Transition Metal Catalyzed Formation and Transformations of allylic N,O-acetals with a focus on olefinic a-amino acids

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CHAPTER 1
OLEFINIC α-AMINO ACIDS

1.1 Introduction

Non-proteinogenic amino acids have received increasing attention in recent years. This trend can be partially explained by the growing desire of biology and material sciences oriented chemists to modify peptide structures with designer made amino acids. Besides, from a synthetic organic viewpoint they represent a class of (enantiomerically pure) starting materials that significantly widen the synthetic utility of amino acids in general, compared to the 'regular' proteinogenic amino acids. Olefinic α-amino acids (e.g. 1a, chart 1.1) constitute a large sub-class of the non-proteinogenic amino acids, the importance of which is expressed by the large number of recent articles appearing on novel (bio)synthetic approaches to prepare these molecules.

Chart 1.1 Olefinic α-amino acids and their applications.

The recent breakthroughs in the metathesis field and the emergence of other types of transition metal catalyzed processes that can be used for the functionalization of olefins have especially contributed to an increased interest in these amino acids. Besides, olefinic α-amino acids nowadays play an important role in peptide chemistry due to their facile incorporation in (biologically relevant) protein structures. Because of the increasing importance, this chapter will review the recent literature that has appeared on applications of olefinic α-amino acids. Moreover, it intends to position the methodology that has been described in this thesis in a broader perspective.
1.2 Applications of olefinic α-amino acids

To stay within the scope of this thesis, the survey will be limited to α-olefinic-α-amino acids of type 1a and the protected (1b) or functionalized forms (1c) thereof, with possible substituents at the places of the dotted lines (chart 1.1). For example, the corresponding amino alcohols or related β-amino acids are not covered in this review. The applications reported can be roughly divided into four categories: (i) those that only modify the olefinic side chain, (ii) cyclizations that utilize the olefinic side chain and a substituent on the nitrogen, (iii) cyclizations that utilize the olefinic side chain and the ester functionality and (iv) biosynthetic applications, often using the free amino acids like 1a. While the side chain modifications provide important and novel linear amino acids, most of the synthetic applications are found in the second group, leading to amino acid derived cyclic compounds, with ring-sizes varying between five and thirty atoms. The third category makes use of the ester functionality for the construction of related cyclic compounds. The next paragraphs review the separate categories, covering the literature from June 2000 to May 2003.

1.3 Side chain modifications

1.3.1 Halogenations

Based on their earlier work on the synthesis of (+)-deoxypyrrololine, Adamczyk and co-workers reported the transformation of isotopically labeled homoallylglycine (Hag) into (+)-deoxypyridinoline 7 (scheme 1.1).

Scheme 1.1

\[
\begin{align*}
\text{(a) BH}_3\cdot\text{THF, 0 °C to rt, 17 h (48%)}; \quad \text{(b) I}_2, \text{PPh}_3, \text{imidazole, THF, rt, 3 h (78%)}; \\
\text{(c) 6, dioxane, reflux, 7 h (40%)}; \quad \text{(d) TFA, H}_2\text{O, rt, 1.5 h (84%)}.
\end{align*}
\]

Hydroboration of the isotopically labeled 4 (derived from L-glutamic acid) and subsequent halogenation of the alcohol led to the formation of iodide 5 in 37% overall yield. Coupling of this enantiomERICALLY pure iodide with pyridine derivative 6 and hydrolysis in aqueous TFA completed the synthesis of labeled (+)-deoxypyridinoline 7. Instead of using a substitution
reaction, a direct method to obtain halogenated unnatural amino acids was studied by Easton et al. (scheme 1.2).\(^6\)

**Scheme 1.2**

\[
\begin{align*}
\text{PhthN}^+ \text{CO}_2\text{Me} & \quad \text{Cl} \quad \text{a} \quad \text{PhthN}^+ \text{CO}_2\text{Me} \quad \text{b} \quad \text{PhthN}^+ \text{CO}_2\text{Me} \quad \text{c} \quad \text{PhthN}^+ \text{CO}_2\text{Me} \\
9 (53\%) & \quad \text{PhthN}^+ \text{CO}_2\text{Me} \quad \text{Br} \quad \text{d} \quad \text{PhthN}^+ \text{CO}_2\text{Me} \\
10 (77\%) & \quad \text{PhthN}^+ \text{CO}_2\text{Me} \quad \text{Br} \quad \text{14 (20\%)} \\
12 (31\%) & \quad \text{PhthN}^+ \text{CO}_2\text{Me} \quad \text{Br} \quad \text{13 (52\%)} \\
8 & \quad \text{PhthN}^+ \text{CO}_2\text{Me} \quad \text{Br} \quad \text{15 (26\%)}
\end{align*}
\]

(a) Cl\(_2\), CCl\(_4\), rt; (b) NBS, CCl\(_4\), reflux; (c) NaH, THF, rt, 48 h. (d) \(n\)-BuLi, dimethyl malonate, THF, 10 min., then 10, 15 h.

Treatment of the unsaturated amino acids 8 and 11 with molecular chlorine at room temperature resulted in the formation of the allylic halogenated products 9 and 12, in 53 and 31% yield, respectively (only major products are given). The corresponding brominated products 10 and 13 were obtained in 77 and 52% yield by treatment with \(N\)-bromosuccinimide in refluxing CCl\(_4\). The same group used bromide 10 to synthesize the cyclopropyl amino acid 14 by a NaH-induced intramolecular C-C bond formation in 20% yield and by the synthesis of malonate 15 through an intermolecular substitution of the bromide with dimethyl malonate.

**1.3.2 Palladium mediated transformations**

An important and frequently used type of side-chain modification involves a transition metal mediated process. A nice example of such a side-chain modification is given by Gurjar and co-worker, who utilized the Heck reaction for this purpose (Scheme 1.3).\(^7\)

**Scheme 1.3**

\[
\begin{align*}
\text{CO}_2\text{t-Bu} & \quad \text{NHCbz} \quad \text{a} \quad \text{R} & \quad \text{CO}_2\text{t-Bu} \quad \text{NHCbz} \\
16 & \quad \text{17 (70\%, R = H, E/Z 96:4)}
\end{align*}
\]

(a) RC\(_4\)H\(_4\), NaHCO\(_3\), Bu\(_4\)NBr, Pd(OAc)\(_2\), MeCN, 70 °C, 6 h.

The palladium catalyzed coupling of protected allylglycine 16 led to the formation of the phenylallylglycine derivatives 17 in 70% yield. Several aryl iodides with electron-withdrawing and electron-donating R-groups were successfully coupled using this protocol.
A similar type of Heck coupling was used by Collier and co-workers to synthesize bishomophenylalanine derivatives such as 19 (scheme 1.4).\(^8\)

**Scheme 1.4**

\[
\begin{array}{c}
\text{CO}_2\text{Me} \\
\text{NHBOc} \\
\text{Me} \\
18 \\
\text{a,b} \\
\text{R} \\
\text{Me} \\
\text{66-79\%} \\
\text{CO}_2\text{Me} \\
\text{NHBOc} \\
19 (66\%, \text{R} = \text{CO}_2\text{Me}) \\
\end{array}
\]

(a) RC\(_6\)H\(_4\)X (X = Br or I), K\(_2\)CO\(_3\), Pd(OAc)\(_2\), n-Bu\(_3\)P, DMF, 100 °C, 1 h; (b) Pd/C, H\(_2\), EtOH.

For example, the Heck coupling of allylglycine derivative 18 with 4-iodobenzoic acid methyl ester, followed by double bond hydrogenation resulted in protected bishomophenylalanine 19 (R = CO\(_2\)Me) in 66% yield over these two steps.

Alternatively, to achieve double bond substitution with aryl groups, the Stille-coupling was applied on different olefinic \(\alpha\)-amino acids. The group of Berkowitz reported a stereodivergent route for \(\alpha\)-alkylated, stannylated vinylglycines that were useful in the Stille-type coupling.\(^9\) The organoselenium oxazoline intermediate 21 was obtained in 79% yield by treatment of the starting vinylglycine 20 with phenylselenenium chloride in the presence of silver triflate at -100 °C in THF (scheme 1.5). The diastereoisomers could be separated by silica gel chromatography. Diastereoselective alkylation of product 21b proceeded in good yields (79-90%) and with excellent e.e.'s (>98%) for different alkyl halides. This resulted in the formation of \(\alpha\),\(\alpha\)-disubstituted vinyl selenides 23 after the base induced ring opening of the alkylation products 22. A novel type of deselenative stannylation upon treatment of the vinyl selenides 23 with Bu\(_3\)SnH in the presence of AIBN, resulted in the vinyl stannanes 24 in good yields (83-87%).

**Scheme 1.5**

\[
\begin{array}{c}
\text{MeO}_2\text{C}^- \\
\text{N} \\
\text{Ph} \\
20 \\
\text{a} \\
\text{MeO}_2\text{C}^- \\
\text{MeO}_2\text{C}^- \\
\text{MeO}_2\text{C}^- \\
\text{Ph} \\
\text{Ph} \\
21\text{a} \\
\text{~1:1} \\
\text{MeO}_2\text{C}^- \\
\text{MeO}_2\text{C}^- \\
\text{MeO}_2\text{C}^- \\
\text{Ph} \\
\text{Ph} \\
21\text{b} \\
\text{b,c} \\
\text{MeO}_2\text{C}^- \\
\text{R}_2\text{SePh} \\
\text{R}_2\text{SePh} \\
\text{R}_2\text{SnBu}_3 \\
\text{R}_2\text{BzH} \\
\text{23 (71-80\%)} \\
\text{24 (83-87\%)} \\
\text{25 (85\%, R = Bn)} \\
\text{d} \\
\text{e} \\
\text{f} \\
\text{MeO}_2\text{C}^- \\
\text{R} \\
\text{R} \\
\text{R} \\
\text{BzHN} \\
\text{BzHN} \\
\text{BzHN} \\
\text{MeO}_2\text{C}^- \\
\text{MeO}_2\text{C}^- \\
\text{MeO}_2\text{C}^- \\
\text{MeO}_2\text{C}^- \\
\text{MeO}_2\text{C}^- \\
\text{MeO}_2\text{C}^- \\
\end{array}
\]

(a) PhSeCl, AgOTf, THF, -100 °C; (b) separation by chromatography; (c) KHMDS, RX, -78 °C; (d) KOt-Bu, DMF; (e) AIBN, Bu\(_3\)SnH, toluene, A; (f) Pd\(_3\)dba\(_3\), p-NO\(_2\)C\(_6\)H\(_4\)I, THF.
These types of stannanes could be hydrolyzed under acidic conditions to the free α-substituted vinylglycines for different R-groups. Alternatively, a palladium catalyzed Stille coupling with p-nitrophenyl iodide resulted in the formation of arylvinylglycine 25 in 85% yield for R = Bn. A full paper published by the same group covered additional examples of couplings performed with stannane 24 (R = Bn).10 The Kazmaier group reported the use of the Stille coupling on the tributyltin substituted allylglycines 26a and 26b that were obtained via the Claisen rearrangement of α-stannylated allylic esters (scheme 1.6).11

Scheme 1.6

![Scheme 1.6](image)

(a) BnBr, Pd2dba3, CHCl3, AsPh3, THF, 20 h; (b) allyl bromide, Pd2dba3, CHCl3, AsPh3, toluene, 60 °C, 20 h; (c) o-BrC6H4CH3Br, Pd2dba3, CHCl3, AsPh3, THF, reflux, 5 h; (d) BzCl, n-C3H5PdCl, MeCN; (e) AcCl, n-C3H5PdCl, MeCN, 10 min.; (f) I2, CHCl3, rt; (g) 33, (MeCN)2PdCl2, DMF, 80 °C, 2 h.

The palladium catalyzed coupling of these stannanes with benzyl bromide was performed with Pd2dba3 and with AsPh3 as the ligand, giving the allylglycines 27a and 27b in 81 and 76% yield. Other examples comprise the introduction of an allyl (28, 72% yield), an o-bromobenzyl (29, 58% yield), a benzoyl (30, 88% yield) and an acetyl group (31, 70% yield). These Stille couplings could also be performed on the crude starting materials with respectable yields. Stannane 26a could also be substituted for an iodide, followed by a palladium catalyzed cross-coupling with the (E)-vinylstannane 33 to afford the allylic alcohol 32 in 57% overall yield.

The hydroboration-Suzuki cross coupling sequence with unsaturated amino acids also proved to be a good strategy for the synthesis of other α-amino acids.12 In this way, Collier et al. showed that hydroboration of protected allylglycine 34 afforded the borane intermediate 35a, which was subjected to Suzuki coupling conditions with various aryl and vinyl halides (X = Br, I, scheme 1.7).13 This resulted in a range of coupling products of type 35b, containing different R-groups. Cbz-protected product 35c with R = 2-pyridine-N-oxide was successfully treated with TFAA to give the Boekelheide reaction. After saponification of the intermediate trifluoroacetates, hydroxy compound 36 was obtained in 62% yield. Oxidation of the 5-hydroxy group with MnO2 afforded the ketone in 71% yield.
Saponification of the ester, followed by hydrogenolysis of the Cbz-group led to cyclization of the free amine onto the ketone. The resulting pyrroline was further hydrogenated in the same pot to afford the substituted proline derivative 37 as a mixture of diastereoisomers in 55% yield over the last three steps.

An organometallic pincer complex-oriented application of the hydroboration-Suzuki cross-coupling sequence with unsaturated amino acids was studied by the group of Van Koten. Allylglycine 38 reacted with 9-BBN to give the hydroborated intermediate, which was reacted with 1-bromo-4-iodo-2,6-bis[(dimethylamino)methyl]benzene (39) under Suzuki-type conditions (scheme 1.8). This afforded the bromide 40 in 72% yield over two steps. Metallation of 40 was carried out with a platinum or palladium complex to afford both the complexes 41 and 42 in good yield. Removal of the Boc-group and saponification was also possible, affording the free amino acids, suitable for incorporation in peptides.
1.3.3 Metathesis-based transformations

A different, but important type of side-chain modification of allylglycines was achieved through olefin metathesis. The cross metathesis of allylglycines with O-allylglycosides was found to be a good route for the synthesis of glycosyl amino acids. An example was published by the Danishefsky group. Cross-metathesis between allylglycine 44 and allylglycoside 43 was successful with an excess of the amino acid (5 equiv) and by applying 20 mol% of catalyst 45 in refluxing dichloromethane (scheme 1.9).

Scheme 1.9

\[ \text{Scheme 1.9} \]

Catalyst 46 was also tested, but appeared inferior compared to 45. In this way, metathesis product 47 was obtained in a yield of 70% as a mixture of double bond isomers. An interesting application was the synthesis of Globo-H-glycosyl amino acid 49, starting from hexasaccharide 48 and allylglycine 44. Applying the optimized cross-metathesis conditions, followed by double bond hydrogenation led to the desired target in a yield of 62% over these two steps.

A related, but different study toward the cross-metathesis of allylglycines with C-glycosides was disclosed by McCarvey et al. They reported the successful metathesis between C-glycosides of type 50 and 51 (R = Bn, Ac) with allylglycines 52 (PG = Boc, Fmoc), to afford the C-neoglycopeptides 53 and 54 in generally good yields (scheme 1.10). This time, the second generation Grubbs catalyst 46 proved to be more satisfactory. The same strategy was applied onto the C-allyllactose 55 and the C-vinylglucoside 56 to give the metathesis products 57 and 58 in yields ranging from 57-73%. After having established this so called, co-translational approach for building up glycopeptides, the post-translational strategy was
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tested with the tripeptide 59 containing the allylglycine moiety. A nice example was the metathesis with C-glycoside 51 to give the desired post-translational metathesis product 60 in 68% yield.

Scheme 1.10

\[
\begin{align*}
\text{Scheme 1.10} \\
\text{(a) } & 46 (10-20 \text{ mol%}), \text{CH}_2\text{Cl}_2, \text{reflux, 16-48 h}; \text{(b) } (\text{Ph}_2\text{MeP})_2\text{IrCOD-PF}_6 (10 \text{ mol%}), \text{THF, rt.}
\end{align*}
\]

A survey on the cross-metathesis of α- and β-C-glycosides with protected vinylglycines and subsequent hydrogenation of the new double bond was published by Nolen and co-workers (scheme 1.11).  

Scheme 1.11

\[
\begin{align*}
\text{(a) } & 46 (20 \text{ mol%}), \text{CH}_2\text{Cl}_2, \text{reflux, 12 h}; \text{(b) with H}_2, \text{Pd/C, Boc}_2\text{O or Pt on alumina, or Pd/C.}
\end{align*}
\]
In this study, a range of α- and β-C-glycosides (61) was tested in the metathesis with differently protected vinylglycines 62. For the substrates with \( n = 0 \), the metathesis proved to be difficult and gave compounds of type 63 in low yield. With the C-allylglycosides, the metathesis was much more successful and afforded the desired metathesis products in good yields using the second-generation Grubbs catalyst 46. Subsequent hydrogenation using different methods were all high yielding. Thus, the targeted synthesis of a range of C-glycosylasparagines of type 64 through cross-metathesis with vinylglycines was achieved.

1.3.4 Miscellaneous modifications

Diaminopimelic acid (DAP) and tetrahydrodipipecolinic acid are part of a class of biologically interesting compounds that have been the subject of recent independent studies by the groups of Vedera and Cox. Starting from protected allylglycine 65, the group of Vederas developed a synthetic route towards the latter compound (scheme 1.12).  

Scheme 1.12

\[
\begin{align*}
65 & \xrightarrow{a} \text{MeO}_2\text{C} \xrightarrow{b} \text{MeO}_2\text{C} \xrightarrow{c} \\
& \xrightarrow{d} \text{HO}_2\text{C} \xrightarrow{e} \text{HO}_2\text{C} \\
66 (79\%) & \quad 67 (86\%) & \quad 68 (75\%) & \quad 69 (76\%) & \quad 70 (66\%)
\end{align*}
\]

(a) \( \text{MeO}_2\text{CCHO} \), SnCl\(_4\), CH\(_2\)Cl\(_2\); (b) \( \text{H}_2\), Rh/C, EtOAc; (c) TsNHCbz, DEAD, PPh\(_3\), THF; (d) LiOH, MeCN, H\(_2\)O; (e) LiOH, MeOH, H\(_2\)O, then Li, NH\(_3\) (l).

The ene-type reaction of 65 with methyl glyoxylate afforded the ene-adduct 66 in 79% yield as a 1:1 mixture of diastereoisomers. Hydrogenation (86%), followed by Mitsunobu reaction with Cbz-protected tosylamide gave the DAP-derivative 68 in 75%. Cyclization was achieved by the action of LiOH in aqueous acetonitrile. This base leads to \( \alpha \)-deprotonation, followed by \( p\)-MeC\(_6\)H\(_4\)SO\(_3\)H elimination to give the imine. Cyclization of the second NHCbz-group onto the imine, followed by enamide formation through the elimination of CbzNH\(_2\) during acidic work up, gives 69 in 76% yield. Subjection of this compound to LiOH in aqueous methanol, followed by reaction with lithium in liquid ammonia gave the desired tetrahydrodipipecolinic acid 70 in 66% yield, which is in equilibrium with the enamine and its open form. Cox et al. used this protocol for the synthesis of a water-soluble epoxide analogue of compound 67 for in vitro activity studies.

Hernández and Martin aimed at a synthetic approach to DAP and 2,7-diaminosuberic acid (DAS) with control over the second stereocenter. Their synthesis proceeded via the olefinic amino acids 71, derived from aspartic (\( n = 1 \)) and glutamic acid (\( n = 2 \), scheme 1.13). The ester was carefully reduced with DIBAL-H to afford only the allylic alcohols in 85-87%. 
The stereochemistry was controlled by the Katsuki-Sharpless asymmetric epoxidation of the allylic alcohols, followed by regioselective epoxide opening with NaN₃ to afford the azides 72 in 58-61% yield over these two steps. For the symmetrically Boc-protected DAP/DAS compounds a sequence involving (i) hydrogenation of the azide, (ii) Boc protection and (iii) esterification afforded the compounds 73 in 71-76% yield over these steps. To achieve Cbz-protection, the vicinal diol had to be protected as the acetonide. Hydrogenation, followed by Cbz-protection of the resulting nitrogen and acetonide cleavage provided the corresponding diol. Further oxidative cleavage and esterification led to the desired chemically differentiated compounds 74 in 49-51% overall yield. By taking the opposite chiral catalyst in the epoxidation step, access to the other diastereoisomer was gained.

Researchers of Hoffmann-La Roche published an asymmetric route to meso-DAP 79 via the substituted allylglycine derivative 75 that was derived from aspartic acid (scheme 1.14). Hydrogenation of 75 in aqueous acetic acid, followed by oxidation led to the α-keto ester 76 in 29% yield.

Scheme 1.14

(a) 10% Pd/C, H₂O-HOAc (45%); (b) CrO₃-Py₂, CH₂Cl₂ (65%); (c) 77, CH₂Cl₂ (86%); (d) MsCl, pyridine, DMAP, CH₂Cl₂ (100%); (e) NaN₃, DMF (100%); (f) Pd/C, H₂ (100%); (g) 2.5N HCl, Δ (100%).
The key-step consisted of the stereoselective reduction of 76 with (R)-(−)-Alpine-Borane 77 to afford the desired (S)-hydroxy ester 78 in 86% yield. A sequence of four quantitative steps eventually led to 79 (DAP) in nearly diastereoisomerically pure form.

Some heterocyclic products were targeted by Wasserman and co-workers following a route that involved a differently substituted allylglycine intermediate, also derived from aspartic or glutamic acid.\textsuperscript{22}

**Scheme 1.15**

Oxidation of 80 with magnesium monoperphthalate (MMPP) led to 81 in 84% yield (scheme 1.15). The heterocycles could be obtained by treatment of 81 with a primary amine leading to the pyrroles 82 and 83 in 47 and 64% yield. Reaction with 1,6-diaminoheptane gave formation of the corresponding alkyl-bridged bipyrrrole 84 in 49% yield.

A different Wittig reaction with glutamic acid aldehyde led to the formation of the substituted homoallylglycine derivative 85 (scheme 1.16).\textsuperscript{23} Reduction of this key-intermediate led to the synthesis of the enantiopure alcohol 86 in 89% yield. Functional group transformations led to a variety of ω-functionalized α-amino acids (86b-86f).

**Scheme 1.16**

(a) MMPP; (b) BnNH\textsubscript{2}, p-anisidine or 1,6-diaminoheptane.
From these examples, it becomes clear that a large variety of side-chains is available starting from olefinic amino acids. Throughout the rest of this chapter, transformations involving more than only the side chain are discussed.

1.4 Cyclizations involving the olefinic side chain and a nitrogen substituent

1.4.1 Metathesis-based transformations

Allylglycines have been the subject of Ring-Closing Metathesis (RCM) ever since this reaction became more widely used and nowadays serves as an important test substrate for novel metathesis catalysts and conditions. A number of reports have recently emerged on this topic. For example, Kobayashi and co-worker cyclized allylglycine 87 with the novel, polymer supported arene-ruthenium catalyst 88, to afford 89 in 98% yield (scheme 1.17).\(^{24}\)

![Scheme 1.17](image)

(a) 20 mol% 88, hexane/toluene (10:1), reflux, 12 h.

The same transformation, but with the precursor containing a Boc-protected allylglycine was performed by Cho and Kim. This transformation was studied amongst others, using an excessive amount of the regular Grubbs catalyst 45, as a way to investigate a novel method for the removal of ruthenium impurities during the workup.\(^{25}\)

In the group of Lamaty, RCM of polymer bound allylglycines was studied. For example, allylglycine 90 was attached to a polyethylene glycol (PEG) linker via an ester functionality using the Mitsunobu reaction (scheme 1.18).\(^{26}\) Alkylation of the sulfonamide with various alkenyl bromides afforded the precursors of type 91.

![Scheme 1.18](image)

(a) PEG-OH, PPh₃, DEAD, THF (83%); (b) CH₂=CHR(CH₃)ₙBr, or propargyl bromide, K₂CO₃, DMF; (c) 45 (20-40 mol%), CH₂Cl₂, rt.
The best RCM conditions were found to be the use of 40 mol% of catalyst 45 at rt, leading to the cyclic amino acids of type 92. With this protocol, various ring-sizes \((n = 1-3\) for \(R = H\)) could be synthesized. Besides, a substituted double bond \((R = Me)\) was also successfully cyclized in the case of a six-membered ring. Enyne metathesis with a propargyl substituted nitrogen afforded the product with \(R = \text{vinyl}\). A similar type of metathesis was performed by the same group on systems with the PEG resin attached to the nitrogen via a silylethylsulfonyl (SES) linker.\(^{27}\) The required polymer bound precursors 94 were obtained by the sulfonylation of allylglycine 93 with PEG-SES-Cl, followed by alkylation with olefinic bromides (scheme 1.19).

Scheme 1.19

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{CO}_2\text{Me} \\
& \quad \text{a, b} \\
\text{R} & \quad \text{SES-PEG} \\
& \quad \text{c} \\
\text{N} & \quad \text{CO}_2\text{Me} \\
& \quad \text{d} \\
\text{H} & \quad \text{CO}_2\text{H}
\end{align*}
\]

(a) PEG-SES-Cl, THF, rt; (b) \(\text{CH}_2=\text{CHR(CH}_2)_n\text{Br}\), or propargyl bromide, \(\text{K}_2\text{CO}_3\), DMF, 48 h; (c) 45 (20-40 mol%), \(\text{CH}_2\text{Cl}_2\), rt; 46 (20 mol%, rt, 14 h) was used for \(R = \text{CO}_2\text{Me}\); (d) 6N HCl, 100 °C, 24 h.

RCM gave very good (83-96%) yields of the cyclic amino acids 95. Also in this case, enyne metathesis with the propargyl as nitrogen substituent gave product 95 \((R = \text{vinyl})\) in good yield. For the precursor with \(R = \text{CO}_2\text{Me}\), the second generation Grubbs catalyst 46 was necessary to obtain the product in a satisfactory yield. The cyclic products could not be cleaved from the resin by standard SES-cleavage conditions (fluoride, DMF). Therefore complete hydrolysis was necessary to afford the free, cyclic amino acids 96. The same group also attached the Hoveyda-Grubbs ruthenium catalyst to the PEG-solid support. With this recyclable polymer bound catalyst, the metathesis with SES protected allylglycines (as 94, but without the PEG) was studied.\(^{28}\)

Closely related to these metathesis reactions is the work of Dondas et al. in which the precursors were obtained via a palladium catalyzed coupling of allylglycine with an aryl iodide and an allene.\(^{29}\) Benzenesulfonyl protected allylglycine 97 was reacted with allene (1 bar) in the presence of \(\text{Pd(OAc)}_2\) and an aryl iodide or heteroaryl iodide (scheme 1.20). Through this protocol, the metathesis precursors 98 \((\text{Ar} = \text{phenyl}, 2\text{-thiophenyl}, 4\text{-}(4\text{-nitro-3-methyl})\text{phenyl}, 1\text{-naphthyl}, m\text{-tolyl and 5-}(1\text{-methyl})\text{indolyl})\) were obtained in yields ranging from 70-81%. RCM using the second generation Grubbs catalyst 46 in toluene at 80 °C afforded the unsaturated cyclic 5-aryl substituted amino acids 99.
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Scheme 1.20

(a) Aryl or heteroaryl iodide, allene (1 bar), Pd(OAc)$_2$ (10 mol%), PPh$_3$ (20 mol%), K$_2$CO$_3$, toluene, 80 °C, 24 h; (b) 46, toluene 80 °C, 3 h.

α,α-Disubstituted allylglycines and homologues, with a CX$_3$ moiety as the additional substituent at the α-position, were subjected to RCM by Osipov et al.$^{30}$ Such fluorinated amino acids are known to function as selective inhibitors of pyridoxal phosphate dependent enzymes. Six- and seven-membered ring formations were studied through metathesis with allyl or butenyl substituents on the nitrogen. The precursors (101) were obtained by the alkylation of the amino acids 100 (PG = SO$_2$Ph, Boc, Cbz, X = F, Cl) which in turn were obtained by the Grignard addition to the corresponding fluorinated imines (scheme 1.21).

Scheme 1.21

(a) NaH, DMF, −5 °C to rt, allyl bromide (m = 1) or butenyl bromide (m = 2); (b) 45 (10 mol%), CH$_2$Cl$_2$, rt, 3-5 h (60 h for 102a and 102b).

RCM took place with the ruthenium catalyst 45 in dichloromethane at room temperature. Moderate yields (45-50%) were obtained for the five-membered rings 102a and 102b, even at prolonged reaction times. For the six- (102c,d) and seven-membered (102e-h) ring systems excellent yields (93-98%) were reported. Clark and Middleton also reported on the metathesis of α,α-disubstituted allylglycine-containing substrates as a novel way to obtain cyclic α,α-disubstituted amino acids.$^{31}$ The diolefinic system 103 served as the RCM precursor and afforded compound 104a in 92% yield with catalyst 45 in dichloromethane and 104b,c in 83-87% yield with catalyst 46 in toluene at elevated temperature (scheme 1.22).
Peptide 105 (85%) was obtained by reaction of compound 104b with glycine ethyl ester. The cyclic, free amino acid 106 was obtained in 73% yield after cleavage of the ester and subsequent hydrogenation of the double bond and hydrogenolysis of the nitrogen substituent. Ring-closing metathesis also served as a way to cyclize the diallylglycine amide 108 into an eight-membered pseudodipeptide (scheme 1.23).

Alkylation of allylglycine 107 via reductive amination with 2,4-dimethoxybenzaldehyde and coupling with Boc-protected allylglycine afforded the diolefin 108. The dimethoxybenzyl moiety on the nitrogen caused the amide to adopt both the cis- and the trans-amide conformation. While without the benzylic moiety no metathesis occurred, compound 108 could be ring-closed to the cyclic amide in 80% yield using Grubbs catalyst 45 in refluxing dichloromethane. Saponification, deprotection and hydrogenation led to the elaboration of the free, eight-membered ring amino acid 110 in 78% yield over these steps. This type of compound may serve as a peptidomimetic for the corresponding cystine eight-membered ring. The topic of pseudopeptide mimetics has also been addressed by Hanessian and Angiolini, studying the synthesis of conformationally stable and constrained mimics of β-hairpin structures. The homoallylglycine-derived peptide 111 underwent metathesis by the action of catalyst 45 in dichloromethane at room temperature (scheme 1.24).
(a) 45, (10 mol%), CH₂Cl₂, rt, 5 h (92%); (b) Pd/C, H₂, MeOH, 16 h (90%).

The cyclic product was obtained as a 1:1 mixture of double bond isomers, which were hydrogenated to afford the cyclic peptide 112 in 83% over both steps. Repetitive deprotection, coupling, metathesis and hydrogenation afforded ultimately the saturated, bridged pseudooctapeptide 113 as a mixture of four conformers, thus providing a synthetic route toward carbocyclic analogues of β-hairpin and β-sheet model systems.

A RCM entry into biologically active dicarba-analogues of the peptide hormone oxytocin was reported by the group of Vederas. The strategy commenced with the solid
phase synthesis of the diolefinic linear peptide backbone 114 (scheme 1.25). Cyclization of the resin bound linear peptide using catalyst 45 afforded a mixture of cyclic olefinic products. DMSO was added to avoid ruthenium-containing contaminants, followed by Fmoc removal and acidic cleavage from the resin together with side chain deprotection. This led in \(~45\%\) yield to the cyclic product after reversed-phase HPLC purification. Hydrogenation then afforded the desired target 115, which was tested for biological activity and compared with oxytocin. The dicarba analog (EC\(_{50}\) 38 ng/mL) showed a 14-fold less activity than oxytocin (EC\(_{50}\) 2.7 ng/mL) itself.

A study towards a better theoretical understanding of cyclic peptide formation via RCM was performed by Toniolo and co-workers.\(^35\) In this study, X-ray diffraction analysis and conformational energy computations of \(\beta\)-turn and \(3_{10}\)-helical peptides based on olefinic \(\alpha\)-amino acids were used. The reported findings established a better picture of the feasibility of ring-closing metathesis in turn/helical peptides. By the same group an application of this principle was published in which the tetrapeptide benzylamide 116 was cyclized using RCM of the two pre-organized (intramolecularly H-bonded, type-II \(\beta\)-turn motif) allylglycine fragments, catalyzed by Nolan’s catalyst 118 to afford the four-carbon cross linked \(\beta\)-turn 117 in 70\% yield after hydrogenation (scheme 1.26).\(^36\)

**Scheme 1.26**

\[
\text{BocHN} \quad \text{NHBz} \quad \text{NHBz} \quad \text{BocHN}
\]

(a) 118 (5 mol\%), toluene, 80 °C, 16 h; (b) \(\text{H}_2\), PtO\(_2\), EtOAc, rt, 20 h.

Allylglycine has also been used in a ring-opening, ring-closing metathesis sequence (ROM-RCM) by the group of Blechert.\(^37\) The palladium-catalyzed allylation of racemic allylglycine 120 with the enantiopure allylic acetate 119 gave the precursor 121 in 71\% yield (scheme 1.27). Subjection of this olefin to Grubbs catalyst 45 completely led to the rearranged pipelic acid derivative 122. Upon treatment of this 1:1 diastereoisomeric mixture with catalytic base, the thermodynamically most stable compound 123 was obtained. Protective group exchange, followed by OsO\(_4\) oxidation of the tetrahydropyridine double bond and subsequent acylation gave the triacetate 125. Double bond cleavage using the OsO\(_4\)/NaIO\(_4\) couple led to the aldehyde, which cyclized to the imine after standard Boc deprotection. The cyclic imine was reduced with NaCNBH\(_3\) at pH 7 to afford the target indolizidine 126 in 60\% yield over the two final steps.
In recent synthetic approaches toward the aza-epothilones, allylglycine was used as a key-building block for the introduction of the thiazole moiety and for the metathesis-based ring formation. In the approach of Schinzer et al., Boc-protected allylglycine 127 was subjected to Weinreb amide formation, followed by the addition of methyllithium to afford 128 in 78% yield (scheme 1.28).³⁸

Scheme 1.27

(a) Pd(OAc)₂, PPh₃, NaH, DMF, rt−40 °C; (b) 45 (5 mol%), CH₂Cl₂, rt; (c) NaOMe, MeOH, rt; (d) Na, naphthalene, THF (63%); (e) Boc₂O, i-Pr₂N, CH₂Cl₂ (94%); (f) OsO₄, NMO, acetone/H₂O, rt (67%); (g) Ac₂O, Et₃N, CH₂Cl₂ (98%); (h) OsO₄, NaIO₄, acetone/H₂O, rt (69%); (i) (i) TFA, CH₂Cl₂, (ii) K₂CO₃, pH 7, NaCNBH₃, MeOH, rt (87%).

(a) HCl.HNMe(OMe), EDCI, CH₂Cl₂ (84%); (b) MeLi (2 equiv), THF, −78 °C (93%); (c) 129; (d) TFA; (e) RCO₂H (R = the substituted olefinic chain), pyBOP, DIPEA, DMF; (f) (i) 45, 1:1 (E/Z) (56%), (ii) separation; (g) HF-pyr (82%).
The thiazole was introduced by reacting 128 with the ylide 129. Deprotection of the nitrogen afforded the free amine 131 in 85% yield, which could be coupled to the second enantiopure olefinic fragment using pyBOP in DMF to afford the metathesis precursor 132 in 80% yield. RCM using catalyst 45 gave the cyclic olefin in 56% yield as a 1:1 mixture of (E/Z)-isomers, which could be separated by chromatography. Deprotection of the (Z)-isomer afforded the desired aza-epothilone (Z)-133 in 82% yield.

The closely related approach by Borzilleri et al. surprisingly delivered the (E)-isomer in excess (5:1). Following approximately the same route, the metathesis precursor 135 was synthesized, starting from allylglycine 127 (scheme 1.29). After coupling of the amine 131 with the second olefinic fragment, the only difference with the previous approach was the free hydroxyl group present in compound 135. Deprotection led to (E)-133, a product that was actually undesired because of the known lower biological activity of the comparable (E)-olefin epothilones C and A.

Scheme 1.29

(a) HCl.HNMe(OMe), EDCI, HOBT, NMM, CHCl₃, 0-25 °C (71%); (b) MeMgBr, THF, 0 °C (76%); (c) n-BuLi, THF, -78 °C to rt (18%, 30-40% recovered SM); (d) 4N HCl, dioxane, 0 °C, 0.5 h (88%); (e) RCO₂H (R = second olefinic fragment), EDCI, HOBT, DMF, 15 h (77%); (f) 45 (0.7 mol%), benzene, 22 h, 5:1 (E/Z) (41%); (g) TFA, CH₂Cl₂, 0 °C, 4 h (68%).

Besides the use of ring-closing metathesis, cross-metathesis with allylglycine derivatives has also found applications. The group of Hiemstra made use of allylglycine methyl ester 136 for the construction of 2,6-bridged diketopiperazines (scheme 1.30). Coupling with N-benzylglycine methyl ester, followed by Boc-deprotection and in situ cyclization gave the diketopiperazine motif. Protection of the lactam with a methoxycarbonyl group gave 137 in 68% yield over three steps. Cross-metathesis with allyltrimethylsilane (ATMS) catalyzed by ruthenium catalyst 46 afforded the allylsilane 138 in 52% yield. Both precursors were subjected to chemoselective reduction with NaBH₄ in methanol, followed by dissolving the crude hemiacetal in formic acid to induce cyclization. This resulted in the bridged diketopiperazines 139 (50%, after formate aminolysis) and 140 (64%).
1.4.2 Other transition metal mediated transformations

Apart from the use of the metathesis as a way to cyclize allylglycine derivatives, other transition metals also play a substantial role. For example, Kotha and co-worker reported the transformation of allylglycine derivative 141 into the cobalt complex 142 in 83% yield (scheme 1.31).\(^{41}\)

\[\text{Scheme 1.31}\]

\[
\begin{align*}
\text{141} & \quad \text{142} \quad \text{143} \quad \text{144} \\
(\text{CO})_6\text{Co} & \quad \text{142} \quad \text{143} \quad \text{144} \\
\text{Ts} & \quad \text{Ts} \quad \text{Ts} \quad \text{Ts}
\end{align*}
\]

(a) Co(CO)$_6$, diethyl ether, rt; (b) (i) toluene, reflux, (ii) 4-methylmorpholine N-oxide, CHCl$_3$; (c) DMAD, toluene, hydroquinone (cat.), sealed tube, 150 $^\circ$C, 48 h.

Heating the cobalt complex in refluxing toluene and subsequent oxidative decomposition with NMO yielded diene 143 in 51% yield. A small amount (11%) of the corresponding Pauson-Khand side-product was formed. A Diels-Alder reaction with dimethyl acetylenedicarboxylate (DMAD) afforded the targeted 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic) derivative 144 in 69% yield.

The Pauson-Khand reaction of vinylglycine derivatives was studied by Jiang and co-worker.\(^{42}\) Heating precursor 145 in benzene at 70 $^\circ$C for 4 h in the presence of 10 mol% Co(CO)$_5$ and 60 mol% Bu$_3$PS as co-catalyst under an atmosphere of carbon monoxide afforded the Pauson-Khand product 146 as a single diastereoisomer in 66% yield (scheme 1.32).
Precursor 147 gave the same product but in lower yield. The best yield was obtained by applying the same conditions to the cyclic precursor 148, affording diastereoisomerically pure 149 in 82% yield.

An efficient hydrocarbonylation of olefinic α-amino acid-containing dipeptides was published by Ojima, using a rhodium catalyzed process. Heating dipeptide 150 in toluene under an atmosphere of H₂/CO in the presence of Rh(acac)(CO)₂ (2 mol%) with BIPHEPHOS (4 mol%) as ligand afforded the aldehyde-hydrocarbonylation product, which cyclized spontaneously in toluene to afford 151 in 96% yield (scheme 1.33).

This process was accelerated by the addition of a catalytic amount of PTSA. In THF or with some base, the cyclization was suppressed which allowed the isolation of the intermediate aldehyde. Applying the same conditions onto precursor 152 resulted in the formation of bicycle 153 in 95% yield. Sulfide 154 could be transformed stepwise into the
similar bicyclic system by performing the hydrocarbonylation in methanol to give the acetal 155 in 86% yield. This acetal was cyclized with a catalytic amount of TFA to afford the bicyclic dipeptide 156 in 89% yield. These products can serve as peptide β-turn mimetics.

A Heck-type reaction of a homoallylglycine derivative was used as the key-step in the synthesis of the benzoazepine 161, which was studied by researchers of GlaxoWellcome for its potential action as an antagonist of the strychnine-insensitive glycine binding site associated with the NMDA receptor (scheme 1.34).44

**Scheme 1.34**

![Chemical structure](image)

(a) OsO₄, NMO, THF/H₂O, rt, 5 h; (b) (i) LiOH, EtOH/H₂O, rt, 2 h, (ii) 1N HCl, THF, 24 h; (c) (COCl)₂, DMSO, TEA, CH₂Cl₂, -78 °C, 1 h; (d) (Ph₃PCHCONHPh)Br, DBU, MeCN, rt, 1 h; (e) (i) Bu₃SnH, Pd(PPh₃)₄, THF, rt, 4 h. (ii) TMSCHN₂, CH₂Cl₂/MeOH, rt, 30 min; (f) Pd(PPh₃)₄, TEA, DMF, 80 °C, 1 h; (g) LiOH, EtOH/H₂O, rt, 1 h.

The route went via allylglycine derivative 157, which was dihydroxylated and cyclized to give 158 in 77% yield. Swern oxidation and a Horner-Emmons coupling of the aldehyde with the requisite phosphorus ylide afforded intermediate 159 in 50% yield over these two steps as a 8:2 mixture of syn- and anti-diastereoisomers and with a 84:16 (E/Z) ratio. Treatment with Bu₃SnH in the presence of Pd(PPh₃)₄ led to reductive ring opening of the γ-lactone ring, after which methylation provided the methyl ester 160a and 160b in a combined yield of 70%. A Heck-type cyclization with Pd(PPh₃)₄ in DMF, followed by saponification gave the desired benzoazepine derivative 161 in 60% yield over these two steps.

### 1.4.3 Radical cyclizations

A radical cyclization reaction of allylglycines was developed by the group of Blechert.46 Irradiation of the compounds 162, 164 and 166 in a mixture of methanol/acetonitrile with photoexcited 9,10-anthracene dicarbonitrile (ADC) and biphenyl
(BP) as co-sensitizer led to the desired photochemically induced electron transfer reaction (PET, scheme 1.35).

Scheme 1.35

![Scheme 1.35](image)

In this way, the cyclic compounds 163 (51%), 165a,b (24-55%) and 167a-d (33-70%) were isolated. This radical cyclization protocol was applied to the allylglycine containing oligopeptides 168 and 170. The successful radical cyclization led to the proline-containing oligomers 169 (86% yield) and 171 (64% yield), thereby causing a structural rearrangement of the peptide backbone and therefore applicable to the formation of β-turn mimetics.

A study of Bowman and co-workers focused on the cyclization of α-chiral aminyl radicals derived from sulfenamides with tributyltin. The homo- and bishomoallylglycine derived sulfenamides 172 were tested (scheme 1.36).
In the case of \( n = 1 \) and \( R = H \), successful radical cyclization induced by BuSn\(_3\)H and AMBN (2-\([(E)-2-(\text{cyano}-1\text{-methylpropyl})\text{-1-diazenyl}]\text{-2-methylbutanitrile}) in cyclohexane at reflux temperature led to the formation of \( 173a \) in 92% yield. For the N-benzyl derivative \( 173b \) the yield was substantially lower, with concomitant formation of \( 174b \) (30%). For the precursor with \( n = 2 \), no cyclization was observed.

### 1.4.4 Miscellaneous cyclizations

Knapp and co-workers reported the oxidation of allylglycine derivatives and subsequent cyclization to form 1,4-diazepan-2-ones (scheme 1.37).\(^{48}\)

### Scheme 1.37

(a) OsO\(_4\), NaIO\(_4\) aq. THF; (b) \( \text{H}_2\), Pd/C, MeOH; (c) (i) \( \text{O}_3\), CH\(_2\)Cl\(_2\), -78 \(^\circ\)C, (ii) Me\(_2\)S, rt; (d) \( \text{H}_2\), Pd/C, MeOH; (e) (i) \( \text{O}_3\), CH\(_2\)Cl\(_2\), -78 \(^\circ\)C, (ii) separation, (iii) PPh\(_3\), THF; (f) NaBH\((\text{OAc})_3\), THF; (g) Ac\(_2\)O, MsOH; (h) HCl salt formation, then [bis(trimethylsilyl)uracil, TMSOTf, MeCN, reflux; (i) 0.5N LiOH, EtOH, RP-HPLC.
For example, oxidative cleavage of the double bond of allylglycine derivative 175 led to the formation of diazepanone 176 in 67% yield after deprotection/reductive amination. In the case of precursor 177, both diastereoisomers were separately cyclized using ozone-oxidation to the corresponding aldehydes and subsequent cyclization by the reductive amination. This led to 178a in 48% yield, starting from the anti-precursor and to 178b in 70% yield, starting from the syn-precursor. The methodology was applied in the synthesis of the Liposidomycin diazepanone nucleoside. Therefore, key-intermediate 179 was synthesized and treated with ozone at -78 °C. The intermediate azido ozonide could be separated and reduced with PPh₃. The resulting imine-intermediate was reduced with triacetoxyborohydride, which also caused elimination of the benzyol moiety. During these steps, presumably by some formaldehyde liberated in the ozonolysis reduction step, the nitrogen was also methylated. Acetylation, coupling with uracil and saponification led to the desired Liposidomycin degradation product 182, useful for the establishment of the absolute stereochemistry of the liposidomycins B and C.

A conformationally restricted farnesyltransferase inhibitor was targeted by Dinsmore et al., starting from N-Boc-allylglycine 183 (scheme 1.38).[^19]

Scheme 1.38

\[
\begin{align*}
\text{Scheme 1.38} & \quad \text{(a)} \quad \text{MeO(Me)NH.HCl, EDC, HOBt, DMF, 0 °C, 24 h (67%); (b)} \quad \text{LiAlH₄, Et₂O, -50 °C to 5 °C, 3 h (85%); (c)} \quad \text{2,4-(MeO)BnNH₂, NaBH(OAc)₃, 4Å MS, 1,2-dichloroethane, 16 h (90%); (d)} \quad \text{CICH₂COCl, NaHCO₃, EtOAc-H₂O, 0 °C, 30 min (93%); (e)} \quad \text{Cs₂CO₃, DMF, 65 °C, 16 h (75%); (f)} \quad \text{OsO₄, NMO, t-BuOH, THF, H₂O, 7 h, then NaIO₄, NaHCO₃, 1.5 h (96%); (g)} \quad \text{NaBH₄, EtOH, 0 °C to rt, 1 h (92%); (h)} \quad \text{PhSO₂Cl, EtsN, CH₂Cl₂, 0 °C to rt, 1 h (83%); (i)} \quad \text{LiHMDS, THF, -78 °C to 0 °C, 40 min. (86%); (j)} \quad \text{HCl, EtOAc, 0 °C, 30 min. (100%); (k)} \quad \text{1-(3-fluoro-4-cyanobenzyl)imidazole-5-carboxaldehyde, NaBH(OAc)₃, 4Å MS, 1,2-dichloroethane, 24 h (56%); (l)} \quad \text{TfOH, Et₂SiH, CH₂Cl₂/MeCN, 14 d (69%); (m)} \quad \text{NaH, DMF, 3-bromomethyl-4-chlorophenylmethanesulfonate, 0 °C, 1 h (55%); (n)} \quad \text{Cs₂CO₃, DMSO, 80 °C, 5 h (34%).}
\end{align*}
\]
Following a straightforward sequence of eight steps, the allylglycine derivative was transformed into the benzenesulfonate 185, which was cyclized by the addition of LiHMDS in THF to afford the bicyclic framework 186 in 86% yield. Replacement of the Boc-protective group by an imidazole-containing moiety through a reductive amination procedure, afforded compound 187 in 56% yield over these steps. A difficult exchange of the 2,4-dimethoxybenzyl group for the methanesulfonate substituted benzyl moiety afforded 188 in 38% yield. Tandem deprotection/cyclization with Cs$_2$CO$_3$ in DMSO at 80 °C afforded the targeted cyclophane 189 in 34% yield. This compound was found to be more potent than the parent, unbridged system in the inhibition of FTase-catalyzed incorporation of [3H]-farnesylpyrophosphate into recombinant Ras-CVIM.

Process researchers from Chirotech Technology developed an interesting large-scale preparation method for all four diastereoisomers of 4-hydroxypipecolic acid. The authors utilized the known procedure for the cyclization of protected allylglycines via an N-acyliminium ion intermediate. Allylglycine 190 was reacted with paraformaldehyde in formic acid to afford a 1:1 mixture of 191 in 96% yield (scheme 1.39).

**Scheme 1.39**

\[
\begin{align*}
\text{CbzHN-} & \text{CO}_2\text{Me} \quad \text{a} \quad \text{OCHO} \\
\text{190} & \quad \text{191 (96\%)} \\
\text{CbzHN-} & \text{CO}_2\text{Me} \quad \text{b} \quad \text{OR} \\
\text{192 R = H} & \quad \text{193 R = Phth (38\%)} \\
\text{CbzHN-} & \text{CO}_2\text{Me} \\
\text{191 (52\%)} & 
\end{align*}
\]

(a) paraformaldehyde, HCO$_2$H; (b) lipase AY30; (c) phthalic anhydride.

This diastereoisomeric mixture was separated by subjection to lipase AY30 that selectively hydrolyzed one isomer. Treatment of this inseparable 1:1 mixture of the 4-hydroxy- and 4-formatepipecolic acid with phthalic anhydride, to form the hemiphthalate ester derivative 193, enabled separation by partitioning between the aqueous and organic layers. Enantiomerically pure 193 was obtained in 38% yield via this procedure and the pure formate 191 was obtained in 52% yield, which could be easily hydrolyzed to the free hydroxyl group.

**Scheme 1.40**

\[
\begin{align*}
\text{a,b} \quad \text{a,b} \\
\text{194} & \quad \text{195 (59\%)} \\
\text{a,b} & \quad \text{a,b} \\
\text{195} & \quad \text{196 (95\%)} \\
\end{align*}
\]

(a) (i) 9-BBN, THF, (ii) separation (78\%); (b) PDC, CH$_2$Cl$_2$ (75\%); (c) H$_2$, Pd/C, MeOH (95\%).
The piperidine skeleton was also targeted by Xue et al., using the reductive amination approach.\textsuperscript{52} Hydroboration of the ester substituted Hag-derivative 194 afforded a mixture of diastereoisomeric alcohols that could be separated from each other (scheme 1.40). Oxidation gave the aldehyde 195 in 59\% yield over these steps. Hydrogenation removed the benzyl groups and led to reduction of the resultant cyclic imine to afford the desired (2S,3S)-196 in 95\% yield.

1.5 Cyclizations involving the olefinic side chain and an ester substituent

In the research group of Hiemstra and Rutjes a diastereoselective synthesis of \( \beta \)-amino alcohols was developed, starting from Cbz-protected allylglycine 197 (scheme 1.41).\textsuperscript{53}

Scheme 1.41

\[
\begin{align*}
&\text{HN} \quad \text{CO}_2\text{Me} \\
&\text{CBz} \\
&197 \\
\end{align*}
\]

\[
\begin{align*}
&a,b &\text{HN} \quad \text{CO}_2\text{Me} \\
&\text{CBz} &R \\
&198a &\text{Me} (68\%) \\
&198b &\text{allyl} (60\%) \\
&198c &\text{PhC}=\text{C} (58\%) \\

&\text{HN} \quad \text{CO}_2\text{Me} \\
&\text{CBz} \quad \text{OH} \\
&199 &\text{Me} (89\%) \\

&\text{HN} \quad \text{CO}_2\text{Me} \\
&\text{CBz} \quad \text{OH} \\
&200 &\text{Me} (60\%) \\
\end{align*}
\]

(a) HCl,HNMe(OMe), AiMe\textsubscript{3}, CH\textsubscript{2}Cl\textsubscript{2} (70\%); (b) RMgBr, THF; (c) allylMgBr, THF, -78 °C, 70:30 (syn/anti); (d) 45 (cat.), CH\textsubscript{2}Cl\textsubscript{2}.

Weinreb amide formation, followed by a Grignard addition led to the ketones 198a-c in 58-68\% yield over the two steps. A second Grignard addition to ketone 198a (R = Me) with allylmagnesium bromide resulted in the formation of 199 in 89\% yield as a 70:30 mixture of syn/anti diastereoisomers. The trans-relationship of the main product was established upon RCM of the diolefin to the cyclohexene derivative 200.

Scheme 1.42

\[
\begin{align*}
&TFAHN \quad \text{CO}_2\text{Me} \\
&\text{R} \\
&201a &\text{R} = \text{H} \\
&201b &\text{R} = \text{Ph} \\
\end{align*}
\]

\[
\begin{align*}
&a &\text{TFAHN} \quad \text{CO}_2\text{Me} \\
&\text{R} \\
&202a \\
\end{align*}
\]

\[
\begin{align*}
&\text{TFAHN} \quad \text{CO}_2\text{Me} \\
&\text{H} \\
&202b \\
&\text{TFAHN} \quad \text{CO}_2\text{Me} \\
&\text{R} \\
&203a (73\%) \\
&203b (55\%) \\
\end{align*}
\]

(a) OsO\textsubscript{4}, NaIO\textsubscript{4}, THF, H\textsubscript{2}O; (b) cysteine, pyridine, 50 °C, 4 d; (c) CH\textsubscript{2}N\textsubscript{2}, CH\textsubscript{2}Cl\textsubscript{2}.

Another type of cyclization involving the ester substituent and the olefin side-chain, was performed by the group of Hruby, in which they targeted the synthesis of a bicyclic \( \beta \)-turn
dipeptide.\textsuperscript{54} Access to the enantiopure $\text{Hag}$-intermediates $201\text{a}$ and $201\text{b}$ was gained through an asymmetric alkylation involving a chiral template nickel(II)-complex. Oxidative cleavage of the double bond resulted in the formation of an equilibrium between compounds $202\text{a}$ and $202\text{b}$, which were subjected to cysteine in the presence of pyridine at 50 °C for 4 days to form the N,S-acetal (scheme 1.42). Essential for this process was the use of the TFA protective group for the starting amino acid. Esterification completed the desired synthesis route to these $[4.3.0]$-bicyclic $\beta$-turn dipeptides, yielding $203\text{a}$ and $203\text{b}$ in 73 and 55\%, respectively over the three steps.

Gmeiner and co-workers reported on the synthesis of dehydro-Freidinger lactams via RCM of allylglycine derived dipeptides and homologues.\textsuperscript{55} RCM of the precursors $204$ was in most cases successful with ruthenium catalyst $45$ in refluxing 1,2-dichloroethane (scheme 1.43).

**Scheme 1.43**

\[
\begin{align*}
\text{BocHN} & \quad \text{N} \quad \text{CO}_{2}\text{Et} \quad \text{a} \quad \text{BocHN} \quad \text{N} \quad \text{CO}_{2}\text{Et} \\
204 & \quad \text{BocHN} \quad \text{N} \quad \text{CO}_{2}\text{Et} \quad \text{a} \quad \text{BocHN} \quad \text{N} \quad \text{CO}_{2}\text{Et} \\
205\text{a} (53\%) & \quad 205\text{b} (68\%) \\
205\text{c} (70\%) & \quad 205\text{d} (86\%) \\
205\text{e} (8\%) & \quad \\
\end{align*}
\]

(a) $45$ (10 mol\%) or $46$ (5 mol\%, only used for $205\text{e}$), 1,2-dichloroethane, reflux.

The ring-closed products $205\text{a-e}$ were generally obtained in good yields except for the ten-membered ring lactam $205\text{e}$. Noteworthy is the excellent yield of the nine-membered dehydro-Freidinger lactam $205\text{d}$ in 86\% isolated yield. These cyclic lactams were used in a study to investigate the conformational preferences of these $\beta$-turn models.

**Scheme 1.44**

\[
\begin{align*}
\text{BnO} & \quad \text{O} \quad \text{NHBo c} \quad \text{a} \quad \text{BnO} \quad \text{O} \quad \text{NHBo c} \\
206 & \quad \text{BnO} \quad \text{O} \quad \text{NHBo c} \quad \text{a} \quad \text{BnO} \quad \text{O} \quad \text{NHBo c} \\
207 (80\%, only cis) & \quad 208 (quant.) \\
\end{align*}
\]

(a) $45$, CH$_2$Cl$_2$, reflux, 48 h; (b) NaOMe; (c) TsNHNH$_2$, 1 M aq. NaOAc, DME.
Westermann and Walter used RCM as the key transformation for the construction of C-glycosidic neoglycoconjugates. Allylglycine derivative 206 was submitted to RCM conditions using Grubbs catalyst 45 in reflux dichloromethane (scheme 1.44). Only the cis-product 207 was isolated after 48 h in 80% yield. Ester cleavage and chemoselective double bond reduction with tosyl hydrazine afforded the C-glycosidic neoglycoconjugate 208.

### 1.6 Miscellaneous applications

Nubbemeyer and Zhang reported on the synthesis of optically active allylglycine derivatives by using a proline-derived unit as the chiral auxiliary (scheme 1.45).

**Scheme 1.45**

![](image)

(a) Cy2BH, CH2Cl2, 0 °C to rt; then NH4Cl, MeOH; (b) 6N HCl, reflux, 20 h; (c) MeOH, SiO2, rt; (d) SOCl2, EtOH (Boc-deprotection), rt; (e) ArCH2Br (213), K2CO3, MeCN, 80 °C; (f) BuLi, THF, -78 °C.

Several building blocks were synthesized via the intermediates 209 (proline as auxiliary) and 212 (prolinol as auxiliary), which had been obtained with high diastereoselectivity via a zwitterionic aza-Claisen rearrangement. Among the targets synthesized were 210 (68%), from 209 (R = R' = N2) and compound 211 (73%, 1:15 mixture, R = CH2CH(OEt)2 and R' = Boc). Via the prolinol-derived allylglycine derivative 212, the intermediate 214 was obtained by removal of the Boc-group and benzylation with bromomethylpiperonyl bromide (213). Finally the isoquinoline 215 was synthesized through lithiation of bromide 214 and subsequent cyclization.

Durand et al. targeted the asymmetric synthesis of natural diheteropeptin, a cyclic tetrapeptide demonstrating TGF-β (transforming growth factor) like biological properties. The strategy was based on the construction of the linear peptide 217, starting from the olefinic α-amino acid 216 (scheme 1.46).
Scheme 1.46

(a) Aib-(L)-Phe-(D)-Pro-OMe, PyBOP, DIEA, CH₂Cl₂, rt (78%); (b) (i) LiOH, DME, H₂O, rt. (ii) TFA, CH₂Cl₂, (iii) pyBOP, DIEA, CH₂Cl₂ (54%); (c) AD-mix-β, CH₃SO₂NH₂, H₂O, t-BuOH, 0 °C, 2 h (95%).

After macrolactamization, the double bond was asymmetrically dihydroxylated using the Sharpless method to afford the desired enantiopure diheteropeptin 218 in 51% yield over these two steps.

Kokotos and co-workers used the olefinic α-amino acid 219 for the synthesis of a lipophilic α-keto amide, a novel inhibitor of pancreatic lipase.⁵⁹ Acyl fluoride formation of the acid 219, followed by reduction to the amino alcohol, alkylation with n-decyl bromide and Boc-deprotection afforded the fatty HCl-salt 220 (scheme 1.47).

Scheme 1.47

Coupling of 220 with 2-hydroxyhexadecanoic acid using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (WSC.HCl) and HOBt, followed by pyridinium dichromate oxidation in acetic acid afforded the desired 221 in 57% yield over all the steps. The inhibition of pancreatic lipase was studied using this lipophilic compound.

The polypyrrolinone structural motif was synthesized by Smith et al., making use of the olefin-containing amino acid 224 on the solid support. Wang resin bound amino acid 222 was oxidized with ozone to afford aldehyde 223 (scheme 1.48).⁹⁰ Dehydrative imine formation of 223 with amino acid 224, followed by treatment with KHMDS led to the metallo-enamine cyclization product 225. Removal of the Teoc group and subsequent imine formation with hydrocinnamaldehyde, followed by metallo-enamine formation with KHMDS led to cyclization and concomitant release of 226 from the resin in 36% overall yield.
This principle, and the use of key-building block 223, led to a strategy for the synthesis of polypyrrolinones 227 on the solid support.

Scheme 1.48

Another application of allylglycine attached to the solid support was given by Kurth and Park. They reported a protocol for the synthesis of the Merrifield resin bound allylglycine derivatives 228 and 230 (scheme 1.49). Cyclization-cleavage led to the release of the hydantoin 229a and 229b in 95 and 92% yield. The differences between the Merrifield and the Wang resins were studied.

Scheme 1.49

1.7 Biosynthetic applications

Numerous recently published applications of olefinic α-amino acids have been given, in which they are used in the synthesis of organic compounds. In addition, they can be directly used in the formation of organometallic complexes, and they can also play a
specific role in the biochemistry of proteins. For example, the research group of Tirrell further widened the possibilities for incorporation of non-proteinogenic amino acids into proteins, with a focus on the use of allylglycine and its homologues. This paragraph gives a few recent examples of such biochemical applications of olefinic α-amino acids.

Hecht and co-workers reported on the site-specific cleavage of proteins, using the chemoselective iodination at the allylglycine position (scheme 1.50).

**Scheme 1.50**

\[
\text{Scheme 1.50} \\
\text{(a) } I_2; \text{ (b) } H_2O.
\]

In this way, allylglycine-containing rat trypsinogen could be activated with iodine. Iodolactonization of the allylglycine-containing protein 231 led to intermediate 232 that could be hydrolyzed to release the protein 234. The same strategy was also applied to allylglycine-containing ecotin analogues. The same group applied this principle, by using a bulky, N-protected allylglycine amino acid as a protective moiety for valyl-tRNA 236 (scheme 1.51). Site-specific cleavage of 235 with iodine, followed by hydrolysis, resulted in the release of the valine-containing tRNA 236.

**Scheme 1.51**

\[
\text{Scheme 1.51} \\
\text{(a) } I_2; \text{ (b) } H_2O.
\]

Verdin and co-workers made special use of ring-closing metathesis to generate an all-hydrocarbon type of cross linking in α-helical peptides, which enhances the metabolic stability. α-Methyl-α-allylglycine amino acids (and homologues) were incorporated in α-helices across either one or two turns. Metathesis in 1,2-dichloroethane with Grubbs' catalyst
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caused the cross-linking within the helix. In general, an increase in ring-size led to a better conversion in the metathesis reaction. Besides, there were large effects in the efficiency of cross-linking upon small variations of these bigger ring-sizes. An example was given, in which the cross-linking leading to a 30-membered macrocycle failed, while the corresponding 31-membered cycle was formed in 50%. Furthermore, the effects of the incorporation of \(\alpha\)-methyl-\(\alpha\)-allylglycine amino acids into \(\alpha\)-helices and the effect of the cross-linking on the helicity was studied.

1.8 Outline of this Thesis

This overview shows that the field of olefinic \(\alpha\)-amino acids is rapidly growing nowadays. New syntheses of these amino acids emerge, because they are versatile building blocks for a wide range of synthetic organic targets. The purpose of this thesis is to develop novel synthetic methodology, with a strong emphasis on the use of catalytic methods, that can be applied for the functionalization of olefinic \(\alpha\)-amino acids. Two important processes constituted the basis of these investigations: (i) a novel biocatalytic process resulting in enantiopure olefinic \(\alpha\)-amino acids, previously developed in our group in collaboration with DSM and (ii) the development of a novel aliphatic \(N,O\)-acetalization reaction. This latter process is presented in chapter two. In chapter three, both processes are applied in the synthesis of conformationally restricted 2,6-disubstituted pipelic acid derivatives. Chapter four discloses the use of \(N\)-phosphoryliminium ion chemistry, applied onto olefinic \(\alpha\)-amino acids. Chapter five exploits the novel aliphatic \(N,O\)-acetalization in the direction of other, aryl-containing amino acids and closely related compounds. In chapter six, both processes are used for a very efficient, asymmetric synthesis of novel alkaloid building blocks. The final chapter seven deals with a spin-off research project concerning ring-closing metathesis reactions of olefin-containing enamides.

1.9 References

Chapter 1


56 Walter, A.; Westermann, B. Synlett 2000, 1682.