* = 7.3 Hz, 3 H), 0.96 (d, *J* = 6.7 Hz, 3 H), 1.37 (m, 2 H), 1.44 (m, 1 H), 1.65 (ddd, *J* = 14.5, 9.7, 4.5 Hz, 1 H), 1.90 (ddd, *J* = 14.3, 8.2, 4.7 Hz, 1 H), 1.96 (dtd, *J* = 7.1, 6.8, 1.3 Hz, 2 H), 2.23−2.38 (m, 2 H), 3.04 (s, 3 H), 3.06 (m, 1 H), 3.17 (dd, *J* = 13.7, 5.6 Hz, 1 H), 4.67 (td, *J* = 6.7, 6.7 Hz, 1 H), 4.73 (ddd, *J* = 7.7, 7.7, 6.0 Hz, 1 H), 5.12 (dt, *J* = 10.8, 7.3 Hz, 1 H), 5.25 (dd, *J* = 9.7, 5.8 Hz, 1 H), 5.55 (dt, *J* = 10.8, 7.4 Hz, 1 H), 6.43 (d, *J* = 6.0 Hz, 1 H), 7.01 (m, 1 H), 7.18−7.22 (m, 2 H), 7.25−7.35 (m, 6 H), 7.54−7.56 (m, 2 H), 8.23 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7, 21.8, 22.6, 23.2, 24.8, 29.3, 29.5, 31.1, 36.2, 38.5, 50.0, 54.4, 56.1, 115.5 (q, J_F = 288 Hz), 119.9, 121.8, 124.3, 127.5, 128.8, 128.9, 129.2, 134.8, 135.2, 137.8, 156.7 (q, J_F = 37.7 Hz), 168.3, 169.4, 172.8. Minor diastereomer (*S*,*S*,*S*)-**12a** (2%): ^{1}H NMR (400 MHz, $CDCl_3$, selected signals): δ = 3.08 (s, 3 H), 4.86 (ddd, *J* = 7.6, 6.2, 6.2 Hz, 1 H), 6.57 (d, *J* = 7.8 Hz, 1 H); HPLC (Reprosil, *n*-hexane/*i*PrOH = 9:1 to 7:3, 40 min, 1 mL/min, 254 nm): t_R [(*S*,*S*,*S*)-**12a**] = 16.12′ (2%), t_R [(*S*,*R*,*S*)-**12a**] = 21.40′ (98%); HRMS (CI) *m*/*z* calcd for $C_{26}H_{35}F_3N_3O_4$ [M − $PhNH_2$]$^+$: 510.2574; found: 510.2563.

(*S*)-*N*-Trifluoroacetyl-phenylalanyl-(*R*)-((4-(4-methoxyphenoxy)-2-(*Z*)-butenyl)-glycyl-(*S*)-*N*-methyl-leucine Anilide (12b). Following the general procedure for Ru-catalyzed allylic alkylation of tripeptide ester enolates **12b** (139 mg, 0.20 mmol, 50% yield) was obtained from allyl phosphate (*Z*)-**11b** (132 mg, 0.40 mmol) and tripeptide **9** (208 mg, 0.40 mmol) as a colorless solid consisting of a mixture of linear, diastereomeric allylation products with a diastereomeric ratio of 98:2 in favor of the (*S*,*R*,*S*)-isomer. $[\alpha]^{20}_{D}$ = −90.4° (*c* = 1.0, $CHCl_3$). Major diastereomer (*S*,*R*,*S*)-**12b** (98%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 6.6 Hz, 3 H), 0.95 (d, *J* = 6.7 Hz, 3 H), 1.43 (m, 1 H), 1.66 (ddd, *J* = 14.6, 10.0, 4.8 Hz, 1 H), 1.90 (ddd, *J* = 14.6, 9.4, 5.5 Hz, 1 H), 2.37−2.54 (m, 2 H), 3.04 (s, 3 H), 3.06−3.12 (m, 2 H), 3.77 (s, 3 H), 4.41 (ddd, *J* = 12.0, 6.3, 0.8 Hz, 1 H), 4.49 (ddd, *J* = 11.8, 6.5, 1.1 Hz, 1 H), 4.68 (ddd, *J* = 7.6, 7.6, 6.2 Hz, 1 H), 4.74 (ddd, *J* = 7.7, 7.1, 7.0 Hz, 1 H), 5.28 (dd, *J* = 10.0, 5.5 Hz, 1 H), 5.46 (dt, *J* = 10.7, 8.3 Hz, 1 H), 5.89 (dt, *J* = 11.4, 6.3 Hz, 1 H), 6.80−6.95 (m, 4 H), 7.01 (d, *J* = 5.8 Hz, 1 H), 7.04−7.14 (m, 3 H), 7.20−7.35 (m, 6 H), 7.54−7.56 (m, 2 H), 8.29 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 23.2, 24.9, 29.8, 31.1, 36.0, 38.4, 49.6, 54.4, 55.7, 56.1, 64.4, 114.9, 115.5 (q, J_F = 288 Hz), 116.0, 119.9, 124.3, 127.5, 127.7, 128.8, 128.9, 129.2, 129.4, 135.1, 137.9, 152.2, 154.5, 156.6 (q, J_F = 37.6 Hz), 168.2, 169.4, 172.3; HPLC (Reprosil, *n*-hexane/*i*PrOH = 9:1 to 7:3, 40 min, 1 mL/min, 254 nm): t_R [(*S*,*S*,*S*)-**12b**] = 35.68′ (2%), t_R [(*S*,*R*,*S*)-**12b**] = 40.11′ (98%); HRMS (CI) *m*/*z* calcd for $C_{31}H_{37}F_3N_3O_6$ [M − $PhNH_2$]$^+$: 604.2629; found: 604.2627.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Analytical data and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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