Preparation and Reactions of Stannylated Amino Acids

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Dedicated to Prof. R. Neidlein on the occasion of his 70th birthday

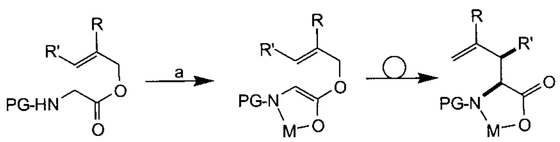
Abstract: Hydrostannations of propargylic glycine esters with the new hydrostannation catalyst $[Mo(CO)_3(CN\textit{t}Bu)_3]$ ($MoBI_3$) gave rise to α-stannylated allylic esters in good yield and with high regioselectivity. The chelate Claisen rearrangements of these esters allow the syntheses of γ,δ-unsaturated amino acids with a vinylstannane moiety in the side chain. The amino acids obtained can be further modified by cross-coupling with various types of electrophiles.

Keywords: amino acids · cross-coupling · hydrostannation · molybdenum · rearrangement

Introduction

γ,δ-Unsaturated amino acids are of great interest, not only as naturally occurring nonproteinogenic amino acids, such as the isoleucine antagonist cyclopentenylglycine[1] and the antibiotic furanomycine,[2] but also as important intermediates for the synthesis of complex amino acids.[3] Therefore, various approaches to the synthesis of this class of amino acids have been described.[4]

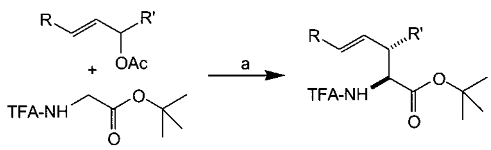
During our studies towards the syntheses of unnatural amino acids we were able to develop a new variation of the ester enolate Claisen rearrangement which is especially suitable for allylic esters of amino acids. Deprotonation of *N*-protected amino acid allylic esters with lithium diisopropylamide (LDA) at $-78\,^{\circ}C$, and subsequent addition of a metal salt (MX_n), presumably results in the formation of a chelated metal enolate (Scheme 1), which undergoes Claisen



Scheme 1. a) 2.2 equiv LDA, 1.2 equiv MX_n.

rearrangement upon warming to room temperature, giving rise to unsaturated amino acids.[5] Due to the fixed enolate geometry the rearrangement proceeds with a high degree of *syn*-selectivity independent of the protecting group (PG) used. This protocol is suitable for various types of allylic and even propargylic esters.[6] Furthermore, chiral amino acids can be obtained through rearrangement and chirality transfer from enantiomerically pure allylic esters,[7] or in the presence of chiral ligands.[8]

Very recently we developed an alternative approach towards this class of unsaturated amino acids through palladium-catalyzed allylic alkylation. We have observed that such chelated ester enolates of amino acids are efficient nucleophiles in palladium-catalyzed allylations (Scheme 2).[9]



Scheme 2. a) 2.5 equiv LHMDS, 1.1 equiv $ZnCl_2$, 1 mol% $[allylPdCl]_2$, 4.5 mol% PPh_3, THF, $-78\,^{\circ}C \rightarrow RT$.

Besides the generally used soft nucleophiles, such as malonates, only a few examples using nonstabilized enolates, such as those of ketones[10] or esters,[11] are described in the literature so far. Therefore, these chelated enolates considerably enlarge the spectrum of potential nucleophiles. If optically active allylic carbonates are used as substrates, the chirality is transferred completely into the amino acid obtained.[12] The *anti*-products are obtained in a highly diastereoselective fashion, and therefore these two protocols complement each other in an ideal way.

A slight drawback of these procedures results from the fact, that each side chain introduced requires the corresponding allylic alcohol, which has to be prepared first. Therefore, we are interested in developing suitable reactions to allow further

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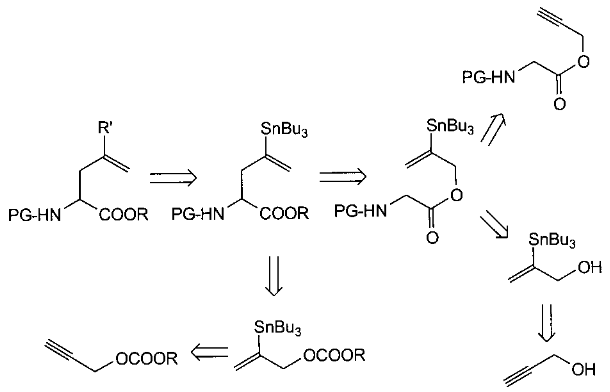
modification of the allylic side chain. Besides heterofunctionalizations,[13] C–C couplings are especially interesting from this point of view. Several examples are reported in the literature so far, in particular, modifications of terminal double bonds. Besides inter-[14] and intramolecular[15] metatheses, Heck-type couplings can also be carried out.[16] Applying this reaction to our rearrangement products, we obtained good results, especially with α-alkylated amino acids.[17] However, optically active allylglycine derivatives showed partial racemization depending on the protecting group used. This epimerization is evidently due to the relatively drastic conditions of the Heck reaction.[18] These couplings are also limited to substitutions on the sterically least hindered side of terminal double bonds.

For these reasons, we focused our investigations on another valuable approach, the Stille coupling reactions.[19] Since these reactions take place under rather mild conditions and are tolerant of a wide variety of functional groups this methodology is especially suitable for side chain modifications.[20] The required amino acids, bearing a vinylstannane side chain, should be accessible through a Claisen rearrangement from the corresponding α-stannylated esters. In turn, these could be obtained by esterification of the amino acids with the stannylated allylic alcohols, or through hydrostannation of propargylic esters (Scheme 3). Alternatively the stannylated

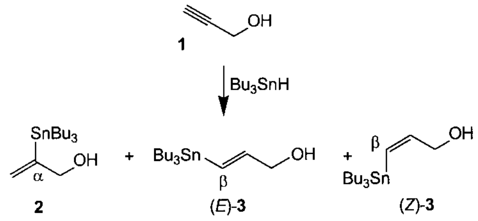


Scheme 3. Retrosynthetic approach.

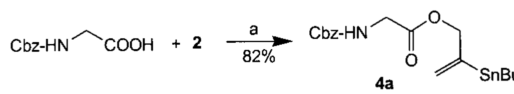
amino acid should also be accessible through palladium-catalyzed allylation directly from a stannylated allylic carbonate (or acetate). This building block, bearing two reactive centers, can be extremely useful. The *vinylstannane* subunit should allow coupling with electrophiles under Stille conditions, and the *allyl ester* moiety should be suitable for Pd-catalyzed allylic alkylations, allowing nucleophilic substitutions at the terminal allylic position. The stannylated substrates should be accessible through hydrostannation, and therefore this transformation plays a significant role in the whole reaction sequence. This is especially true because the regioselectivity of the tin hydride addition to the triple bond is the product determining step. For our approach, only the α-stannylated allylic alcohols or esters are interesting as only they give rise to the desired vinylstannane side chain.

Results and Discussion

Synthesis of stannylated allylic esters: Our studies on the synthesis of the required stannylated allylic esters began with the hydrostannation of propargylic alcohol (**1**) under different reaction conditions (Scheme 4). Two differing procedures are



	2	(E)-3	(Z)-3
AIBN, 85°C, 2 h	10%	45%	16%
0.2 % [Pd(COD)Cl$_2$], 0.4 % PPh$_3$, THF	49%	24%	-

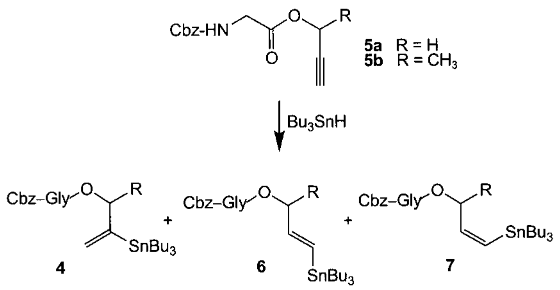


Scheme 4. a) 1.2 equiv DCC, 10 mol% DMAP, CH_2Cl_2, $-20\,^{\circ}C \rightarrow RT$ (82%).

common for this purpose: the radical and the catalytic pathway. Following the pioneering work of Leusink et al.,[21] radical tin hydride additions to acetylenic bonds have been extensively used.[22] Applying this procedure to the hydrostannation of propargylic alcohols provides a mixture of all three possible isomers. In this case the product distribution depends not only on the substrate but also on the reaction conditions used.[23] Unfortunately, the desired α-substituted compound **2** was only obtained as a minor product, the β-stannylated allylic alcohol **3a** was obtained preferentially, as an *E*/*Z*-isomeric mixture.[24]

The regioisomers were separated by flash column chromatography, giving pure (*E*)-**3** and an inseparable mixture of **2** and (*Z*)-**3**.[25] Therefore, we also examined the metal-catalyzed version using [Pd(COD)Cl$_2$] as a catalyst. The catalytically active Pd^0-complex is probably formed in situ through reduction of the palladium(II) species by the tin hydride.[26] In accordance with the reaction mechanism, the hydrostannation proceeded with clean *syn*-addition,[27] giving rise to **2** and (*E*)-**3** with a slight preference for the required α-product **2**. Flash chromatography furnished the pure regioisomers, which were coupled with benzyloxycarbonyl (Cbz)-glycine, using the Steglich protocol,[28] to give rise to the stannylated allylic esters **4a** and **6a**, respectively, in high yields. The regioselectivity in the hydrostannation step towards the α-product was acceptable in this case, although the selectivities obtained with other, sterically more hindered propargylic alcohols, such as 3-butyn-2-ol, are worse.[27] Therefore, from a synthetic point of view, only the hydrostannation of **1** is useful for this purpose, especially because the purification of the stannylated products is often not a trivial issue.[29]

For these reasons we also investigated the hydrostannation of propargylic esters **5** (Scheme 5). This approach should give direct access to the required esters **4**, and should reduce the number of stannylated intermediates. Again, under radical reaction conditions, a mixture of all possible isomers was formed, containing (*Z*)-isomer **7** as the major product (Table 1). Because only a small amount of the desired ester **4** was obtained, we also applied the palladium-catalyzed methodology to these substrates. However, no hydrostannated products were obtained, and cleavage of the ester moiety was the only reaction observed. Fortunately, besides palladium complexes, other transitions metals can also be used as catalysts; for example rhodium[30] or molybdenum complexes.[26] Indeed, hydrostannation of ester **5a** in the presence of Wilkinson's catalyst (1 mol%) gave the required ester **4a** with acceptable yield and selectivity. Even better results were obtained with a new hydrostannation catalyst,[31] developed in our laboratory. $[Mo(CO)_3(CNtBu)_3]$ ($MoBI_3$), easily obtained by ligand exchange from $[Mo(CO)_6]$,[32] proved to be a highly efficient catalyst for regioselective hydrostannations for various types of alkynes. In all examples investigated so far, the tin moiety was transferred preferentially to the sterically more hindered position of the triple bond. With this catalyst, we observed excellent α-regioselectivity in the reaction of **5a**, and the sterically more hindered derivative **5b** as well.[33] With the last substrate an even higher yield was obtained. When traces of hydroquinone were added to the reaction mixture (to suppress competitive radical reactions) the *syn*-addition products were formed exclusively.

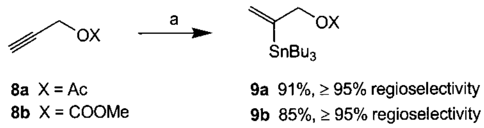


Scheme 5. Hydrostannation of propargylic esters.

Table 1. Hydrostannation of propargylic esters **5**.

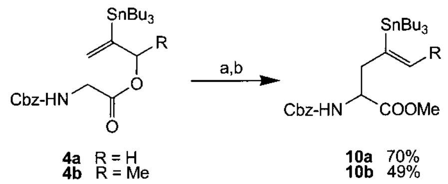
Reaction conditions	substrate	yield [%]	**4**:**6**:**7**
AIBN, CCl_4, 60 °C, 15 h	**5a**	67	12:26:62
$[Pd(COD)Cl_2]$, THF, RT, 1 h	**5a**	–	–
$[Rh(PPh_3)_3Cl]$, THF, 60 °C, 15 h	**5a**	57	81:19:0
$MoBI_3$, THF, 50 °C, 5 h	**5a**	70	95:5:0
$MoBI_3$, THF, 50 °C, 6 h	**5b**	85	92:8:0

After we successfully applied our methodolody to glycine esters, we transferred the optimized reaction conditions towards the hydrostannation of propargylic acetate (**8a**) and carbonate (**8b**) (Scheme 6). Both substrates gave the desired α-stannylated products **9** in very high yields as single regioisomers.[34] Fortunately, these compounds are stable towards protodestannylation, which allows purification by flash column chromatography without decomposition, and explains the high yields obtained.



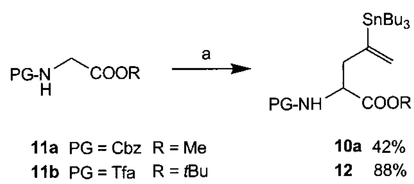
Scheme 6. a) 3 equiv Bu_3SnH, 2 mol% $MoBI_3$, THF, 50 °C, 4 h.

Syntheses of stannylated amino acid esters: With the stannylated allylic esters in hand, we firstly investigated the chelate Claisen rearrangement[35] of the α-stannylated esters **4a** and **4b** (Scheme 7). Deprotonation of these esters with excess LDA at -78 °C in the presence of $ZnCl_2$, resulted in a clean rearrangement when the reaction mixture was warmed to room temperature. In the rearrangement of **4b**, the product with (*E*)-olefin geometry (**10b**) was obtained nearly exclusively (less than 5% of (*Z*)-olefin); this can be explained by the rearrangement occurring via a *chairlike* transition state.[36] The reaction mixture was quenched with 1N $KHSO_4$ solution (no protodestannylation was observed during this workup procedure) and the crude amino acids were converted into the corresponding methyl esters **10** with diazomethane. In general, these esters can be used directly for further modifications without purification. In contrast to the stannylated allylic acetates and carbonates **9**, these stannylated amino acids (and esters) are sensitive toward protodestannylation, and decompose during flash chromatography, even in the presence of triethylamine. Although the crude product was obtained nearly quantitatively, the yield, especially of the substituted derivative **10b**, dropped to around 50% after chromatography.



Scheme 7. a) 3.5 equiv LDA, 1.2 equiv $ZnCl_2$, THF, -78 °C → RT. b) CH_2N_2.

In the alternative approach towards these stannylated amino acid derivatives we investigated the palladium-catalyzed allylic alkylation of two different protected glycine esters **11** using the carbonate **9b** as an allylic substrate (Scheme 8).[37] Both derivatives gave the desired products in a

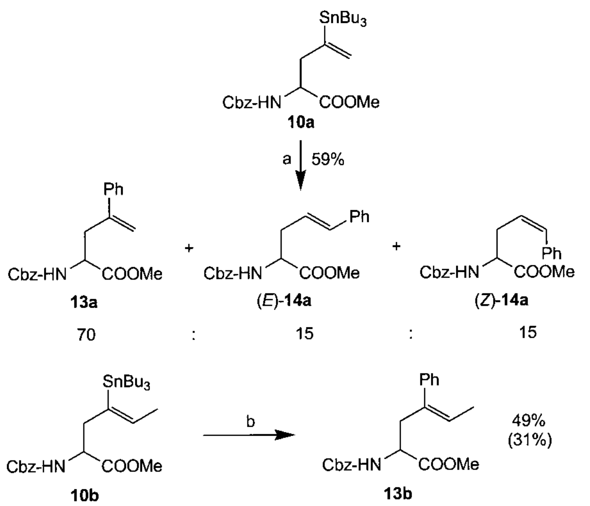


Scheme 8. a 1) 2.5 equiv LDA, 1.1 equiv $ZnCl_2$, THF, -78 °C; 2) 0.8 equiv **9b**, 1% $[allylPdCl]_2$, 4.5% PPh_3, -78 °C → RT.

very clean reaction and reasonable to good isolated yields. Best results were obtained if the chelated enolates were used, and the allylic carbonate **9b** was consumed completely. In these cases, the highly unpolar amino acid esters were separated from the starting materials **11** by rapid column chromatography (silica gel, 2% triethylamine added to the solvent).

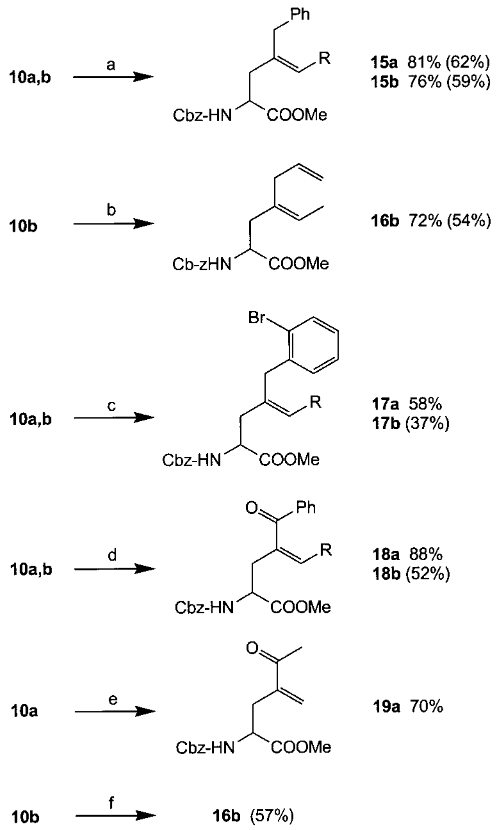
Stille couplings with stannylated amino acid esters: The stannylated amino acid esters **10** were subjected to cross-coupling reactions with various types of electrophiles (Scheme 9 and Scheme 10). In those cases, where the crude rearrangement product was used, the yields (in brackets) are overall yields for both steps: Claisen rearrangement and cross-coupling reaction.

We began our investigations with the coupling of ester **10a** with bromobenzene (Scheme 9). Instead of $[Pd(PPh_3)_4]$, which was originally used as catalyst by Stille et al., we chose $[Pd_2(dba)_3] \cdot CHCl_3$ as a palladium source and $AsPh_3$ as ligand.



Scheme 9. a) 3 equiv PhBr, 2.5 mol% $[Pd_2(dba)_3] \cdot CHCl_3$, 20 mol% $AsPh_3$, THF, 65°C, 20 h (59%). b) 3 equiv PhBr, 2.5 mol% $[Pd_2(dba)_3] \cdot CHCl_3$, 20 mol% $AsPh_3$, toluene, 90°C, 20 h.

As shown by Farina et al., this combination is significantly superior in cross-coupling reactions, in comparison to phosphine containing catalysts.[38] It is proposed that a π-complex, between the metal and the stannylated double bond, is involved in the transmetallation, the rate determining step of the catalytic cycle. Ligands such as $AsPh_3$, which readily dissociate from Pd^{II} and allow ready formation of this π-complex, are those which produce the fastest coupling rates. However, even with this reactive catalyst, the reaction was rather sluggish. After 20 h at 65°C, the coupling product was obtained as a mixture of three regioisomers. Besides the expected *ipso* substitution product **13a**, the δ-regioisomers (*E*)-**14a** and (*Z*)-**14a**, resulting from *cine* substitution, were also obtained. This is in good agreement with the observations made by Crisp and Glink with similar substrates.[20] Unfortunately, the regioisomers could not be separated by chromatography. The product ratio was determined by HPLC and NMR spectroscopy, which was also used to identify the



Scheme 10. a) 3 equiv BnBr, 2.5 mol% $[Pd_2(dba)_3] \cdot CHCl_3$, 20 mol% $AsPh_3$, THF, 20 h. b) 3 equiv allylBr, 2.5 mol% $[Pd_2(dba)_3] \cdot CHCl_3$, 20 mol% $AsPh_3$, toluene, 60°C, 20 h. c) *o*-Br-BnBr, 2.5 mol% $[Pd_2(dba)_3] \cdot CHCl_3$, 20 mol% $AsPh_3$, 20 h. d) 1.05 equiv BzCl, 2.5 mol% $[allylPdCl]_2$, MeCN. e) 1.05 equiv AcCl, 2.5 mol% $[allylPdCl]_2$, MeCN, RT, 10 min. f) 1.1 equiv ClCOOAll, 2.5 mol% $[allylPdCl]_2$, MeCN, RT, 10 min.

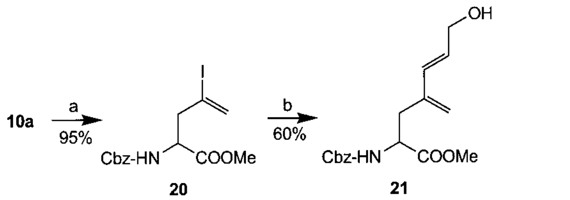
compounds in the reaction mixture. The three isomers were easily characterized by the vinylic proton signals in their ^1H NMR spectra. In the major isomer **13a** the terminal olefinic protons gave two singlets at $\delta = 5.30$ and 5.35. For the (*E*)-isomer a doublet of triplets ($\delta = 6.06$, $J = 15.8$, 7.3 Hz) and a doublet ($\delta = 6.47$, $J = 15.8$ Hz) were observed, whilst the (*Z*)-isomer gave a multiplet ($\delta = 5.60$) for the γ-proton and a doublet ($\delta = 6.61$, $J = 11.4$ Hz) for the δ-proton.

cine Substitution of vinyl stannanes during Stille couplings is a general problem of this reaction, and occurs preferentially during aryl couplings, especially if sterically hindered stannanes are used. In this cases, the rate of transmetallation might be rather slow. The formation of the *cine* product probably results from a Heck reaction between the terminal alkene position of **10a** and the electrophile, followed by a palladium-catalyzed loss of tributyltin bromide.[39] If this is true, one might expect that these side reactions should be suppressed if substituted derivatives such as **10b** are subjected to the same conditions. In this case, the competitive Heck coupling should also be retarded for steric reasons. Indeed, no *cine* products were obtained in the reaction of this substrate, but in addition, the desired *ipso* substitution was noticeably retarded, and therefore the reaction was carried out in toluene at higher temperature. The product was obtained in about 50% yield from the purified ester **10b**, and in 31% (overall yield for both steps) if the crude rearrangement product was used directly.

Significantly higher reactivities and selectivities (no *cine* products at all) were obtained with allyl and benzyl bromides. For example, ester **10a** reacted readily with benzyl bromide at room temperature, and after stirring overnight the coupling product **15a** was obtained in high yield (Scheme 10). In the coupling of ester **10b** the reaction mixture was warmed to 60 °C to ensure completion. The same reaction conditions were used for the reaction with allyl bromide as well, and the allylated product **16b** was obtained in comparable yield. Because of the higher reactivity of the benzylic halides in comparison to the aryl halides, we also investigated the reaction of *o*-bromobenzyl bromide with our stannylated esters. In principle this substrate has two reactive centers, but, as expected, reaction occurred exclusively at the more reactive benzylic position, giving rise to the brominated products **17**. Subsequent Heck reaction was not observed under the reaction conditions used.

Good reactivities were also observed with acyl halides such as benzoyl chloride or acetyl chloride.[40] These reactions can be carried out in acetone or, even better, acetonitrile without additional ligands. Probably these polar solvents can coordinate to the palladium complexes formed during the reaction, keeping them in solution.[41] Surprisingly, the reaction of **10a** with benzoyl chloride (Scheme 10) gave comparable yields in both solvents, while the same reaction with acetyl chloride proceeded only in acetonitrile. In the reactions of **10a**, the products were formed in a few minutes. After this time the reaction had to be complete, otherwise it stopped, because palladium(0) precipitated from the reaction mixture. Obviously, the coordinating effects of the solvents are not very strong. This fact might explain the somewhat lower yields obtained with substrate **10b**, which generally reacted more slowly in comparison to **10a**. The amino acids **18** and **19** obtained in these acylation reactions are interesting substrates for further modifications, for example through Michael additions. In contrast, the analogous reaction with allyl chloroformate does not provide the expected allylic ester, but the allylated product **16b** by decarboxylation. The yield obtained was comparable to that from the reaction with allyl bromide, which was discussed earlier. This reaction probably proceeds via a π-allyl palladium intermediate, formed from the chloroformate.

In all reactions described so far, the stannylated amino acid esters reacted as nucleophiles with several types of electrophilic coupling partners. However, this concept for side chain modification is not limited to this approach; it can also be carried out vice versa. Thus, when ester **10a** was subjected to a metal halogen exchange with iodine,[25] the corresponding amino acid **20**, with a "vinyliodide" side chain, was obtained in nearly quantitative yield (Scheme 11). By this procedure, the original nucleophile is converted into an electrophile, which can now be coupled with, for example, other vinylstannanes. Unfortunately we were not able to couple our two amino acid esters **10a** and **20** to afford the corresponding dimer, probably for steric reasons. Pleasingly, however, with the terminal stannane (*E*)-**3**, the coupling product **21** was obtained in good yield.



Scheme 11. a) 1.1 equiv I_2, $CHCl_3$, RT. b) (*E*)-**3**, $[(MeCN)_2PdCl_2]$, DMF, 80 °C, 2 h.

Conclusion

In summary, we have shown that $MoBI_3$ is an efficient catalyst for the regioselective hydrostannation of propargylic esters and carbonates. α-Stannylated amino acid allyl esters obtained by this protocol can be subjected to chelate Claisen rearrangements, giving rise to the corresponding amino acids. These amino acids, bearing a "vinylstannane" side chain are suitable substrates for subsequent Stille couplings. Therefore, this sequence provides a flexible strategy for the synthesis of unnatural, highly functionalized amino acids. Further applications are currently under investigation.

Experimental Section

General remarks: All reactions were carried out in oven-dried glassware (80 °C) under argon. All solvents were dried before use. THF and toluene were distilled from sodium/benzophenone, dichloromethane, acetonitrile, and diisopropylamine from calcium hydride. LDA solutions were prepared from freshly distilled diisopropylamine and commercially available *n*-butyllithium solution (15% in hexane) in THF at −20 °C directly before use. The starting materials and the products were purified by flash column chromatography on silica gel (32–63 μm). Mixtures of ethyl acetate and petrol ether (40–60 °C) were generally used as eluents. 1% Triethylamine was added to the solvent if stannylated compounds were subjected towards flash chromatography. TLC: commercially precoated Polygram SIL-G/UV 254 plates (Macherey–Nagel). Visualization was accomplished with UV light, iodine, and potassium permanganate solution. ^1H and ^{13}C NMR spectroscopy: Bruker AC300 spectrometer. Isomeric ratios were determined by NMR and/or analytical HPLC using a Knauer Eurosphere column (250 × 4 mm, Si80, 5 μm, flow: 2 ml min^{-1}) and a Knauer UV detector. Bu_3SnH, $[Pd(MeCN)_2Cl_2]$ and $[allylPdCl]_2$ were purchased from Fluka, $[Rh(PPh_3)_3Cl]$ from Aldrich, $[Pd_2(dba)_3]\cdot CHCl_3$,[42] $[Pd(COD)Cl_2]$[43] and were prepared according to the literature.

General procedure for esterifications: Dicyclohexylcarbodiimide (DCC) (2.46 g, 12 mmol) and 4-dimethylaminopyridine (DMAP) (125 mg, 1 mmol) were added to a solution of the alcohol (10 mmol) in methylene chloride (30 mL) at 0 °C. The clear solution was cooled to −20 °C, before Cbz-glycine (2.10 g, 10 mmol) was added after 5 min. The mixture was allowed to warm to room temperature overnight. After filtration of the precipitate, the organic phase was extracted with 1N $KHSO_4$ solution, sat. $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4 and evaporation of the solvent gave crude ester which was purified by flash chromatography.

Radical hydrostannations: The alkyne (1 mmol) was dissolved in a Schlenk tube under argon in CCl_4 (1 mL). Bu_3SnH (0.8 mL 3 mmol) and AIBN (20 mg) were added and the mixture was warmed to 60 °C for 15 h. After cooling to room temperature, the reaction mixture was subjected to flash chromatography. Excess of Bu_3SnH was removed using hexane as an eluent. The stannylated products were obtained using hexanes/ethyl acetate containing 1% triethylamine as eluent. The isomeric ratios observed are given in Table 1.

Palladium-catalyzed hydrostannation: Propargyl alcohol (**1**) (1.58 g, 28.2 mmol), $[Pd(COD)Cl_2]$ (14 mg, 50 μmol), and triphenylphosphine (26 mg, 0.1 mmol) were dissolved in THF (2.5 mL) in a Schlenk tube under argon. Bu_3SnH (9 g, 33.2 mmol) was added slowly during 30 min at 0 °C. The mixture was allowed to warm to room temperature after further 10 min and was subjected to flash chromatography.

Rhodium-catalyzed hydrostannations: The alkyne (1 mmol) was dissolved in a Schlenk tube under argon in THF (1 mL). Bu_3SnH (0.8 mL, 3 mmol) and $[Rh(PPh_3)_3Cl]$ (9 mg, 10 µmol) were added and the mixture was warmed to 60 °C for 15 h. After cooling to room temperature, the reaction mixture was subjected to flash chromatography.

$MoBI_3$-catalyzed hydrostannations: The alkyne (1 mmol), hydroquinone (10 mg), and $[Mo(CO)_3(CNtBu)_3]$ ($MoBI_3$) (8.6 mg, 20 µmol) were dissolved in a Schlenk tube under argon in THF (1 mL). Bu_3SnH (0.8 mL, 3 mmol) was added slowly and the mixture was warmed to 55 °C until all starting material was consumed. After cooling to room temperature, the reaction mixture was subjected to flash chromatography.

Stannylated ester 4a: Ester **4a** was obtained in a 20 mmol scale from the stannylated alcohol **2**[23] using the general procedure for esterifications in 82 % yield. The $MoBI_3$-catalyzed hydrostannation of propargylic ester **5a** was carried out in a 5 mmol scale. The crude product was purified by flash column chromatography (hexanes/ethyl acetate/NEt_3 84:15:1) giving rise to ester **4a** as a pale yellow oil (70 %). R_f: 0.39 (hexanes/ethyl acetate 85:15); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.34$ (m, 5H; H_{ar}), 5.86 (d, $J = 1.8$ Hz, 1H; $C{=}CH_{trans}$, J(Sn,H) = 120 Hz), 5.29 (d, $J = 1.9$ Hz, 1H; $C{=}CH_{cis}$, J(Sn,H) = 59 Hz), 5.27 (brs, 1H; NH), 5.12 (s, 2H; $PhCH_2$), 4.79 (s, 2H; OCH_2, J(Sn,H) = 28 Hz), 4.00 (d, $J = 5.2$ Hz, 2H; NCH_2), 1.53–1.43 (m, 6H; $SnCH_2$), 1.36–1.26 (m, 6H; CH_2CH_3), 0.97–0.85 (m, 15H; CH_2, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 169.5$ (CO), 156.1 (NCO), 148.2 (C=CSn), 136.2, 128.5, 128.2, 128.1 (C_{ar}), 126.0 (C=C), 71.9 (OCH_2), 67.1 ($PhCH_2$), 42.8 (NCH_2), 28.9 (CH_2CH_3, J(Sn,C) = 20 Hz), 27.3 (CH_2, J(Sn,C) = 58 Hz), 13.6 (CH_3), 9.6 ($SnCH_2$, J(Sn,C) = 335 Hz); elemental analysis calcd (%) for $C_{25}H_{41}NO_4Sn$ (538.3): C 55.78, H 7.68, N 2.60; found C 55.71, H 7.73, N 2.51.

Stannylated ester 4b: Ester **4b** was obtained in a 10 mmol scale from ester **5b** through $MoBI_3$-catalyzed hydrostannation as a pale yellow oil (85 %). R_f: 0.44 (hexanes/ethyl acetate 85:15); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.33$ (m, 5H; H_{ar}), 5.80 (s, 1H; $C{=}CH_{trans}$, J(Sn,H) = 125 Hz), 5.51 (q, $J = 7.0$ Hz, 1H; OCH), 5.26 (brs, 1H; NH), 5.22 (s, 1H; $C{=}CH_{cis}$, J(Sn,H) = 75 Hz), 5.11 (s, 2H; $PhCH_2$), 3.97 (dd, $J = 12.8$, 5.5 Hz, 1H; NCH), 3.93 (dd, $J = 12.9$, 5.3 Hz, 1H; NCH), 1.50–1.43 (m, 6H; $SnCH_2$), 1.36–1.24 (m, 6H; CH_2CH_3), 0.92–0.85 (m, 18H; CH_2, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 169.0$ (CO), 156.1 (NCO), 154.3 (C=CSn), 136.2, 128.5, 128.15, 128.07 (C_{ar}), 125.1 (C=C J(Sn,C) = 19 Hz), 79.0 (OCH), 67.0 ($PhCH_2$), 43.0 (NCH_2), 29.0 (CH_2CH_3, J(Sn,C) = 20 Hz), 27.3 (CH_2, J(Sn,C) = 44 Hz), 21.5 (CH_3), 13.6 (CH_3), 10.1 ($SnCH_2$, J(Sn,C) = 334 Hz); elemental analysis calcd (%) for $C_{26}H_{43}NO_4Sn$ (552.3): C 56.54, H 7.85, N 2.54; found C 56.59, H 7.92, N 2.52.

Propargyl *N*-(benzyloxycarbonyl)glycinate (5a): Ester **5a** was obtained in a 40 mmol scale from propargylic alcohol and Cbz-glycine using the general procedure for esterifications in 87 % yield. Crystallization from ether/petrol ether gave colorless crystals. M.p. 78–79 °C; R_f: 0.54 (hexanes/ethyl acetate 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.33$ (m, 5H; H_{ar}), 5.35 (brs, 1H; NH), 5.11 (s, 2H; $PhCH_2$), 4.73 (d, $J = 2.2$ Hz, 2H; OCH_2), 4.00 (d, $J = 5.7$ Hz, 2H; NCH_2), 2.49 (t, $J = 2.4$ Hz, 1H; C≡CH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 169.2$ (CO), 156.1 (NCO), 135.9, 128.3, 128.1, 127.9 (C_{ar}), 76.7 (C≡CH), 75.4 (C≡CH), 67.0 ($PhCH_2$), 52.6 (OCH_2), 42.4 (NCH_2); elemental analysis calcd (%) for $C_{13}H_{13}NO_4$ (247.2): C 63.15, H 5.30, N 5.67; found C 63.22, H 5.28, N 5.66.

Ester 5b: Ester **5b** was obtained in a 40 mmol scale from 3-butyne-2-ol and Cbz-glycine using the general procedure for esterifications in 81 % yield. The crude product was purified by flash chromatography (hexanes/ethyl acetate 8:2) giving rise to a pale yellow oil. R_f: 0.49 (hexanes/ethyl acetate 1: 1); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.33$ (m, 5H; H_{ar}), 5.46 (qd, $J = 6.7$, 2.0 Hz, 1H; OCH), 5.31 (brs, 1H; NH), 5.11 (s, 2H; $PhCH_2$), 3.99 (dd, $J = 13.0$, 5.8 Hz, 1H; NCH), 3.96 (dd, $J = 12.9$, 5.5 Hz, 1H; NCH), 2.46 (d, $J = 2.1$ Hz, 1H; C≡CH), 1.50 (d, $J = 6.7$ Hz, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 168.8$ (CO), 156.0 (NCO), 136.0, 128.3, 128.0, 127.9 (C_{ar}), 81.2 (C≡CH), 73.4 (C≡CH), 66.9 ($PhCH_2$), 61.0 (OCH), 42.6 (NCH_2), 20.9 (CH_3); elemental analysis calcd (%) for $C_{14}H_{15}NO_4$ (261.3): C 64.35, H 5.79, N 5.36; found C 64.25, H 5.60, N 5.33.

Stannylated ester 6a: Ester **6a** was obtained in a 10 mmol scale from the stannylated alcohol (*E*)-**3** using the general procedure for esterifications in 92 % yield. Ester **6a** was also formed as the minor product in the rhodium- (1 mmol) and molybdenum (5 mmol) catalyzed reaction. R_f: 0.31 (hexanes/ethyl acetate 85:15); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.35$ (m, 5H; H_{ar}), 6.29 (d, $J = 18.8$ Hz, 1H; C=CHSn, J(Sn,H) = 57 Hz), 6.02 (dt, $J = 19.2$, 5.3 Hz, 1H; CH=CH, J(Sn,H) = 72 Hz), 5.26 (brs, 1H; NH), 5.11 (s, 2H; $PhCH_2$), 4.66 (d, $J = 4.9$ Hz, 2H; OCH_2), 3.94 (d, $J = 4.9$ Hz, 2H; NCH_2), 1.55–1.44 (m, 6H; $SnCH_2$), 1.39–1.26 (m, 6H; CH_2CH_3), 0.96–0.87 (m, 15H; CH_2, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 171.7$ (CO), 158.3 (NCO), 148.9 (C=C), 142.6 (C=C), 138.3, 130.6, 130.3, 130.2 (C_{ar}), 74.0 (OCH_2), 68.9 ($PhCH_2$), 45.5 (NCH_2), 31.1 (CH_2CH_3, J(Sn,C) = 20 Hz), 29.1 (CH_2, J(Sn,C) = 59 Hz), 15.8 (CH_3), 11.7 ($SnCH_2$, J(Sn,C) = 332 Hz); elemental analysis calcd (%) for $C_{25}H_{41}NO_4Sn$ (538.3): C 55.78, H 7.68, N 2.60; found C 55.87, H 7.76, N 2.56.

Stannylated ester 7a: Ester **7a** was obtained in a 5 mmol scale as the major product through radical hydrostannation of ester **5a**. Flash chromatography (hexanes/ethyl acetate/NEt_3 84:15:1) gave a inseparable mixture of **4a** and **7a** (total 50 %). R_f: 0.39 (hexanes/ethyl acetate 85:15); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.37$ (m, 5H; H_{ar}), 6.60 (dt, $J = 12.9$, 6.6 Hz, 1H; $CH_2CH{=}C$), 6.27 (d, $J = 12.9$ Hz, C=CHSn), 5.32 (brs, 1H, NH), 5.14 (s, 2H; $PhCH_2$), 4.59 (d, $J = 6.6$ Hz, 2H; OCH_2), 4.01 (d, $J = 5.5$ Hz, 2H; NCH_2), 1.55–1.43 (m, 6H; $SnCH_2$), 1.39–1.26 (m, 6H; CH_2CH_3), 0.99–0.88 (m, 15H; CH_2, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 169.7$ (CO), 156.2 (NCO), 140.8 (C=C), 136.5 (C=C), 136.2, 128.5, 128.2, 128.1 (C_{ar}), 68.2 (OCH_2), 67.1 ($PhCH_2$), 42.8 (NCH_2), 30.0 (CH_2CH_3, J(Sn,C) = 21 Hz), 27.3 (CH_2, J(Sn,C) = 55 Hz), 13.6 (CH_3), 10.4 ($SnCH_2$, J(Sn,C) = 337 Hz); elemental analysis calcd (%) for $C_{25}H_{41}NO_4Sn$ (538.3) (mixture **4a**/**7a**): C 55.78, H 7.68, N 2.60; found C 55.60, H 7.55, N 2.53.

2-Tributylstannyl-allyl acetate (9a): Ester **9a** was obtained through $MoBI_3$-catalyzed hydrostannation of ester **8a** (617 mg, 6.30 mmol). Flash chromatography (hexanes/ethyl acetate/NEt_3 95:4:1) provided ester **9a** (2.225 g, 5.72 mmol, 91 %). R_f: 0.46 (hexanes/ethyl acetate 95:5); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.85$ (m, 1H; $C{=}CH_{trans}$, J(Sn,H) = 121 Hz), 5.28 (m, 1H; $C{=}CH_{cis}$, J(Sn,H) = 60 Hz), 4.69 (m, 2H; OCH_2, J(Sn,H) = 31 Hz), 2.05 (s, 3H; $COCH_3$), 1.63–1.40 (m, 6H; $SnCH_2$), 1.35–1.23 (m, 6H; CH_2CH_3), 1.10–0.84 (m, 15H; CH_2, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.3$ (CO), 148.9 (C=CSn), 125.5 (C=CSn), 71.0 (OCH_2), 28.9 (CH_2CH_3), 27.1 (CH_2), 20.7 ($COCH_3$), 13.4 (CH_3), 9.3 ($SnCH_2$); elemental analysis calcd (%) for $C_{17}H_{34}O_2Sn$ (389.1): C 52.48, H 8.74; found C 52.23, H 8.78.

Methyl (2-tributylstannyl-allyl) carbonate (9b): Ester **9b** was obtained through $MoBI_3$-catalyzed hydrostannation of ester **8b** (250 mg, 2.19 mmol). Flash chromatography (hexanes/ethyl acetate/NEt_3 98:1:1) provided ester **9b** (750 mg, 1.86 mmol, 85 %). R_f: 0.36 (hexanes/ethyl acetate 98:2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.89$ (m, 1H; $C{=}CH_{trans}$, J(Sn,H) = 112 Hz), 5.29 (m, 1H; $C{=}CH_{cis}$, J(Sn,H) = 59 Hz), 4.75 (m, 2H; OCH_2, J(Sn,H) = 28 Hz), 3.76 (s, 3H; OCH_3), 1.57–1.39 (m, 6H; $SnCH_2$), 1.34–1.22 (m, 6H; CH_2CH_3), 1.08–0.81 (m, 15H; CH_2, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 155.4$ (CO), 148.5 (C=CSn), 125.5 (C=CSn), 74.1 (OCH_2), 54.4 (OCH_3), 28.7 (CH_2CH_3), 27.0 (CH_2), 13.4 (CH_3), 9.4 ($SnCH_2$); elemental analysis calcd (%) for $C_{17}H_{34}O_3Sn$ (405.1): C 50.40, H 8.45; found C 50.35, H 8.46.

General procedure for chelate Claisen rearrangements: A freshly prepared LDA solution (2.5 mmol) in THF (7 mL) was added under argon to a stirred solution of the stannylated allylic ester **4** (1 mmol) and $ZnCl_2$ (1.1 mmol) in dry THF at −78 °C. The mixture was allowed to warm to room temperature overnight. The resulting clear solution was diluted with ether and hydrolyzed with 1N $KHSO_4$ solution. After separation of the aqueous layer, the organic layer was dried (Na_2SO_4) and the solvent was removed in vacuo. The crude product was treated with a solution of diazomethane in ether. The esters **10** obtained were purified by flash chromatography on silica gel (hexanes/ethyl acetate/NEt_3 90:9:1). In general, they can directly be used for subsequent cross-coupling reactions.

General procedure for palladium-catalyzed allylic alkylations: The protected amino acid ester **11** (1 mmol) was dissolved in THF (4 mL). At −78 °C a freshly prepared solution of lithium 1,1,1,3,3,3-hexamethyldisilazane (LHMDS) (2.5 mmol) in THF (2 mL) was added. After 30 min at −78 °C, a solution of $ZnCl_2$ (1.1 mmol) in THF (5 mL) was added under vigorous stirring. After additional 30 min a solution of $[allylPdCl]_2$ (1 mol %), PPh_3 (4.5 mol %), and the corresponding allylic ester (0.80 mmol) in THF (3 mL) was added. The solution was stirred and warmed up to room temperature overnight. Subsequently, the solution was diluted with diethyl ether and hydrolyzed with 1N $KHSO_4$ solution. The aqueous phase was extracted twice with diethyl ether, and the combined organic phases were dried over anhydrous Na_2SO_4. After evaporation of the solvent the crude product was purified by silica gel column chromatography (hexanes/ethyl acetate/NEt_3 90:9:1).

Stannylated amino acid ester 10a: Ester **10a** was obtained from **4a** (3.23 g, 6.0 mmol) following the general procedure for chelate Claisen rearrangements (2.32 g, 4.2 mmol, 70%) after flash chromatography (hexanes/ethyl acetate/NEt_3 90:8:2). Alternatively, ester **10a** was also prepared from **9b** (86 mg, 0.21 mmol) according to the general procedure for palladium-catalyzed allylic alkylations (49 mg, 0.089 mmol, 42%). R_f: 0.34 (hexanes/ethyl acetate 85:15); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.34$ (m, 5H; H_{ar}), 5.72 (s, 1H; C=CH_{trans}, J(Sn,H) = 119 Hz), 5.24 (s, 1H; C=CH_{cis}, J(Sn,H) = 57 Hz), 5.06 (m, 1H; NH), 5.09 (s, 2H; $PhCH_2$), 4.34 (dd, J = 8.3, 4.9 Hz, 1H; NCH), 3.74 (s, 3H; OCH_3), 2.80 (dd, J = 14.3, 4.5 Hz, 1H; CH_2CSn), 2.50 (dd, J = 14.0, 9.0 Hz, 1H; CH_2CSn), 1.51–1.43 (m, 6H; $SnCH_2$), 1.34–1.27 (m, 6H; CH_2CH_3), 0.96–0.86 (m, 15H; CH_2, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.9$ (CO), 153.9 (NCO), 148.0 (C=CSn), 134.4 (C_{ar}), 127.5 (C=CH_2), 126.7, 126.3 (C_{ar}), 65.2 ($PhCH_2$), 51.9 (NCH), 50.4 (OCH_3), 41.7 (CH_2), 27.2 (CH_2CH_3, J(Sn,C) = 20 Hz), 25.6 (CH_2, J(Sn,C) = 57 Hz), 11.9 (CH_3), 7.9 ($SnCH_2$, J(Sn,C) = 332 Hz); elemental analysis calcd (%) for $C_{26}H_{43}NO_4Sn$ (552.3): C 56.54, H 7.85, N 2.54; found C 56.52, H 7.85, N 2.51.

Stannylated amino acid ester 10b: Ester **10b** was obtained from **4b** (630 mg, 1.14 mmol) following the general procedure for chelate Claisen rearrangements (316 mg, 0.56 mmol, 49%) after flash chromatography. R_f: 0.32 (hexanes/ethyl acetate 85:15); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.32$ (m, 5H; H_{ar}), 6.09 (q, J = 6.5 Hz, 1H; C=CH, J(Sn,H) = 123 Hz), 5.06 (s, 2H; $PhCH_2$), 5.00 (d, J = 7.4 Hz, 1H; NH), 4.21 (ddd, J = 9.2, 7.4, 5.1 Hz, 1H; NCH), 3.70 (s, 3H; OCH_3), 2.69 (dd, J = 13.6, 4.8 Hz, 1H; CH_2CSn), 2.38 (dd, J = 13.6, 9.2 Hz, 1H; CH_2CSn), 1.67 (d, J = 6.4 Hz, 3H; C=$CHCH_3$), 1.49–1.41 (m, 6H; $SnCH_2$), 1.35–1.18 (m, 6H; CH_2CH_3), 0.98–0.84 (m, 15H; CH_2, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 172.7$ (CO), 155.5 (NCO), 139.0 (C=C), 138.8 (C=C), 136.1, 128.3, 127.9 (C_{ar}), 66.7 ($PhCH_2$), 53.9 (NCH), 51.9 (OCH_3), 43.1 (CH_2CSn), 28.8 (CH_2CH_3, J(Sn,C) = 29 Hz), 27.2 (CH_2, J(Sn,C) = 59 Hz), 19.8 ($CHCH_3$), 13.4 (CH_2CH_3), 9.9 ($SnCH_2$, J(Sn,C) = 326 Hz); elemental analysis calcd (%) for $C_{27}H_{45}NO_4Sn$ (566.4): C 57.26, H 8.01, N 2.47; found C 57.07, H 8.07, N 2.45.

Stannylated amino acid ester 12: Ester **12** was obtained from **9b** (83 mg, 0.205 mmol) following the general procedure for palladium-catalyzed allylic alkylations (100 mg, 0.180 mmol, 88%) after flash chromatography. R_f: 0.26 (hexanes/ethyl acetate 98:2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.52$ (d, J = 6.0 Hz, 1H; NH), 5.70 (s, 1H; C=CH, J(Sn,H) = 127 Hz), 5.25 (s, 1H; C=CH, J(Sn,H) = 57 Hz), 4.36 (m, 1H; NCH), 2.85 (dd, J = 14.2, 9.1 Hz, 1H; CH_2CSn), 2.49 (dd, J = 14.1, 9.4 Hz, 1H; CH_2CSn), 1.55–1.42 (m, 6H; $SnCH_2$), 1.49 (s, 9H; CCH_3), 1.36–1.23 (m, 6H; CH_2CH_3), 0.96–0.81 (m, 15H; CH_2, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 169.4$ (CO), 156.1 (q, J(Sn,C) = 37 Hz, CF_3CO), 149.0 (C=CSn), 129.0 (C=CH_2), 115.5 (q, J(Sn,C) = 285 Hz, CF_3), 82.8 ($OCCH_3$), 52.4 (NCH), 43.5 (CH_2CSn), 28.7 (CH_2CH_3, J(Sn,C) = 20 Hz), 27.7 (CCH_3), 27.1 (CH_2, J(Sn,C) = 57 Hz), 13.4 (CH_2CH_3), 9.9 ($SnCH_2$, J(Sn,C) = 327 Hz); elemental analysis calcd (%) for $C_{23}H_{42}F_3NO_3Sn$ (555.9): C 49.66, H 7.61, N 2.52; found C 49.94, H 7.72, N 2.62.

General procedure for Stille coupling reactions using $[Pd_2(dba)_3]\cdot CHCl_3$ as catalyst: The stannylated ester **10** (1 mmol) was placed in a Schlenk tube under argon, before the corresponding halide (3 mmol) was added in THF or toluene (5 mL). The catalyst was added as a solution of $[Pd_2(dba)_3]\cdot CHCl_3$ (25 mg, 25 mmol, 5 mol%) and triphenylarsine (68 mg, 226 mmol) in THF (3 mL) or toluene, respectively. The reaction mixture was heated to 60°C (THF) or 90°C (toluene) for about 20 h. After cooling to room temperature, saturated KF solution (5 mL) was added, and the mixture was stirred for further 15 h, before diethyl ether (30 mL) was added. The aqueous layer was separated and the organic layer was washed with H_2O (15 mL). The combined aqueous layers were extracted with diethyl ether (10 mL). The combined organic layers were evaporated to dryness, and the residue obtained was dissolved in ethyl acetate. The insoluble tributyltin fluoride was filtered off, the solvent was removed in vacuo, and the crude product was purified by flash chromatography.

Methyl 2-(benzyloxycarbonyl)amino-4-phenyl-4-pentenoate (13a): Coupling product **13a** was obtained from **10a** (55 mg, 0.1 mmol) and bromobenzene (32 μL, 0.3 mmol) following the general procedure for $[Pd_2(dba)_3]\cdot CHCl_3$ catalyzed reactions at 60°C using THF as solvent. The crude product was purified by flash chromatography (hexanes/ethyl acetate 9:1) giving rise to a pale yellow oil (20 mg, 59 μmol, 59%), which was a inseparable mixture of **13a** and the isomers **14a**. R_f: 0.49 (hexanes/ethyl acetate 8:2). **13a**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.40$–7.20 (m, 10H; H_{ar}), 5.35 (s, 1H; C=CH), 5.30 (s, 1H; C=CH), 5.22 (d, J = 8.5 Hz, 1H; NH), 5.10 (s, 2H; $PhCH_2$), 4.47 (m, 1H; NCH), 3.55 (s, 3H; OCH_3), 3.07, (dd, J = 14.0, 4.4 Hz, 1H; CH_2), 2.98 (dd, J = 14.0, 7.0 Hz, 1H; CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 172.1$ (CO), 155.5 (NCO), 143.7 (C=C), 140.4, 136.3, 128.5, 128.4, 128.13, 128.08, 127.9, 126.3 (C_{ar}), 116.6 (C=C), 66.9 ($PhCH_2$), 53.0 (NCH), 52.0 (OCH_3), 38.1 (CH_2). **(*E*)-14a**: ^{1}H NMR (selected signals): $\delta = 6.47$ (d, J = 15.8 Hz, 1H; PhCH=C), 6.06 (dt, J = 15.8, 7.3 Hz, 1H; CH_2CH=C); **(*Z*)-14a**: ^{1}H NMR (selected signals): $\delta = 6.61$ (d, J = 11.4 Hz, 1H; PhCH=C), 5.60 (m, 1H; CH_2CH=C); HRMS (FAB): $C_{20}H_{21}NO_4$ $[M]^+$ (mixture **13a**/**14a**): calcd 339.1471; found 339.1473; MS (FAB): m/z (%): 339 (2.5), 280 (3.3), 188 (20.3).

Methyl 2-(benzyloxycarbonyl)amino-4-phenyl-4(*Z*)-hexenoate (13b): Coupling product **13b** was obtained from purified (or crude) **10b** (283 mg, 0.5 mmol) and bromobenzene (0.16 mL, 1.5 mmol) following the general procedure for $[Pd_2(dba)_3]\cdot CHCl_3$ catalyzed reactions at 90°C using toluene as a solvent. The crude product was purified by flash chromatography (hexanes/ethyl acetate 8:2) giving rise to **13b** (86 mg, 0.245 mmol, 49%) (55 mg, 1.55 mmol, 31% from the crude product) as a pale yellow oil. R_f: 0.32 (hexanes/ethyl acetate 8: 2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.34$ (m, 9H; H_{ar}), 7.09 (d, J = 7.5 Hz, 1H; H_{ar}), 5.50 (q, J = 6.3 Hz, 1H; C=$CHCH_3$), 5.24 (d, J = 7.1 Hz, 1H; NH), 5.09 (s, 2H; $PhCH_2$), 4.39 (dt, J = 7.9, 5.8 Hz, 1H; NCH), 3.72 (s, 3H; OCH_3), 2.45 (brs, 2H; CH_2), 1.64 (d, J = 6.3 Hz, 3H; $CHCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 172.1$ (CO), 155.5 (NCO), 136.1 (C_{ar}), 130.0 (C=CH), 128.5, 128.3, 128.1, 127.93, 127.87, 127.5, 125.6 (C_{ar}), 124.1 (C=CH), 66.7 ($PhCH_2$), 53.4 (NCH), 52.0 (OCH_3), 35.3 (CH_2), 17.7 ($CHCH_3$); HRMS (FAB): $C_{21}H_{23}NO_4$ $[M]^+$: calcd 354.1705; found 354.1726.

Methyl 4-benzyl-2-(benzyloxycarbonyl)amino-4-pentenoate (15a): Coupling product **15a** was obtained from **10a** (359 mg, 0.65 mmol) and benzyl bromide (0.23 mL, 2 mmol) following the general procedure for $[Pd_2(dba)_3]\cdot CHCl_3$ catalyzed reactions using THF as a solvent. The reaction mixture was stirred overnight at room temperature and was heated 1 h to 60°C for completion. The crude product was purified by flash chromatography (hexanes/ethyl acetate 9:1) giving rise to **15a** (186 mg, 0.53 mmol, 81%) as a pale yellow oil. R_f: 0.31 (hexanes/ethyl acetate 8: 2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.40$–7.14 (m, H_{ar}), 5.19 (d, J = 7.7 Hz, 1H; NH), 5.13 (d, J = 12.4 Hz, 1H; $PhCH_2O$), 5.08 (d, J = 12.3 Hz, 1H; $PhCH_2$), 4.89 (s, 1H; C=CH_2), 4.85 (s, 1H; C=CH_2), 4.52 (ddd, J = 8.3, 8.2, 5.6 Hz, 1H; NCH), 3.71 (s, 3H; OCH_3), 3.34 (s, 2H; $PhCH_2$), 2.51 (dd, J = 14.2, 5.3 Hz, 1H; CH_2C=C), 2.32 (dd, J = 14.2, 8.6 Hz, 1H; CH_2C=C); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 172.4$ (CO), 155.5 (NCO), 143.4 (C_{ar}), 138.5 (C=CH_2), 136.1, 128.8, 128.3, 128.2, 127.9, 127.8, 126.1 (C_{ar}), 115.4 (C=CH_2), 66.8 ($PhCH_2$), 52.1 (NCH), 52.0 (OCH_3), 42.0, 38.1 (CH_2); $C_{21}H_{23}NO_4$ (353.4): calcd C 71.37, H 6.56, N 3.96; found C 70.99, H 6.60, N 3.74; HRMS (FAB): $C_{21}H_{23}NO_4$ $[M+H]^+$: calcd 354.1705; found 354.1680.

Methyl 4-benzyl-2-(benzyloxycarbonyl)amino-4-hexenoate (15b): Coupling product **15b** was obtained from **10b** (566 mg, 1 mmol) and benzyl bromide (0.36 mL, 3 mmol) following the general procedure for $[Pd_2(dba)_3]\cdot CHCl_3$ catalyzed reactions at 60°C in THF. The crude product was purified by flash chromatography (hexanes/ethyl acetate 8:2) giving rise to **15b** (280 mg, 0.76 mmol, 76%) as a pale yellow oil. R_f: 0.28 (hexanes/ethyl acetate 8:2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.34$–7.12 (m, H_{ar}), 5.46 (q, J = 6.7 Hz, 1H; C=CH), 5.07–5.13 (m, 1H; NH), 5.12 (d, J = 12.2 Hz, 1H; $PhCH_2O$), 5.06 (d, J = 12.3 Hz, 1H; $PhCH_2$), 4.41 (ddd, J = 8.3, 8.2, 5.4 Hz, 1H; NCH), 3.68 (s, 3H; OCH_3), 3.43 (d, J = 15.2 Hz, 1H; $PhCH_2$), 3.34 (d, J = 15.1 Hz, 1H; $PhCH_2$), 2.43 (dd, J = 13.9, 5.0 Hz, 1H; CH_2), 2.20 (dd, J = 14.0, 8.8 Hz, 1H; CH_2), 1.72 (d, J = 6.7 Hz, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 172.6$ (CO), 155.5 (NCO), 139.0, 136.1 (C_{ar}), 133.4 (C=CH), 128.3, 128.2, 128.2, 127.93, 127.86, 125.9 (C_{ar}), 124.9 (C=CH), 66.7 ($PhCH_2$), 52.3 (NCH), 51.9 (OCH_3), 39.1, 34.8 (CH_2), 13.6 (CH_3); elemental analysis calcd (%) for $C_{22}H_{25}O_4N$ (367.4): C 71.91, H 6.86, N 3.81; found C 71.81, H 6.86, N 3.76.

Methyl 4-allyl-2-(benzyloxycarbonyl)amino-4-hexenoate (16b): Coupling product **16b** was obtained from **10b** (283 mg, 0.5 mmol) and allyl bromide (0.13 mL, 1.5 mmol) following the general procedure for $[Pd_2(dba)_3]\cdot$

$CHCl_3$ catalyzed reactions at 60 °C in THF. The crude product was purified by flash chromatography (hexanes/ethyl acetate 8:2) giving rise to **16b** (114 mg, 0.36 mmol, 72%) as a pale yellow oil. R_f: 0.32 (hexanes/ethyl acetate 8:2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.33$ (m, 5H; H_{ar}), 5.66 (ddt, $J = 16.3$, 9.9, 6.6 Hz, 1H; CH=CH_2), 5.34 (q, $J = 6.7$ Hz, 1H; C=$CHCH_3$), 5.14 (m, 1H; NH), 5.10 (d, $J = 12.4$ Hz, 1H; $PhCH_2$), 5.05 (d, $J = 12.2$ Hz, 1H; $PhCH_2$), 5.01–5.10 (m, 2H; CH=CH_2), 4.39 (ddd, $J = 8.3$, 8.2, 5.4 Hz, 1H; NCH), 3.71 (s, 3H; OCH_3), 2.76 (d, $J = 6.3$ Hz, 2H; CH_2CH=C), 2.51 (dd, $J = 13.8$, 5.2 Hz, 1H; CH_2), 2.27 (dd, $J = 13.9$, 8.8 Hz, 1H; CH_2), 1.57 (d, $J = 6.7$ Hz, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 172.68$ (CO), 155.52 (NCO), 136.13 (C_{ar}), 134.85 (CH=CH_2), 132.16 (C=CH), 128.28, 127.92, 127.84 (C_{ar}), 124.68 (C=CH), 115.61 (CH=CH_2), 66.70 ($PhCH_2$), 52.29 (NCH), 52.00 (OCH_3), 39.52, 33.52 (CH_2), 13.16 (CH_3); elemental analysis calcd (%) for $C_{18}H_{23}NO_4$ (317.4): C 68.12, H 7.30, N 4.41; found C 67.71, H 7.32, N 4.35; HRMS (FAB): $C_{18}H_{23}NO_4$ $[M+H]^+$: calcd 318.1705; found 318.1712.

Methyl 2-(benzyloxycarbonyl)amino-4-(*o*-bromobenzyl)-4-pentenoate (17a): Coupling product **17a** was obtained from **10a** (220 mg, 0.4 mmol) and *o*-bromobenzyl bromide (100 mg, 0.4 mmol) following the general procedure for $[Pd_2(dba)_3]\cdot CHCl_3$ catalyzed reactions in THF. The reaction mixture was refluxed for 5 h. The crude product was purified by flash chromatography (hexanes/ethyl acetate 9:1) giving rise to **17a** (101 mg,0.23 mmol, 58%) as a pale yellow oil. R_f: 0.37 (hexanes/ethyl acetate 8:2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.42$–7.20 (m, 9H; H_{ar}), 5.21 (d, $J = 8.1$ Hz, 1H; NH), 5.13 (d, $J = 12.1$ Hz, 1H; $PhCH_2O$), 5.10 (d, $J =$ 12.1 Hz, 1H; $PhCH_2O$), 4.90 (s, 1H; C=CH_2), 4.86 (s, 1H; C=CH_2), 4.53 (ddd, $J = 8.5$, 8.1, 5.5 Hz, 1H; NCH), 3.72 (s, 3H; OCH_3), 3.35 (s, 2H; $PhCH_2$), 2.52 (dd, $J = 14.3$, 5.5 Hz, 1H; CH_2), 2.32 (dd, $J = 14.3$, 8.5 Hz, 1H; CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 172.7$ (CO), 155.8 (NCO), 143.6 (C=CH), 138.7, 136.1 (C_{ar}), 129.1, 128.6, 128.5, 128.2, 126.4 (C_{ar}), 115.7 (C=CH_2), 67.0 ($PhCH_2$), 52.3 (NCH), 52.0 (OCH_3), 42.2, 38.4 (CH_2); HRMS (FAB): $C_{21}H_{23}{}^{81}BrNO_4$ $[M+H]^+$: calcd 434.0790; found 434.0770.

Methyl 4-allyl-2-(benzyloxycarbonyl)amino-4-hexenoate (17b): Coupling product **17b** was obtained from crude **10b** (181 mg, 0.32 mmol) and *o*-bromobenzyl bromide (240 mg, 0.96 mmol) following the general procedure for $[Pd_2(dba)_3]\cdot CHCl_3$ catalyzed reactions at 90 °C in toluene. The crude product was purified by flash chromatography (hexanes/ethyl acetate 8:2) giving rise to **17b** (53 mg, 0.12 mmol, 37%) as a pale yellow oil. R_f: 0.26 (hexanes/ethyl acetate 8:2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.53$ (d, $J =$ 7.7 Hz, 1H; H_{ar}), 7.29–7.40 (m, 5H; H_{ar}), 7.22–7.02 (m, 3H; H_{ar}), 5.56 (q, $J = 6.8$ Hz, 1H; C=CH), 5.25 (d, $J = 7.4$ Hz, 1H; NH), 5.12 (d, $J = 12.3$ Hz, 1H; $PhCH_2O$), 5.06 (d, $J = 12.3$ Hz, 1H; $PhCH_2O$), 4.42 (ddd, $J = 9.2$, 8.5, 4.4 Hz, 1H; NCH), 3.73 (s, 1H; $PhCH_2$), 3.68 (s, 3H; OCH_3), 3.50 (s, 1H; $PhCH_2$), 2.44 (dd, $J = 13.6$, 4.5 Hz, 1H; CH_2), 2.21 (dd, $J = 14.3$, 8.8 Hz, 1H; CH_2), 1.65 (d, $J = 6.7$ Hz, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 172.7$ (CO), 155.5 (NCO), 137.9, 136.1, 132.63 (C_{ar}), 131.9 (C=CH), 129.4, 128.3, 127.9, 127.9, 127.6, 127.2, 126.3 (C_{ar}), 124.9 (C=CH), 66.7 ($PhCH_2O$), 52.5 (NCH), 52.0 (OCH_3), 39.4, 35.2 (CH_2), 13.6 (CH_3); elemental analysis calcd (%) for $C_{22}H_{24}NO_4Br$ (446.34): C 59.20, H 5.42, N 3.14; found C 59.34, H 5.67, N 2.93.

Methyl 4-benzoyl-2-(benzyloxycarbonyl)amino-4-pentenoate (18a): Ester **10a** (220 mg; 0.4 mmol) and benzoyl chloride (58 mg; 0.42 mmol) were dissolved in acetonitrile (2 mL) under argon. $[AllylPdCl]_2$ (4.0 mg, 11 µmol) was added to the solution, which immediately turned yellow. After 30 s the mixture turned black from precipitated palladium(0). TLC control showed complete consumption of **10a**. A saturated solution of KF in H_2O (10 mL) was added, and the mixture was vigorously stirred overnight. The solution was extracted twice with diethyl ether and the combined organic layers were washed with H_2O. After drying (Na_2SO_4) and evaporation of the solvent, the crude product obtained was dissolved in ethyl acetate. The precipitated tin fluoride was filtered off and the residue obtained after evaporation of the solvent was purified by flash chromatography (hexanes/ethyl acetate 85:15) to yield a colorless oil (130 mg, 0.35 mmol, 88%). R_f: 0.17 (hexanes/ethyl acetate 8:2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.69$ (d, $J = 7.4$ Hz, 2H; H_{ar}), 7.53 (m, 1H; H_{ar}), 7.43 (t, $J =$ 7.4 Hz, 2H; H_{ar}), 7.34–7.26 (m, 5H; H_{ar}), 5.97 (s, 1H; C=CH_2), 5.74 (s, 1H; C=CH_2), 5.71 (d, $J = 8.1$ Hz, 1H; NH), 5.08 (d, $J = 12.1$ Hz, 1H; $PhCH_2$), 5.05 (d, $J = 12.1$ Hz, 1H; $PhCH_2$), 4.53 (m, 1H; NCH), 3.70 (s, 3H; OCH_3), 3.02 (dd, $J = 13.8$, 5.5 Hz, 1H; CH_2), 2.90 (dd, $J = 13.8$, 8.0 Hz, 1H; CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 197.4$ (ArCO), 172.0 (CO), 155.8 (NCO), 143.0 (C=CH_2), 137.2, 136.4, 132.1 (C_{ar}), 130.2 (C=CH_2), 129.6, 128.5, 128.2, 120.1, 128.0 (C_{ar}), 66.9 ($PhCH_2$), 53.7 (NCH), 52.4 (OCH_3), 34.8 (CH_2); elemental analysis calcd (%) for $C_{21}H_{21}NO_5$ (367.4): C 68.65, H 5.76, N 3.81; found C 68.47, H 5.85, N 3.69.

Methyl 4-benzoyl-2-(benzyloxycarbonyl)amino-4-hexenoate (18b): The crude ester **10a** (283 mg, 0.5 mmol) and benzoyl chloride (73 mg, 0.52 mmol) were dissolved in acetonitrile (2 mL) under argon. $[AllylPdCl]_2$ (4.0 mg, 11 µmol) was added to the solution, and the reaction mixture was heated to 60 °C for 1 h. The solution was cooled to room temperature, before a saturated solution of KF in H_2O (5 mL) was added. After stirring overnight the workup was carried as described for **18a**. Flash chromatography (hexanes/ethyl acetate 8:2) provided **18b** (100 mg, 0.26 mmol, 52%) as a colorless oil. R_f: 0.12 (hexanes/ethyl acetate 8:2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.82$ (dd, $J = 8.3$, 1.4 Hz, 2H; H_{ar}), 7.53 (td, $J = 7.4$, 1.4 Hz, 1H; H_{ar}), 7.41 (dd, $J = 7.7$, 7.3 Hz, 2H; H_{ar}), 7.29 (m, 5H; H_{ar}), 5.95 (q, $J = 7.2$ Hz, 1H; C=CH), 5.64 (d, $J = 7.5$ Hz, 1H; NH), 5.01 (s, 2H; $PhCH_2$), 4.44 (ddd, $J = 7.3$, 7.2, 5.7 Hz, 1H; NCH), 3.64 (s, 3H; OCH_3), 2.88 (dd, $J = 14.1$, 5.2 Hz, 1H; CH_2), 2.78 (dd, $J = 14.5$, 7.0 Hz, 1H; CH_2), 1.47 (d, $J = 7.2$ Hz, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 198.9$ (ArCO), 171.6 (CO), 155.5 (NCO), 136.9, 136.1 (C_{ar}), 135.2 (C=CH), 133.1 (C_{ar}), 132.8 (C=CH), 129.0, 128.5, 128.2, 127.83, 127.76 (C_{ar}), 66.6 ($PhCH_2$), 53.8 (NCH), 52.0 (OCH_3), 37.1 (CH_2), 16.0 (CH_3); HRMS (FAB): $C_{22}H_{23}NO_5$ $[M+H]^+$: calcd 382.1655; found 382.1669.

Methyl 4-acetyl-2-(benzyloxycarbonyl)amino-4-pentenoate (19a): Ester **10a** (220 mg, 0.4 mmol) and acetyl chloride (32 mg, 0.42 mmol) were dissolved in acetonitrile (1 mL) under argon. $[AllylPdCl]_2$ (4.0 mg, 11 µmol) was added to the solution, which turned black after 30 s. Usual workup and purification of the crude product by flash chromatography (hexanes/ethyl acetate 8:2) yielded **19a** (84 mg, 0.28 mmol, 70%) as a colorless oil. R_f: 0.08 (hexanes/ethyl acetate 8:2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.35$–7.33 (m, 5H; H_{ar}), 6.06 (s, 1H; C=CH_2), 5.86 (s, 1H; C=CH_2), 5.50 (d, $J = 7.9$ Hz, 1H; NH), 5.08 (d, $J = 12.2$ Hz, 1H; $PhCH_2$), 5.06 (d, $J = 12.2$ Hz, 1H; $PhCH_2$), 4.44 (m, 1H; NCH), 3.72 (s, 3H; OCH_3), 2.81 (dd, $J = 13.6$, 4.9 Hz, 1H; CH_2), 2.63 (dd, $J = 13.6$, 8.2 Hz, 1H; CH_2), 2.30 (s, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 199.5$ (CH_3CO), 172.1 (CO), 155.7 (NCO), 144.1 (C=CH_2), 136.4 (C_{ar}), 128.7 (C=CH_2), 128.5, 128.1, 128.1 (C_{ar}), 66.9 ($PhCH_2$), 53.5 (NCH), 52.4 (OCH_3), 33.7 (CH_2), 25.5 (CH_3); elemental analysis calcd (%) for $C_{16}H_{19}NO_4$ (305.3): C 62.94, H 6.27, N 4.59; found C 62.66, H 6.29, N 4.47.

Methyl 2-(benzyloxycarbonyl)amino-4-iodo-4-pentenoate (20): Iodine (80 mg, 0.31 mmol), dissolved in $CHCl_3$ (1 mL), was added to a solution of **10a** (166 mg, 0.3 mmol) in $CHCl_3$ (0.5 mL). After 1 h saturated KF solution (2 mL) and ethyl acetate (10 mL) were added. After vigorous stirring for 2 h the aqueous layer was removed and the organic layer was filtrated and dried (Na_2SO_4). After evaporation of the solvent, the crude product was purified by flash chromatography (hexanes/ethyl acetate 9:1). to yield a pale yellow oil (110 mg, 0.28 mmol, 94%). R_f: 0.32 (hexanes/ethyl acetate 8:2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.37$–7.33 (m, 5H; H_{ar}), 6.10 (d, $J =$ 0.7 Hz, 1H; C=CH_2), 5.84 (d, $J = 0.8$ Hz, 1H; C=CH_2), 5.34 (d, $J = 7.7$ Hz, 1H; NH), 5.13 (s, 2H; $PhCH_2$), 4.58 (m, 1H; NCH), 3.78 (s, 3H; OCH_3), 3.01 (dd, J = 14.6, 4.8 Hz, 1H; CH_2), 2.84 (dd, J = 14.6, 7.7 Hz, 1H; CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 171.3$ (CO), 155.6 (NCO), 136.2 (C_{ar}), 129.8 (C=CH_2), 128.5, 128.2, 128.1 (C_{ar}), 102.8 (C=CH_2), 69.1 ($PhCH_2$), 53.3 (NCH), 52.6 (OCH_3), 47.2 (CH_2); elemental analysis calcd (%) for $C_{14}H_{16}INO_4$ (388.2): C 43.21, H 4.14, N 3.60; found C 43.38, H 4.15, N 3.51.

Methyl 2-(benzyloxycarbonyl)amino-7-hydroxy-4-methylene-5-heptenoate (21): $[(MeCN)_2PdCl_2]$ (1.0 mg, 4 µmol, 5 mol%) was added to a solution of (*E*)-**3** (28 mg, 80 µmol) and **20** (31 mg, 80 µmol) in DMF (1 mL) under argon. The mixture was heated to 80 °C for 2 h, followed by the usual workup. The crude product was purified by flash chromatography (hexanes/ethyl acetate 1:1) giving rise to **21** (19 mg, 60 µmol, 75%) as a pale yellow oil. R_f: 0.26 (hexanes/ethyl acetate 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.36$–7.26 (m, 5H; H_{ar}), 6.24 (d, $J = 15.8$ Hz, 1H; CCH=CH), 5.92 (dt, $J = 15.8$, 5.5 Hz, 1H; CH_2CH=C), 5.24 (d, $J = 5.1$ Hz, 1H; NH), 5.11 (s, 1H; C=CH_2), 5.09 (s, 2H; $PhCH_2$), 4.98 (s, 1H; C=CH_2), 4.55 (m, 1H; NCH), 4.20 (d, $J = 5.5$ Hz, 2H; CH_2OH), 3.73 (s, 3H; OCH_3), 2.78 (dd, $J = 14.0$, 5.8 Hz, 1H; CH_2), 2.58 (dd, $J = 14.0$, 7.5 Hz, 1H; CH_2), 1.96 (brs, 1H; OH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 172.4$ (CO), 155.7 (NCO), 140.1 (C=CH_2), 136.2, 131.9, 128.5, 128.2, 128.1 (Car, CH=CH), 119.0 (C=CH_2), 67.0 ($PhCH_2$), 63.4 (CH_2OH), 52.9 (NCH), 52.3 (OCH_3), 35.5 (CH_2); elemental analysis calcd (%) for $C_{17}H_{21}NO_5$ (319.4): C 63.94, H 6.63, N 4.39; found C 63.68, H 6.58, N 4.33.

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