REVIEW

Applications of aliphatic unsaturated non-proteinogenic α-H-α-amino acids

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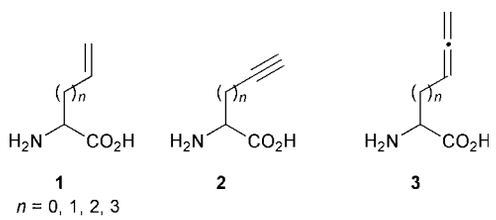
Covering the literature from 1990 to May 2000.

1 Introduction

Naturally occurring amino acids have been extensively applied in the area of synthetic organic chemistry.[1] They may serve as cheap, commercially available enantiomerically pure starting materials for synthetic purposes,[2] as key building blocks for the synthesis of ligands for homogeneous catalysis[3] and, as a result of their diversity, be incorporated in libraries of compounds that are built from amino acids.[4] However, opportunities for the use of proteinogenic amino acids for synthetic purposes are still rather limited because of the narrow range of functional groups present in the side chains.

In recent years, the use of racemic and enantiomerically pure non-proteinogenic amino acids in different areas of chemistry, biology and material science has surfaced as an additional means for structural modification using the non-proteinogenic functionality in the amino acid side chain. In this review, we will provide an overview of efforts in this direction that were carried out during the past decade. Due to the abundance of examples, we have limited ourselves to the application of the unsubstituted, unsaturated aliphatic α-H-α-amino acids **1**, **2** and **3** ($n = 0$–3) as depicted in Scheme 1.[5] The syntheses of these amino acids are only covered in a general manner. Furthermore, all the examples in this review are restricted to transformations of the amino acids themselves or in protected form, rather than on amino acid derived compounds, such as, for example, the corresponding amino alcohols.



Scheme 1

Before going into the applications of such amino acids, we will briefly examine the occurrence of several of the amino acids **1**–**3** ($n = 0$–3) in nature.[6] Most of the olefinic amino acids **1** have been isolated at least in one of the enantiomeric forms from natural sources, especially from mushrooms. Vinylglycine (**1**, $n = 0$) was isolated in the (*R*)-form from *Rhodophyllus nidorosus*[7] and is an irreversible inhibitor of a variety of enzymes and inhibits photorespiration. (*S*)-Allylglycine (**1**, $n = 1$) was isolated from *Amanita* mushrooms, while its homologue (*S*)-homoallylglycine (**1**, $n = 2$) was found in the mushroom *Amanita gymnopus*. (*S*)-Ethynylglycine (**2**, $n = 0$) was isolated from *Streptomyces catenulae*[8] and was reported to possess antiobiotic activity against Gram-positive bacteria. The homologous (*S*)-propargylglycine (**2**, $n = 1$, propargyl = prop-2-ynyl) was isolated from a *Streptomyces* strain[9] and also found in the mushroom *Amanita pseudoporphyria*. It is a potent inactivator of the pyridoxal-P dependent γ-cystathionase.[10] Homopropargylglycine (**2**, $n = 2$) was encountered in the mushroom *Cortinarius claricolor*,[11] while the isomeric allenic amino acid homoallenylglycine (**3**, $n = 1$) was isolated from the mushroom *Amanita solitaria*[12] and, more recently, from other sources as well.[13]

To meet the demand for α-amino acids with specific non-proteinogenic functional groups, over the years a large number of methods have been developed to synthesise such amino acids in enantiomerically pure form.[14] In addition, many of these amino acids are by now commercially available.[15] Without being complete, a summary of well-established and relatively new methods for amino acid synthesis in enantiopure form is depicted in Scheme 2. They can be roughly divided into three different strategies: (i) stoichiometric approaches employing a chiral auxiliary, (ii) biocatalytic procedures involving enzymatic transformations (iii) asymmetric catalytic processes using asymmetric (transition metal) catalysts. Examples of the first class are diastereoselective alkylations of enantiopure glycine derivatives with carbon electrophiles (*e.g.* the Schöllkopf template **4**[16] and the Myers pseudo-ephedrine moiety **5**),[17] diastereoselective alkylations of enantiopure ester enolates with nitrogen electrophiles (*e.g.* the Evans oxazolidinone system **6**[18] and the Oppolzer auxiliary **7**[19]) and diastereoselective Strecker reactions of imines bearing a chiral auxiliary (*viz.* **8**).[20] Among the enzymatic methods,[21] enzyme classes that have been frequently applied to resolve a broad range of amino acid derivatives include esterases or proteases,[22] acylases,[23] hydantoinases,[24] and aminopeptidases[25] starting from the amino esters **9**, the *N*-acylated amino acids **10**, the hydantoins **11** and the amino acid amides **12**, respectively. Furthermore, several catalytic asymmetric approaches emerged of which the most powerful methods seem the metal-catalysed asymmetric hydrogenation of dehydro amino acids **13**[26] and the asymmetric alkylation of glycine equivalents such as **14** using base, an alkylating agent and an enantiomerically pure phase transfer

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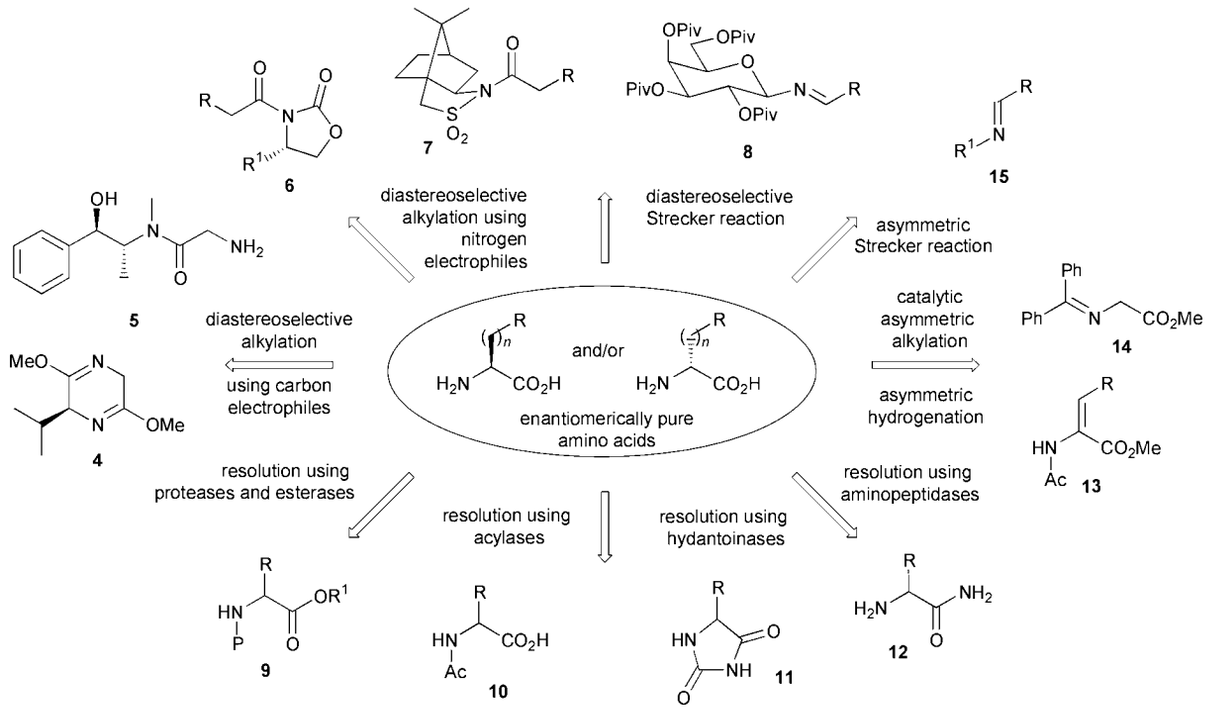
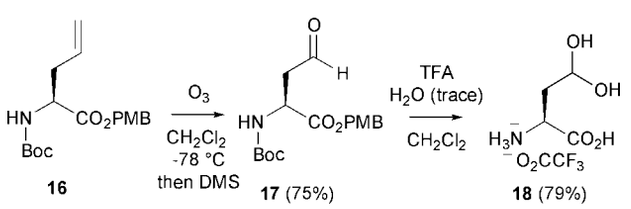


Scheme 2

catalyst.[27] In addition, asymmetric catalytic Strecker reactions have been developed, which also give access to enantiomerically pure amino acids from the imines **15** in an efficient manner.[28]

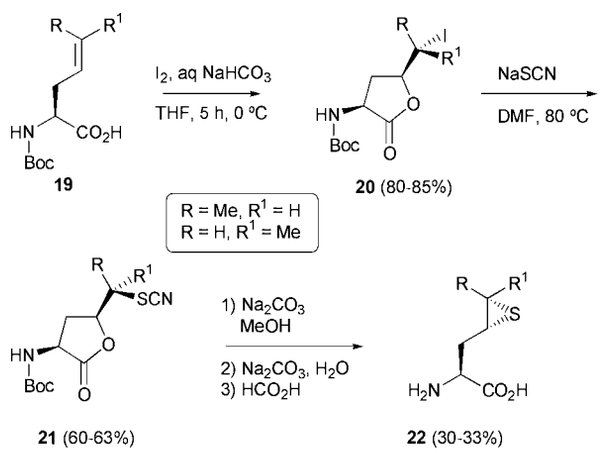
2 Side chain modifications

One of the most straightforward transformations on unsaturated amino acids is direct oxidative cleavage *via* for example ozonolysis. While the ozonolysis of non-protected allylglycine led to the corresponding aldehyde of variable purity, Tudor *et al.*[29] demonstrated that conversion of the doubly protected allylglycine derivative **16** into the corresponding aldehyde **17** using ozone, followed by quenching with TFA led to the free amino acid hydrate **18** as a stable salt of reproducible quality (Scheme 3). The trifluoroacetate salt **18** was used as a substrate for the enzymes homoserine dehydrogenase and dihydrodipicolinic acid (DHDPA) synthase.



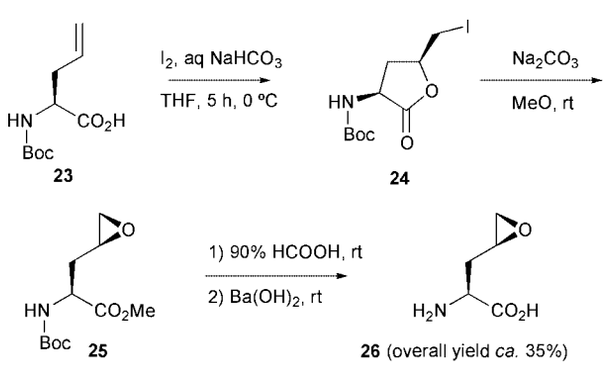
Scheme 3

In the group of Guillerm,[30] the allylglycine derivatives **19** were utilised as precursors for the synthesis of conformationally restricted methionine analogues containing an episulfide moiety. These analogues were considered to be useful inhibitors of the enzyme S-adenosyl transferase. Suitably protected (*E*)- and (*Z*)-but-2-enylglycines **19** were subjected to iodolactonisation conditions to give the lactones **20**,[23a] which in turn were reacted with sodium thiocyanate to give **21** (Scheme 4). Opening of the lactone under the influence of sodium carbonate in MeOH provided the corresponding episulfides, which were subsequently converted into the free amino acids **22** in reasonable overall yields. A similar protocol was followed by the same group to arrive at the corresponding epoxides.[31] In this case, the lactones **24** were directly cyclised using Na_2CO_3 in MeOH to



Scheme 4

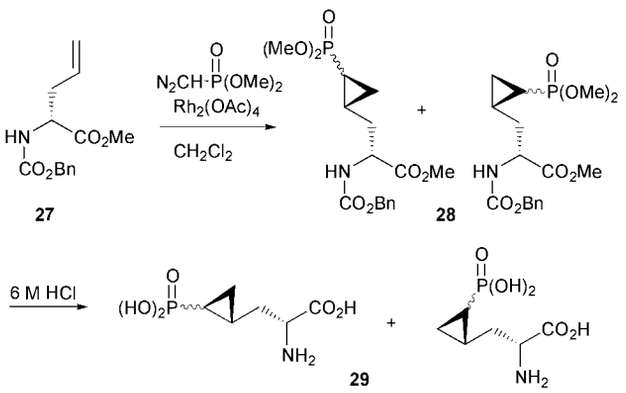
provide the epoxides **25** in diastereomerically pure form, which were readily deprotected to provide the free epoxy amino acids **26** (Scheme 5).



Scheme 5

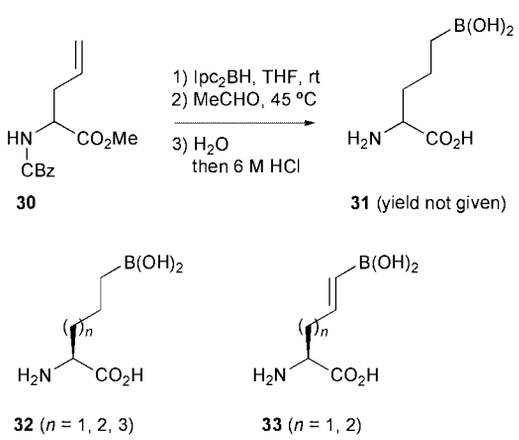
A series of 2-amino-5-phosphonopentanoic acid derivatives were synthesised to assess their biological activity as competitive antagonists for the *N*-methyl-D-aspartate (NMDA) receptor.[32] Some of these compounds were prepared starting from non-proteinogenic amino acids as exemplified in

Scheme 6. Thus, protected allylglycine **27** was treated with diazomethylphosphonate and rhodium acetate dimer to give the corresponding product **28** as a mixture of all four possible diastereoisomers. Subjection of this mixture to 6 M HCl at 100 °C provided the corresponding free amino acids **29**, which were tested as such and showed moderate affinity for the NMDA receptor.



Scheme 6

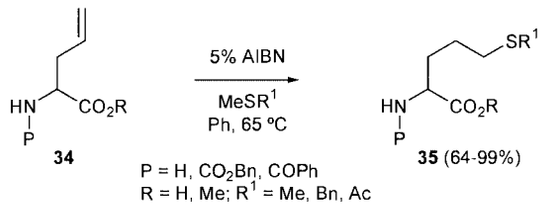
The group of Danion exploited the unsaturated functionality of allylglycine to arrive at boronic acid containing amino acids (Scheme 7).[33] Initially, racemic protected allylglycine **30** was hydroborated using diisopinocampheylborane, followed by oxidative cleavage of the pinene-moieties using acetaldehyde and acidic hydrolysis leading to the free amino acids **31**. Application of this methodology to enantiopure allylglycine derivatives provided the boronic acids **32**, while application to propargyl- and homopropargylglycine eventually led to the geometrically pure (*E*)-vinylboronic acids **33**.[34] The enantiomerically pure amino acids **32** and **33**, which are potential mimics of (*S*)-arginine, were evaluated as active site probes of the enzymes arginine synthase and nitric oxide synthase.[35]



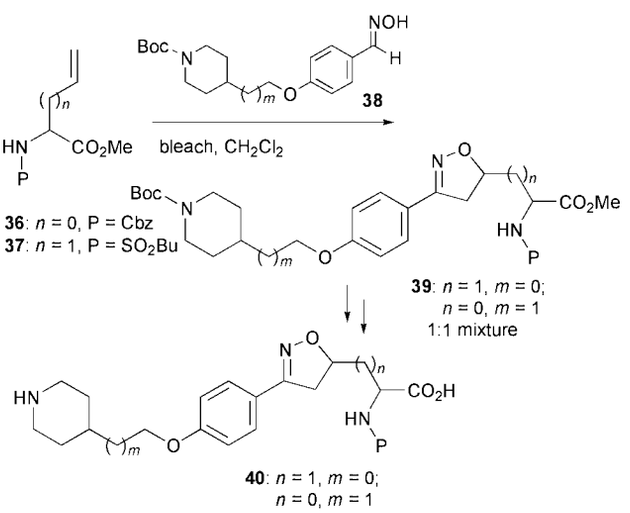
Scheme 7

Broxterman *et al*. developed efficient methodology to convert allylglycine derivatives into the corresponding thioethers (Scheme 8).[36] Both free and protected allylglycine derivatives (**34**) were treated with different thioethers and esters in the presence of a catalytic amount of AIBN to generate the corresponding homomethionine derivatives **35** in good to excellent yields. Application to enantiopure starting material showed that, in some cases, racemisation occurred to a small extent. However, this problem was overcome by purification of the final product *via* crystallisation.

An interesting example of utilising the unsaturation of olefinic amino acids is shown in Scheme 9.[37] A 1,3-dipolar cycloaddition reaction of the vinyl- and allylglycine derivatives **36** and **37**, respectively, with the oximes **38** ($m = 0$, 1) provided



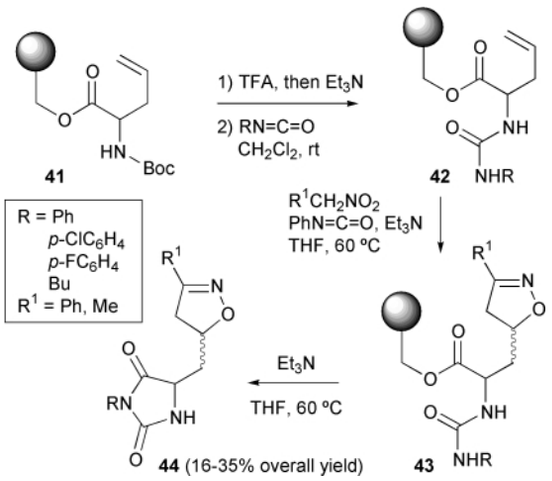
Scheme 8



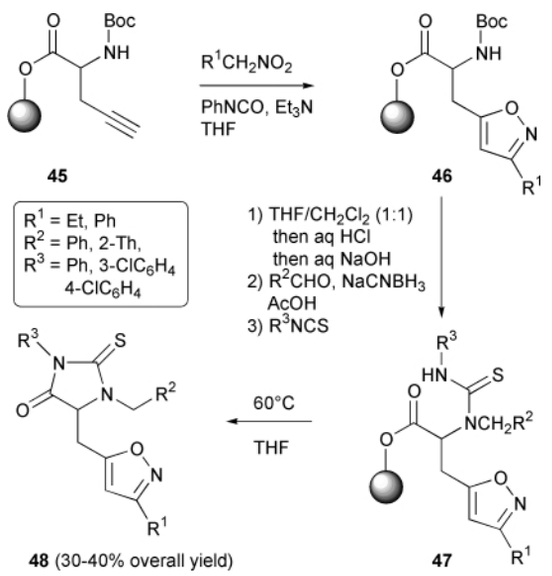
Scheme 9

the corresponding adducts **39** as mixtures of diastereoisomers. After deprotection, the amino acid derivatives **40** were evaluated as antagonists of the glycoprotein IIb/IIIa receptor. In reactions reminiscent of the 1,3-dipolar additions shown in the previous scheme, Kurth and co-workers set out to prepare compounds that contain a hydantoin and an isoxazoline moiety starting from unsaturated amino acids. Beside a solution phase approach, they demonstrated the validity of this methodology in a solid phase pathway, which is shown in Scheme 10.[38] The sequence commenced with the immobilized allylglycine moiety **41** (connected to a standard Merrifield resin), which was deprotected with TFA and reacted with different isocyanates to give the corresponding urea derivatives **42**. Subsequent 1,3-dipolar cycloaddition with Mukaiyama-generated nitrile oxides gave the isoxazolines **43**, which were cleaved from the resin *via* cyclative release. The target compounds **44** were obtained in 16–35% overall yield as 1 : 1 mixtures of diastereoisomers. In a similar manner, the same group produced compounds that contain both a thiohydantoin and an isoxazole moiety (Scheme 11).[39] 1,3-Dipolar cycloaddition of resin bound propargylglycine **45** with Mukaiyama-generated nitrile oxides provided the cycloadducts **46**, which in a series of steps were further converted into the thioureas **47**. Simple heating in THF then led to cyclization induced cleavage to liberate the desired products **48** in 30–40% overall yields.

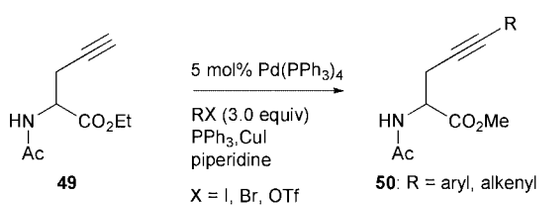
Crisp and Robinson pioneered Pd-catalysed functionalisation reactions of unsaturated amino acids, and in particular, propargylglycine derivatives. They demonstrated in a preliminary report that suitably protected propargylglycine derivatives **49** could be efficiently transformed into the substituted counterparts **50** using Sonogashira-type coupling conditions [cat. $Pd(PPh_3)_4$, excess RX, PPh_3 (0.1 equiv.) CuI (0.1 equiv.) in piperidine or DMF] in good to excellent yields (Scheme 12).[40] A range of aromatic groups was coupled in this way, with X being Br, I or OTf. While all reactions were carried out on racemic propargylglycine, a single reaction on (*S*)-propargylglycine proceeding without detectable racemisation, showed the viability of this type of transformation on amino acids. The usefulness of this reaction was further underlined by recent work by Lee



Scheme 10

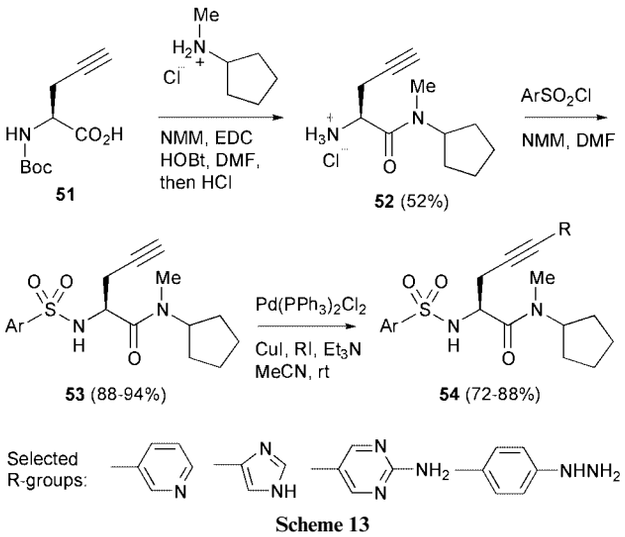


Scheme 11

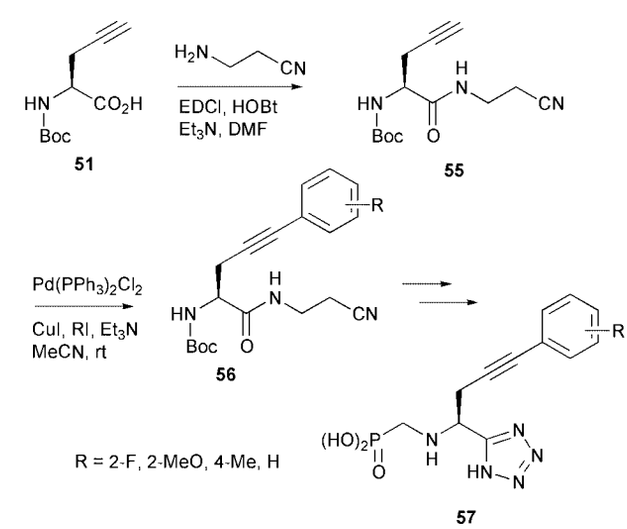


Scheme 12

et al., who employed this reaction to synthesise a small library of thrombin inhibitors.[41] Thus, Boc-protected propargylglycine **51** was reacted with an appropriate amine to arrive at amide **52** in 52% yield (Scheme 13). Deprotection of the amine, followed by sulfonylation provided the desired Sonogashira precursors **53**. Subjection to standard Sonogashira conditions with a variety of iodobenzenes, iodopyridines and iodopyrimidines led to the targeted thrombin inhibitors **54** in yields around 80%. In a similar strategy, researchers at Novartis prepared different types of endothelin-converting enzyme inhibitors starting from the propargylglycine containing fragment **55** (Scheme 14).[42] The Sonogashira functionalisation proceeded in generally satisfactory yields, followed by a multi-step conversion into the tetrazolyl aminophosphonates **57**, the activity of which was evaluated. In addition to the Sonogashira functionalisations of protected amino acids in organic media, Dibowski and Schmidtchen demonstrated the feasibility of modifying free propargylglycine **2** ($n = 1$) in an aqueous environment

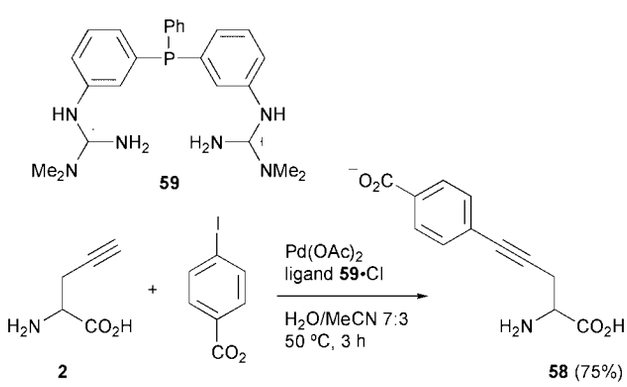


Scheme 13



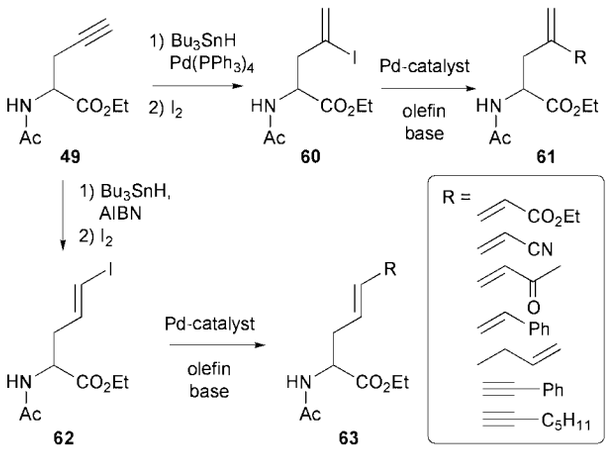
Scheme 14

(Scheme 15).[43] Iodobenzoic acid was reacted with the amino acid in the presence of $Pd(OAc)_2$ and the water soluble phosphine ligand **59** in a water–acetonitrile mixture at 50 °C to produce the corresponding adduct **58** in a yield of 75% without formation of homo-coupled propargylglycine.



Scheme 15

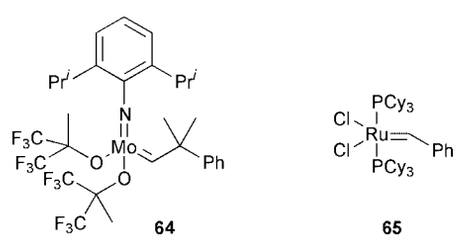
An alternative way of modifying propargylglycine *via* Pd-catalysis was developed by Crisp and co-workers. In this case, protected propargylglycine **49** was reacted with Bu_3SnH to give the corresponding hydrostannylated product (Scheme 16).[44] Depending on the conditions (Pd(0)-catalysed addition *vs.* AIBN-mediated radical addition) either the internal or terminal vinylstannane was formed with reasonable to good



Scheme 16

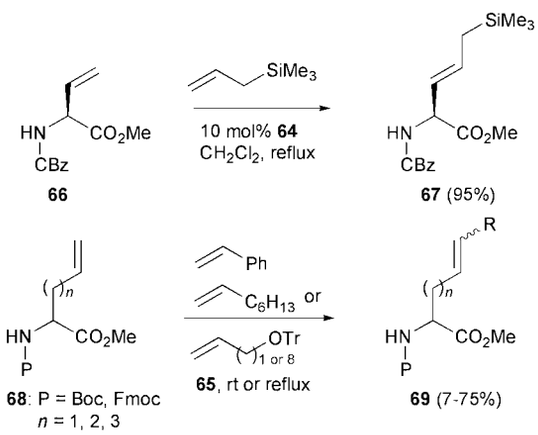
selectivity. Subsequent reaction of either of these products with iodine provided the vinyl iodides **60** and **62**, respectively. These iodinated allylglycine derivatives appeared good substrates for further functionalisation *via* a Heck reaction with a variety of olefins or a Sonogashira reaction using different acetylenes.[45] Thus, the corresponding allylglycines **61** and **63** were obtained in varying yields. It is also noteworthy that these reactions were all carried out with racemic substrates leaving unanswered the question of whether these conditions will affect the amino acid enantiopurity.

The pioneering work of Schrock and Grubbs in the area of olefin metathesis[46] has strongly contributed to widespread applications for unsaturated amino acid derivatives. The compatibility of the metathesis catalysts **64** and **65** (Scheme 17) with the functionalities present in amino acids and peptides has led to an enormous number of possibilities for exploiting the olefinic side chain to modify amino acids and peptides.



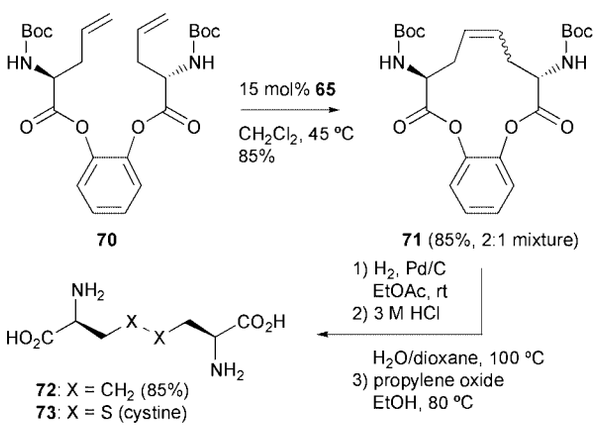
Scheme 17

Early applications for amino acid modification were reported by the group of Blechert.[47] Vinylglycine derivative **66** was reacted with allyltrimethylsilane in the presence of the Schrock Mo-catalyst **64** to give the corresponding cross-metathesis product **67** as a single geometrical isomer in excellent yield (Scheme 18). A drawback, however, was the fact that the reaction proceeded with a slight decrease of optical activity (from 97 to 92% ee). This principle was further elaborated by the same group[48] and by the group of Gibson,[49,50] but now using the Ru-catalyst **65**. A large variety of cross-metathesis products **69** was prepared by both groups, this time without detectable racemisation of the amino acid moiety. Surprisingly, incorporation of a phenyl-substituent using styrene proceeded remarkably well to give conformationally restricted homologues of phenylalanine (**69**, R = Ph). In a number of these cross-metathesis reactions, side products were formed in varying amounts as a result of self-metathesis between two amino acid residues. Selective self-metathesis of allylglycine derivatives, however, to deliberately obtain the self-metathesis product in high yield appeared unsuccessful.[51] Therefore, in order to selectively obtain the allylglycine self-metathesis product, an alternative strategy was devised by several groups. The first example was published by the group of Grubbs,[51] who showed



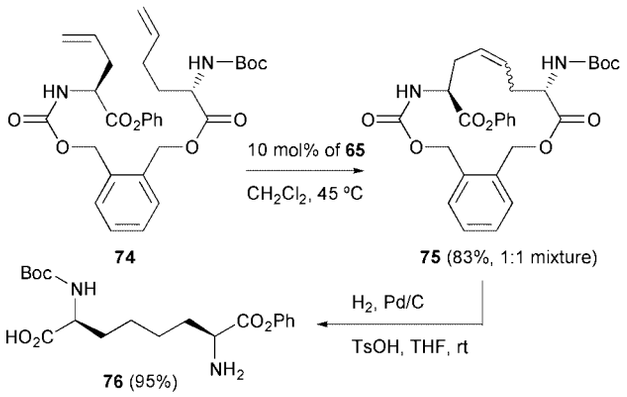
Scheme 18

that ring-closing metathesis (RCM) of the tethered bis(allylglycine) system **70** gave the cyclic olefin **71** in 85% yield, albeit as a 2:1 mixture of geometrical isomers (Scheme 19). Hydrogenation of the double bond and concomitant hydrogenolysis of the phenolic esters, followed by deprotection provided (2*S*,7*S*)-2,7-diaminosuberic acid (**72**)—which is an isostere of (*S*)-cystine (**73**)—in excellent overall yield. A similar strategy was independently developed in the groups of Williams[52] and Vederas[53] to prepare analogous compounds. A subtle variation on this theme was also published by the Williams group (Scheme 20).[52] In this case, rather than the C_2-symmetrical dimer, the differently connected diolefin **74** was used as the metathesis precursor, which upon hydrogenolysis gave the enantiomerically pure and orthogonally protected 2,7-diaminosuberic acid **76** in excellent overall yield. Again, the intermediate cyclic olefin **75** was produced in good yield as a 1:1 mixture of the two double bond isomers. The advantage of the latter pathway is that the final product is suitably protected for selective incorporation in peptides or other molecules.

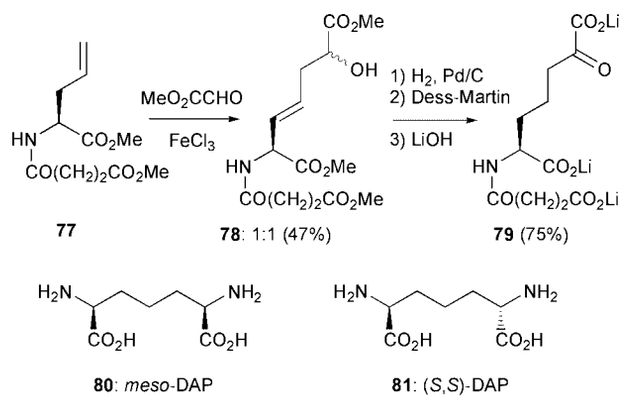


Scheme 19

An ene reaction on the allylglycine side-chain of **77** was utilised to synthesise *N*-succinyl-α-amino-ε-ketopimelic acid (**79**), which is the natural substrate for the enzyme *N*-succinyl-(*S,S*)-diaminopimelic acid (DAP) aminotransferase (Scheme 21). This is an essential enzyme in the bacterial biosynthesis of *meso*-diaminopimelic acid (*meso*-DAP) (**80**) and (*S*)-lysine, which are the key cross-linking amino acids in the peptidoglycan layer in the cell wall of Gram-negative and Gram-positive organisms, respectively.[54] Thus, an ene reaction of **77** with methyl glyoxylate in the presence of $FeCl_3$ provided **78** as a 1:1 mixture of diastereoisomers in 47% yield. Hydrogenation, followed by oxidation and hydrolysis provided target compound **79**, which appeared only stable as the tri-Li-salt. In addition, use of a CBz instead of a succinate group on the

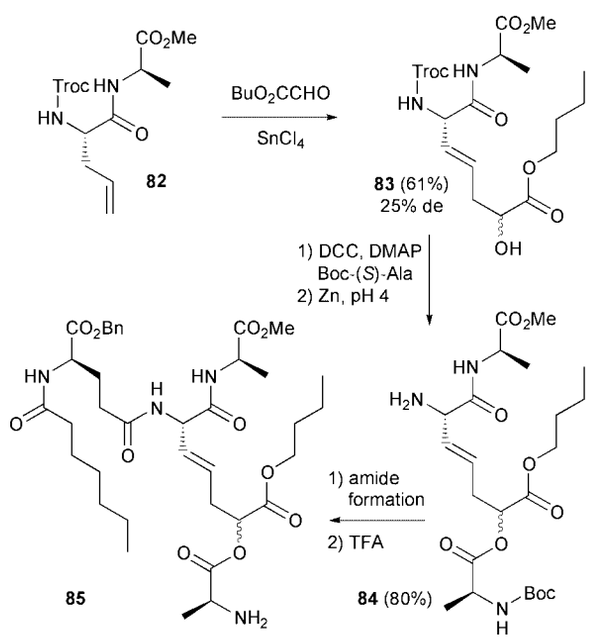


Scheme 20



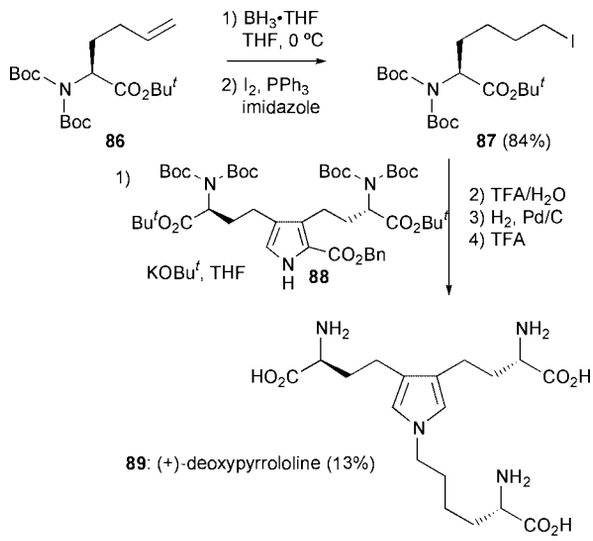
Scheme 21

nitrogen atom and subsequent reaction with NH_4OAc, followed by $NaBH_3CN$ reduction, gave both *meso*-DAP (**80**) and (*S*,*S*)-DAP (**81**). The group of Berner used the same transformation to synthesise the diastereomeric lipopeptides **85**,[55] which can be regarded as conformationally restricted analogues of the known immunostimulating lipopeptides FK-156 and the synthetic analogue FK-565 (Scheme 22). The synthesis proceeded through a Lewis acid-catalysed ene reaction on the allyl side chain of the dipeptide **82**. Unfortunately, the de of product **83** was rather low, but eventually after suitable further functionalisation and separation by column chromatography the desired lipopeptide mimics **85** were obtained.



Scheme 22

At Abbott Laboratories, (+)-deoxypyrrololine (**89**)—a potential biochemical marker for diagnosis of osteoporosis—was synthesised by functionalisation and coupling of protected homoallylglycine **86** (Scheme 23).[56] Hydroboration of **86**, followed by conversion of the hydroxy group into the iodide provided **87**, which was coupled with the protected core **88** in a satisfactory yield. Boc-removal, hydrogenolysis and finally TFA-mediated decarboxylation of the pyrrole moiety gave rise to the desired product **89** in a reasonable yield over four steps.

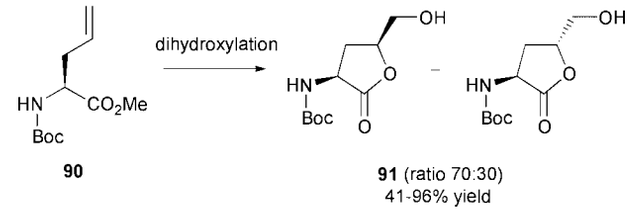


Scheme 23

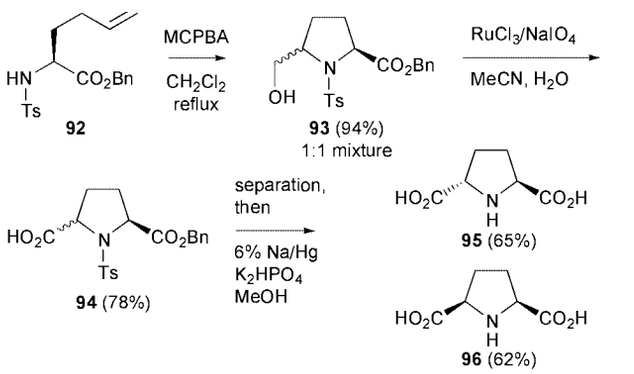
3 Direct cyclisation of the amino acids *via* the side chain

The group of Genêt pursued a dihydroxylation strategy to transform allylglycine derivative **90** into the corresponding α-aminolactones (Scheme 24).[57] Dihydroxylation *via* different methods (OsO_4/tetramethylamine *N*-oxide, AD-mix α, or AD-mix β) all resulted in formation of a mixture of the lactones **91** in a 7:3 ratio, albeit in different yields. The enantiomerically pure (*S*)-homoallylglycine derivative **92** was cyclised by the Baldwin group *via* MCPBA-mediated epoxidation of the double bond, which, not surprisingly, led to a 1:1 *cis*/*trans*-mixture of prolines **93** in 94% yield (Scheme 25).[58] Oxidation to the carboxylic acids **94**, followed by chromatographic separation and double deprotection using sodium amalgam then gave the desired pyrrolidine dicarboxylic acids *trans*-**95** and *meso*-**96** in satisfactory overall yields, which were tested as substrates for the enzyme proline hydroxylase. The enantiopure (*R*)-homoallylglycine derivative **97** was used as the starting point to construct 5-hydroxypipecolic acids in the unnatural (*R*)-configuration (Scheme 26).[59] Epoxidation of the olefin afforded two diastereomeric epoxides in a *ca.* 1:1 ratio. Since direct cyclization (K_2CO_3 in MeOH, 80 °C) gave the corresponding proline derivatives (see also Scheme 25), an alternative route was sought. Ring-opening with LiBr, followed by protection of the secondary alcohols with TBSCl gave the cyclisation precursors **98** and **99**, which were ring-closed using NaH in DMF at elevated temperatures. After desilylation with TBAF, both diastereoisomers could be separated by column chromatography and were independently converted into the free pipecolic acid derivatives **100** and **101**, respectively, in reasonable overall yields.

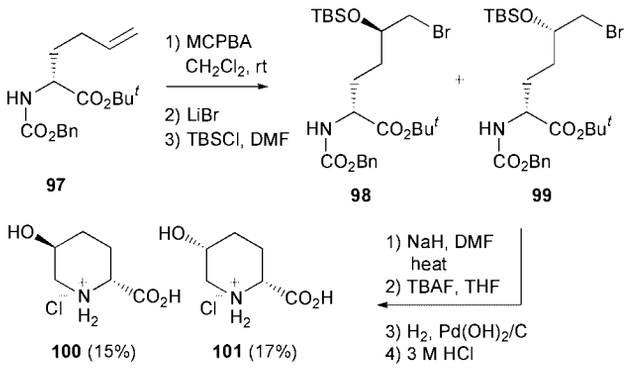
Bowman *et al.* used an alternative approach to transform homoallylglycine into the proline derivative **103** (Scheme 27).[60] The *N*-thiophenyl-substituted starting material **102** was converted with the aid of AIBN into the corresponding *N*-centered radical, which in a 5-*exo* type cyclisation and concomitant reduction of the exocyclic methylene radical gave **103** in 92% yield as a 1:1 mixture of diastereoisomers. In addition, a trace of the reduced *N*-centered radical was observed (*viz.* **104**).



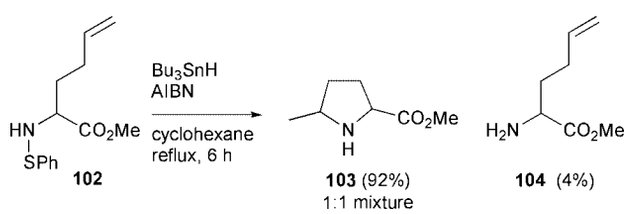
Scheme 24



Scheme 25



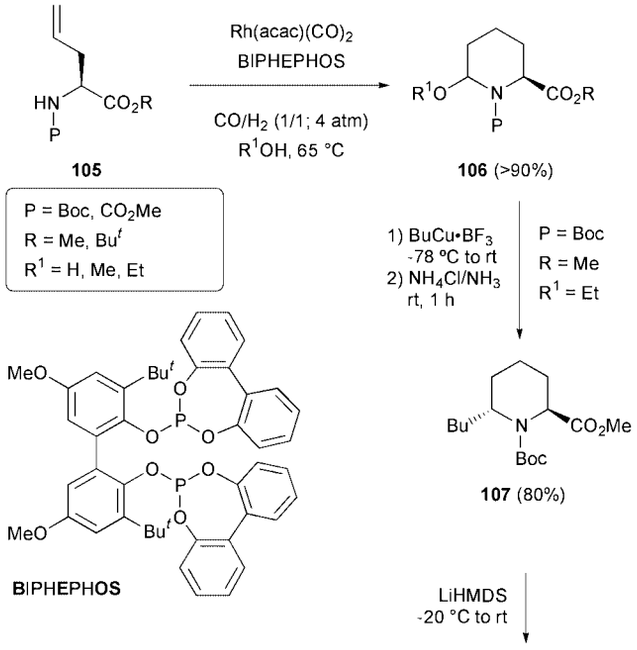
Scheme 26



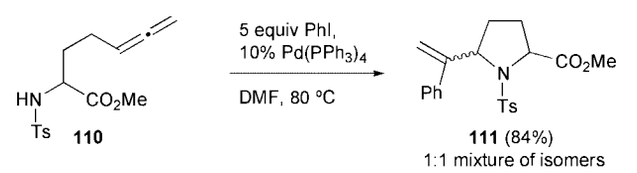
Scheme 27

In the group of Ojima, the allylglycine derivatives **105** were subjected to Rh-catalysed hydroformylation conditions (Scheme 28).[61] While with simple Rh–PPh_3-complexes both linear and branched hydroformylation products were formed, use of the BIPHEPHOS ligand resulted selectively in the linear product, which under the reaction conditions gave the *N*,*O*-acetals **106** in nearly quantitative yields. The *N*,*O*-acetal was reacted with BuCu·BF_3 to give **107** as a single *trans*-diastereoisomer, which in turn could be epimerised to the *cis*-compound **108**. In addition, subjection of **105** to identical conditions in a non-nucleophilic solvent such as THF resulted in the formation of the enamide **109** in quantitative yield.

Palladium-catalysts have been used to cyclise allene-containing amino acids. The first example of such a reaction was published by Gallagher and co-workers (Scheme 29).[62] Reaction of the racemic allenic amino acid **110** under the influence of catalytic $Pd(PPh_3)_4$ and an excess of PhI provided the corresponding styrene-substituted proline derivative **111** in



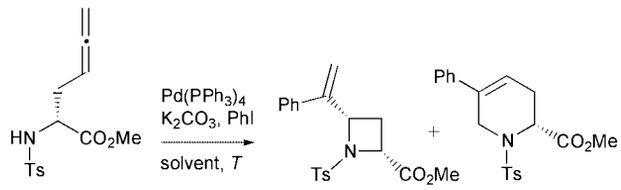
Scheme 28



Scheme 29

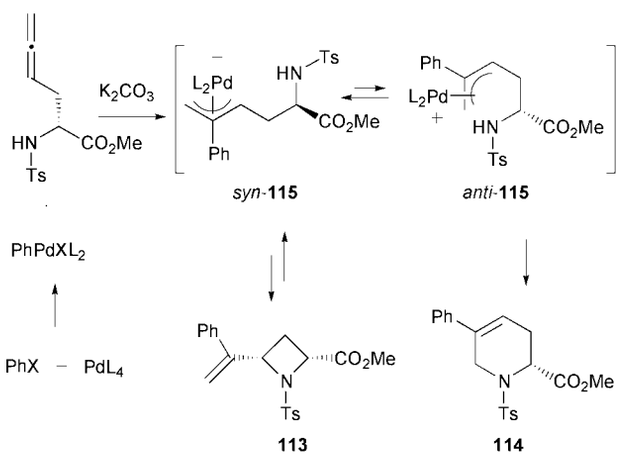
84% yield as a 1 : 1 mixture of diastereoisomers. This reaction presumably proceeded *via* initial reaction of the allene with an arylpalladium(II) species formed *in situ* to the corresponding π-allylpalladium complex, which then cyclised *via* intramolecular attack of nitrogen in a 5-*exo* fashion. Remarkably, subjection of the enantiopure allenic amino acids **112** (having a shorter side chain by one carbon) to almost identical conditions led to interesting results (Scheme 30).[63] In this case, short reaction times led to excess formation of the four-membered ring azetidines **113** (as the single *cis*-diastereoisomer), while longer reaction times favoured formation of the corresponding six-membered ring **114**. It was also shown that this reaction did not lead to any loss of optical activity. A rationale for this phenomenon is depicted in Scheme 31. Most likely, reaction of the allene gives rise to the formation of the π-allylpalladium complexes *syn*- and *anti*-**115**, which are in equilibrium with each other. While initial kinetic cyclisation of *syn*-**115** gives the azetidine, ring-opening followed by isomerisation will eventually lead to the thermodynamically most stable six-membered ring.

Propargylglycine derivatives have also been exposed to analogous Pd-catalysed reaction conditions to produce functionalised heterocycles in enantiomerically pure form (Scheme 32).[64] For example, the free carboxylic acids **116** and **117** could be converted into the corresponding lactones **118**, **119** and **120**, albeit in moderate yields. With the carboxylic acid protected as the methyl ester (*viz*. **121** and **122**), reaction under similar conditions gave rise to the unsaturated proline derivatives **123** and

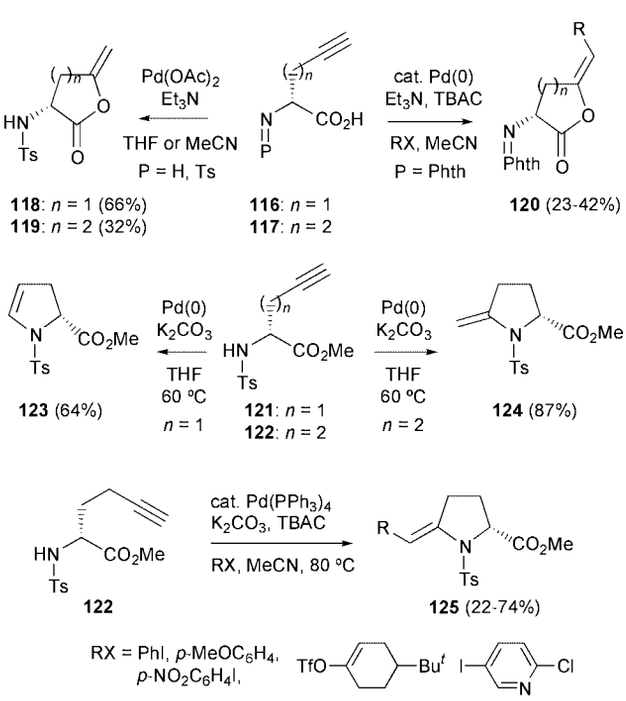


Entry	Solvent	*T*/°C	Time	Ratio (**113**:**114**)	Combined yield (%)
1	DMF	80	10 min	70:30	84
2	DMF	80	4 h	0:100	78
3	THF	60	1.5 h	88:12	45

Scheme 30



Scheme 31

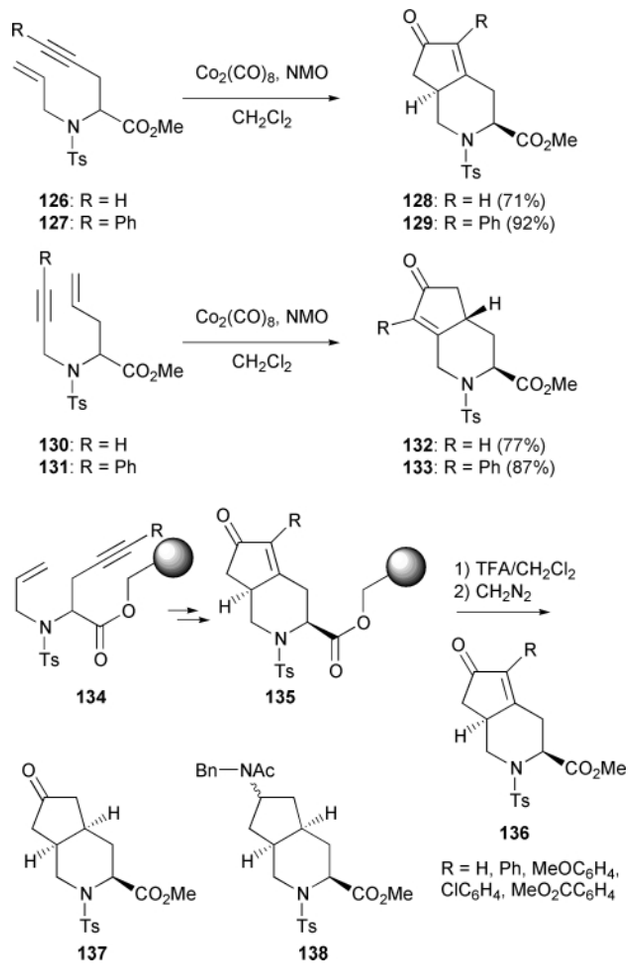


Scheme 32

124 in good yields. Furthermore, subjection of **122** to analogous conditions in the presence of tetrabutylammonium chloride (TBAC) and an aryl halide or vinyl triflate resulted in cyclisation followed by cross-coupling to provide the substituted proline derivatives **125** in reasonable to good yields.

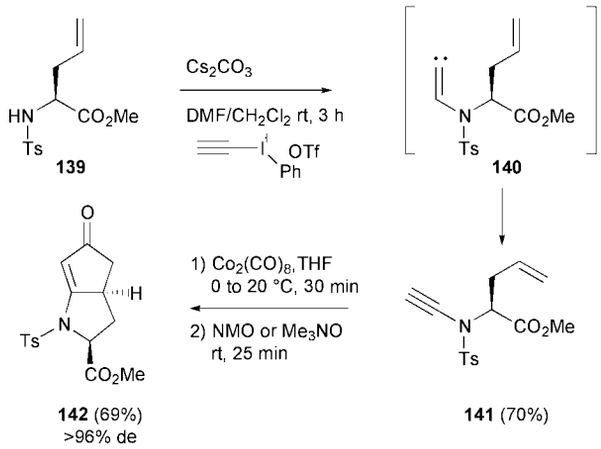
4 Cyclisation reactions involving a functional group on the nitrogen atom

Amino acid-derived enynes appeared suitable substrates for Pauson–Khand type ring closure reactions (Scheme 33). The resulting products were of interest as scaffolds with drug-like character that can be used for further functionalisation.[65] Both the propargylglycine-derived substrates **126** and **127** and the allylglycine-derived compounds **130** and **131** were readily converted into the corresponding bicyclic enones **128**, **129** and **132**, **133** in good yield and with excellent diastereoselectivity. Without much difficulty, both of these sequences were translated to the solid phase (*viz*. **134**), where Sonogashira functionalisation of the acetylene, followed by the Pauson–Khand protocol and subsequent cleavage and re-esterification resulted in the synthesis of a modest library of the bicyclic amino acids **136**. In addition, a variety of follow-up reactions were carried out, leading to, amongst others, the saturated pipecolic acid derivatives **137** and **138**. An interesting alternative entry into Pauson–Khand reactions was developed by Witulski and Gößmann commencing with the unprecedented *N*-(ethynyl)-allylglycines **141** (Scheme 34).[66] Smooth ethynylation of **139** upon treatment with base and the iodonium triflate provided **141** in satisfactory yield, which was cyclised under standard Pauson–Khand conditions to give the enone **142** as a virtually single diastereoisomer. This reaction was carried out with a number of electron-withdrawing groups at the nitrogen atom.

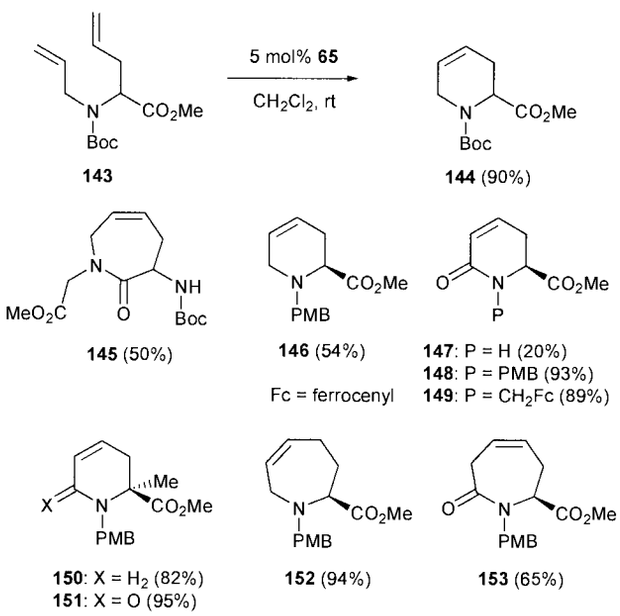


Scheme 33

In pioneering work by Miller and Grubbs, the first example of an amino acid derivative that was cyclised using the Ru-catalyst was the conversion of racemic **143** into **144** (Scheme 35), which proceeded in excellent yield.[67] In the same group, this cyclisation was extended to the amino acid-derived azepine **145**. Rutjes and Schoemaker further applied this pathway to enantiomerically pure examples and various substitution patterns and protecting groups (see products **144**–**153**),[68] thus clearly showing the potential of this type of conversion on amino acids. In



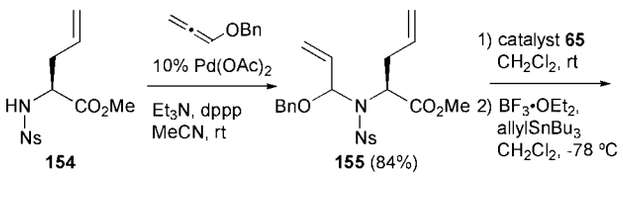
Scheme 34

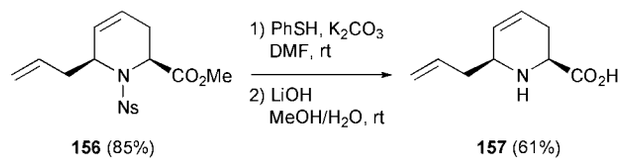


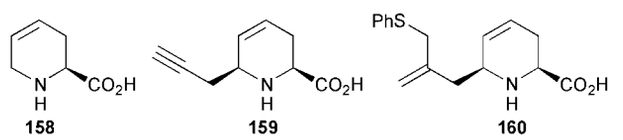
Scheme 35

particular, the cyclisation to the α,β-unsaturated systems **147**–**149** and **152** was remarkable, since electron-poor olefins usually are bad substrates for this catalyst. Furthermore, the basic amine-containing azepine **152** was obtained in good yield from the corresponding diolefin. Recently, the same group reported an extension of this methodology, which commenced with unprecedented *N*,*O*-acetal formation *via* Pd-catalysed reaction of 4-nitrophenylsulfonyl-(Ns)-protected allylglycine **154** with benzyl propa-1,2-dienyl ether (Scheme 36).[69] Cyclisation of **155** under the influence of catalyst **65**, followed by Lewis acid-mediated diastereoselective alkylation at the 6-position then provided the substituted unsaturated pipecolic ester **156**, which was readily deprotected to the free amino acid **157**. A similar sequence led to the pipecolic acid derivatives **159** and **160** and the natural product baikian (**158**).

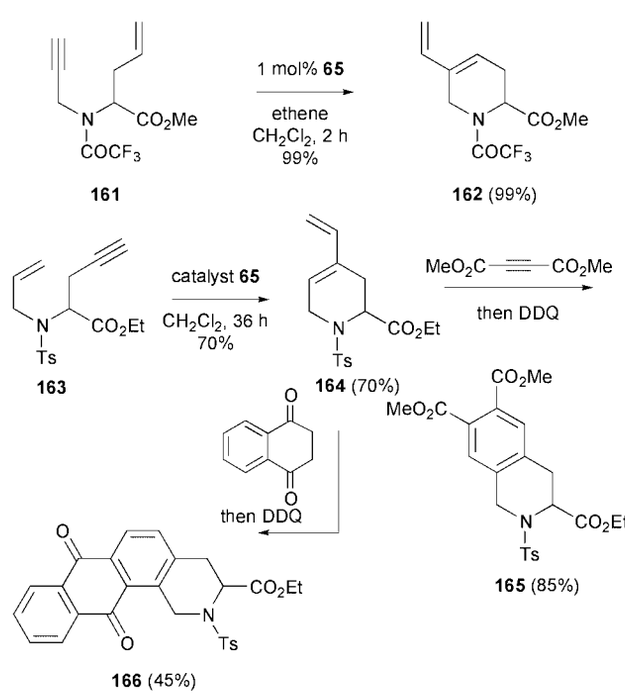
Both allyl- and propargylglycine derivatives have been utilised for ring-closing enyne metathesis approaches towards heterocycles. The first example is shown in Scheme 37, where the enyne **161** was cyclised under an ethylene atmosphere in excellent yield under mild conditions to the diene **162**.[70] This approach was later followed by a different group starting from propargylglycine derivative **163**.[71] In the latter case, the reactions were not carried out under an ethylene atmosphere and proceeded in somewhat lower yields. The resulting dienes **164** were subjected to Diels–Alder reactions with the dienophiles shown, which upon DDQ oxidation eventually led to the systems **165** and **166**.





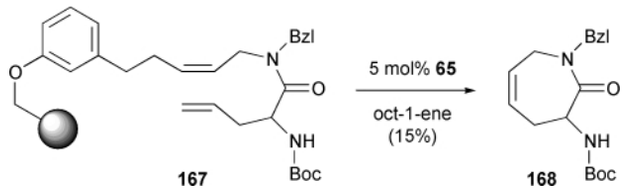


Scheme 36

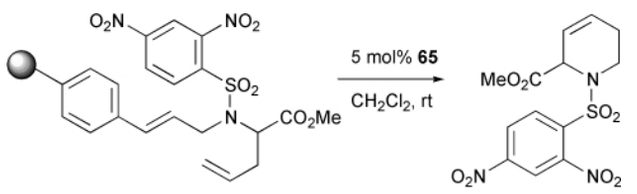


Scheme 37

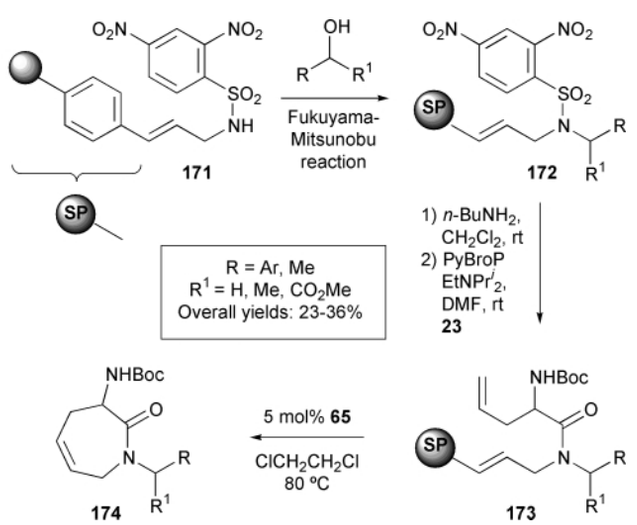
The Ru-mediated metathesis cyclisation to azepine **168** was chosen to prove the viability of a new cyclisation–cleavage concept in solid phase chemistry (Scheme 38).[72] Van Maarseveen *et al*. demonstrated that the olefinic linker could serve as a reactive functional group to liberate the corresponding azepine *via* ring-closing metathesis with the allylglycine moiety in the substrate. Because of the relative inertness of the double bond, one can consider this as a traceless linker. This example was soon followed by other groups that further proved the potential of this type of release. The Amgen group demonstrated the efficient formation of cyclic dehydropipecolic acids **170** *via* this cyclorelease strategy (Scheme 39).[73] This approach was elaborated by the same group and eventually turned into an efficient solid phase protocol for the synthesis of so-called Freidinger lactams **174** (Scheme 40).[74] The immobilised sulfonamide **171** was reacted in a Mitsunobu-type fashion with a variety of secondary alcohols to give the sulfonamides **172**, which then in a two-step procedure were deprotected and reacted with Boc-protected allylglycine **23**. Ru-mediated cyclorelease finally provided the desired target compounds **174** in overall yields varying from 23–36%. An interesting modification on this



Scheme 38

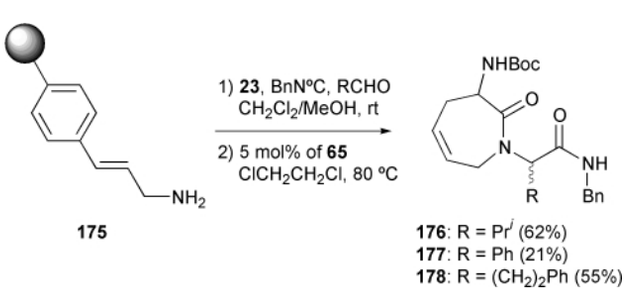


Scheme 39



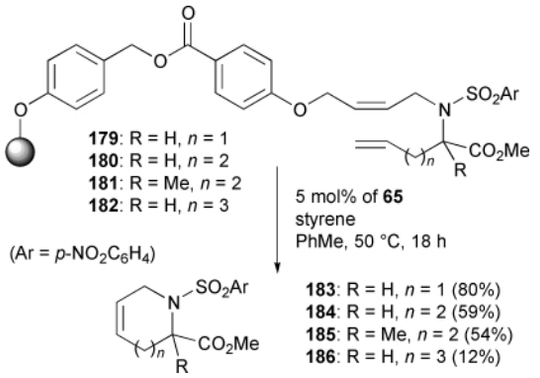
Scheme 40

theme was also published by the Amgen group, showing that the immobilised allylic amine **175** could be readily reacted in a four-component Ugi reaction to give the corresponding dipeptides (Scheme 41).[75] These intermediates were then cyclised and cleaved from the resin in the same manner to provide the cyclic functionalised amino acids **176**–**178** in reasonable overall yields. Similar type of cyclisations were also carried out by Veerman *et al*. with the immobilised homologous unsaturated amino acids **179**–**182** to give rise to the corresponding 6-, 7- and 8-membered ring systems **183**–**186** (Scheme 42).[76] In this work, the beneficial effect of the addition of an equimolar amount of styrene as an additive was shown.

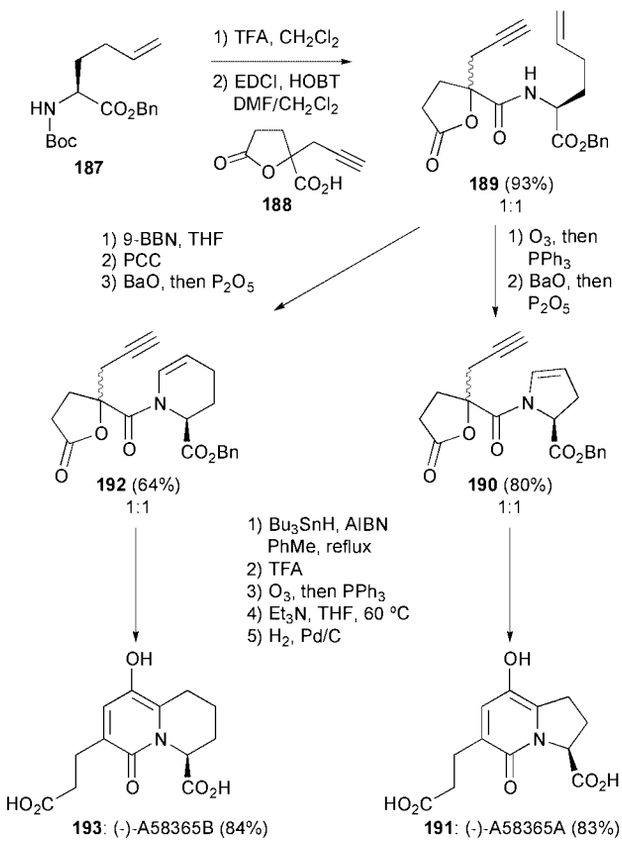


Scheme 41

The enantiomerically pure homoallylglycine derivative **187** served as a starting material to synthesise the natural products **191** and **193**, which have been shown to display powerful inhibitory activity against angiotensin-converting enzyme (ACE, Scheme 43).[77] After deprotection of the nitrogen, **187**



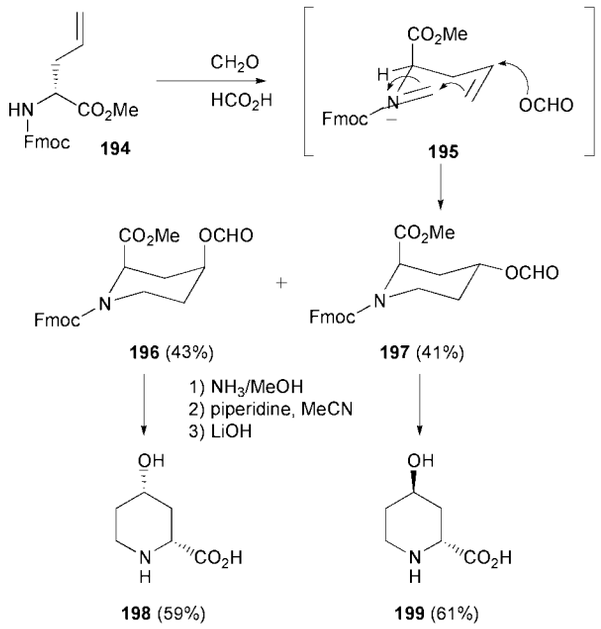
Scheme 42



Scheme 43

was coupled to the lactone **188** to give a separable mixture of the two diastereoisomers **189** in excellent yield. The sequence to **191** involved ozonolysis of the olefin, followed by intramolecular enamide formation giving rise to **190**. Subsequent radical cyclisation, followed by TFA-mediated destannylation, ozonolysis, opening of the lactone and hydrogenolysis of the benzyl ester finally gave the target compound **191** in good overall yield. A similar sequence, this time commencing with 9-BBN-mediated hydroboration of the olefin **189**, followed by oxidation and enamide formation provided **192**, which was efficiently converted using the same steps into the homologous product **193**.

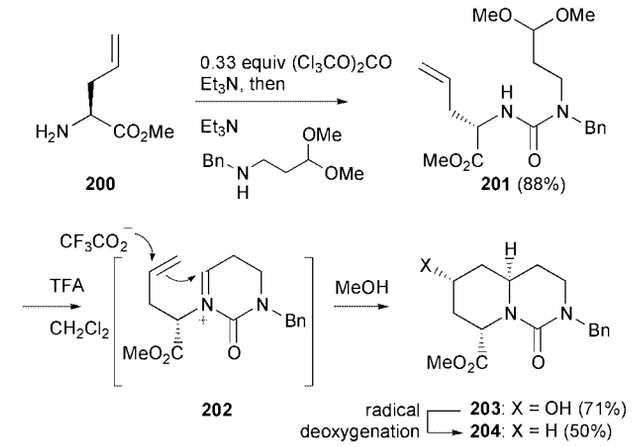
Scheme 44 illustrates a straightforward method to convert allylglycine derivatives in a one-pot procedure into the corresponding 4-substituted pipecolic acid derivatives.[78] Simple stirring of **194** in a mixture of paraformaldehyde and formic acid led to the intermediate *N*-acyliminium intermediate **195**, which underwent intramolecular nucleophilic attack by the internal double bond. The developing positive charge at the 4-position was captured by the formate nucleophile to give **196** and **197** in 84% yield This *cis–trans* mixture was readily separated and subsequently converted into the free 4-hydroxypipecolic acids



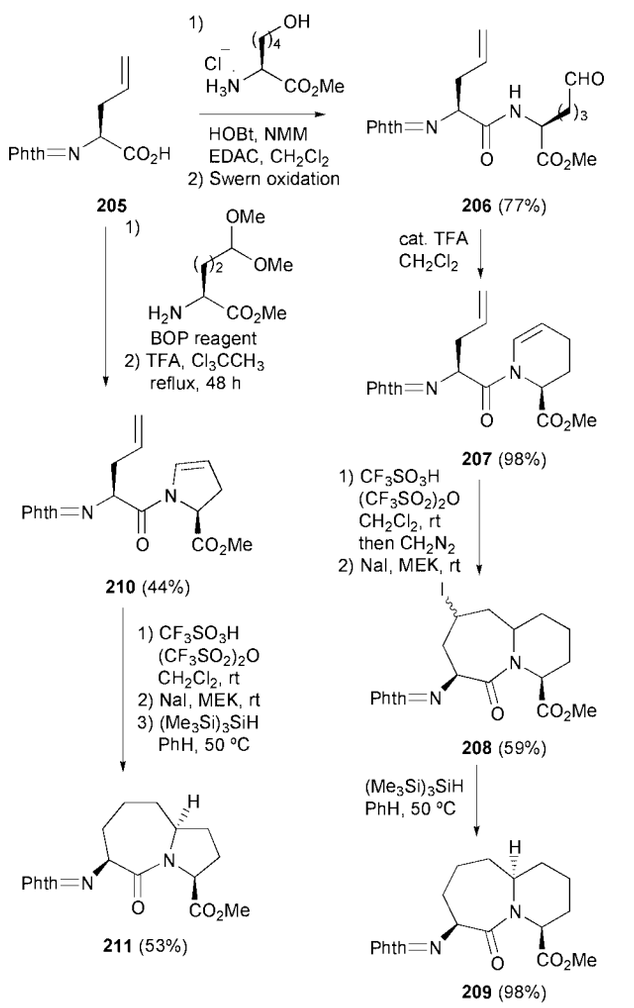
Scheme 44

198 and **199**, *via* ammoniolysis of the formate, Fmoc-deprotection and ester hydrolysis. It was shown that the *N*-acyliminium ion-mediated cyclisation proceeded without racemisation of the amino acid center. At Agouron Pharmaceuticals, novel urea-containing FKBP12 inhibitors were synthesised and tested. The synthesis of the core of several of these inhibitors also proceeded *via* *N*-acyliminium ion-mediated cyclisation of allylglycine-derived starting materials (Scheme 45).[79] Thus, reaction of allylglycine methyl ester (**200**) with triphosgene [bis-(trichloromethyl) carbonate], followed by reaction with the amino acetal provided the cyclisation precursor **201** in 88% yield. Treatment with TFA led to generation of the cyclic *N*-acyliminium ion intermediate **202**, which cyclised to the bicyclic system. The ester that was formed on capture of the developing cationic charge probably underwent methanolysis under the reaction conditions to give the corresponding alcohol **203**. Finally, radical deoxygenation afforded the bicyclic core, which was used to prepare a series of FKBP12 inhibitors. Robl utilised *N*-acyliminium ion methodology to cyclise the phthaloyl-protected allylglycine derivative **205** into the corresponding 5,6- and 5,7-bicyclic conformationally restricted Ala-Pro-mimics **209** and **211** (Scheme 46).[80] Coupling of **205** with (*S*)-ε-hydroxynorleucine methyl ester, followed by Swern oxidation provided dipeptide **206**, which was readily converted into the corresponding cyclic enamide **207** in excellent yield. Protonation using an excess of a protic acid (TfOH–Tf_2O) led to generation of the corresponding *N*-acyliminium ion, followed by cyclisation *via* nucleophilic attack of the olefin to form the 6,7-bicyclic system. Under these conditions, the methyl ester was also hydrolysed and had to be re-esterified. Subsequent replacement of the intermediate triflate by iodide provided **208** in 59% yield as a mixture of diastereoisomers. Finally, $(Me_3Si)_3$-SiH-mediated reduction of the C–I bond gave rise to the target system **209** in virtually quantitative yield. A similar sequence was applied to the norderivative **210**, eventually resulting in the 5,7-bicyclic system **211**.

The group of Baldwin used the allylglycine containing dipeptide **212** as a starting material in an attempt to prepare β-lactam analogues (Scheme 47).[81] Oxidative cleavage of the double bond provided a hydroxy lactam, that was converted into the corresponding methoxy lactam *via* treatment with acidic methanol. Then, deprotection of the serine hydroxy function *via* hydrogenolysis, acid-catalysed cyclisation and ester hydrolysis eventually led to the target compound **213** (obtained as a mixture of isomers). Unfortunately, none of the isomers

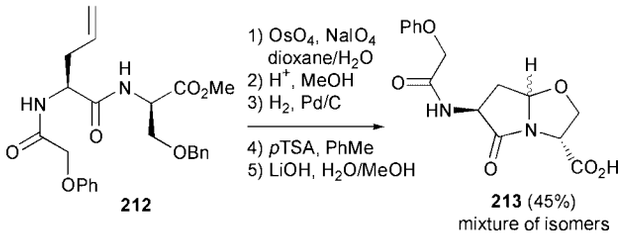


Scheme 45

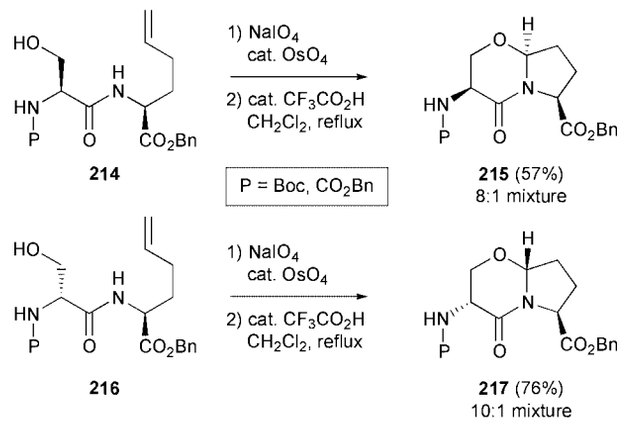


Scheme 46

possessed detectable antibiotic activity against *Staphylococcus aureus* bacteria. The same group used comparable methodology in the synthesis of potential β-turn dipeptide mimetics (Scheme 48).[82a] The protected dipeptide **214** was oxidatively cleaved into the corresponding aldehyde, which upon treatment with catalytic TFA cyclised to the bicyclic *N*,*O*-acetal **215** as an 8 : 1 mixture of isomers (the predominant isomer with the α-bridgehead hydrogen is shown). In addition, the diastereomeric dipeptide **216** (containing an (*R*)-serine moiety) was subjected to a similar sequence of reactions to yield the bicyclic *N*,*O*-acetal **217** in 76% yield as a 10 : 1 mixture of diastereoisomers (the major isomer is shown). The conformational effects of both β-turn mimetics were evaluated by incorporation in Leu-enkephalin

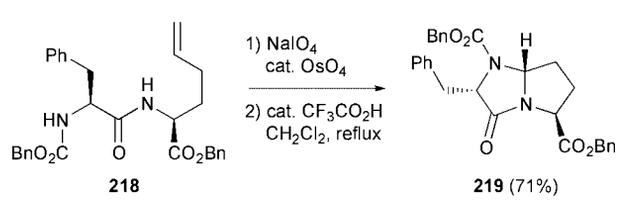


Scheme 47



Scheme 48

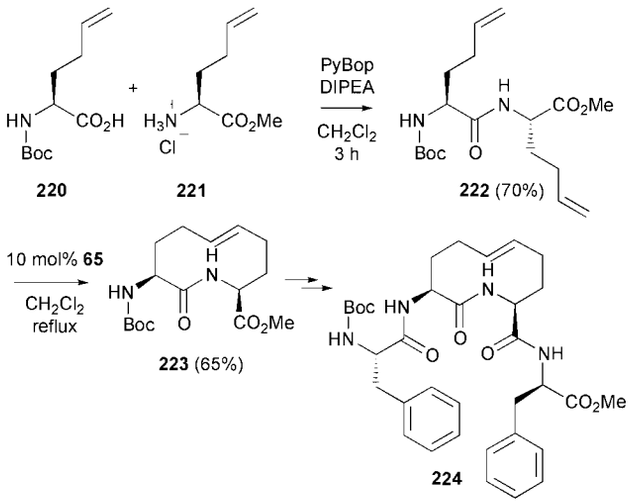
to study the properties of the resulting restrained peptide.[82b] Beside the synthesis of dipeptides that might serve as β-turn mimetics, this methodology was also applied to construct conformationally restricted dipeptide units (Scheme 49).[83] This approach commenced with the protected dipeptide **218** that was again subjected to the oxidative cleavage conditions. Treatment with catalytic TFA now resulted in the selective formation of the bicyclic *N*,*N*-acetal **219** in 71% yield and was obtained as a single isomer. Hydrogenolysis of both protecting groups provided the unprotected conformationally restricted dipeptide.



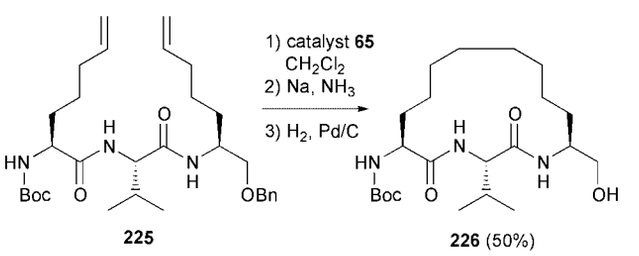
Scheme 49

The group of Katzenellenbogen was involved in designing and constructing novel type I β-turn mimics (*viz*. **224**) derived from unsaturated amino acids (Scheme 50).[84] One of the sequences that was applied started from the dipeptide **222** that was obtained in 70% yield *via* coupling of the amino acid derivatives **220** and **221**. Subjection of this diolefin to the RCM conditions (18 h, 0.2 mM) provided the corresponding 10-membered lactam **223** in 65% as the geometrically pure (*E*)-isomer. This cyclisation represented the first example of 10-membered lactam formation *via* the metathesis reaction. Further elaboration of the β-turn core provided the type I β-turn mimic **224**, the structure of which was confirmed by thorough NMR analysis.

Scheme 51 details a cyclisation reaction of a tripeptide consisting of two bis(homoallylglycine) residues tethered by the amino acid valine.[85] RCM using the standard Grubbs catalyst **65** proceeded in 88% yield to afford the macrocycle as a mixture of geometrical isomers. Dissolving metal hydrogenolysis of the benzyl ether, followed by double bond hydrogenation gave rise to the cyclic tripeptide **226**, which appeared a potent inhibitor of the enzyme *Rhizopus chinensis* pepsin and thus represented a novel class of simplified aspartic protease inhibitors.

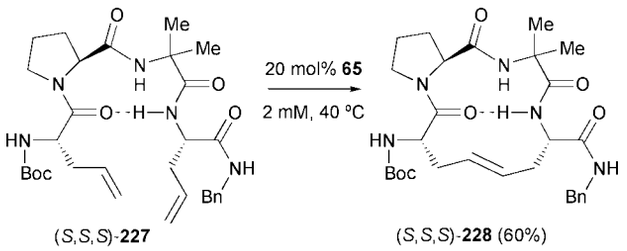


Scheme 50

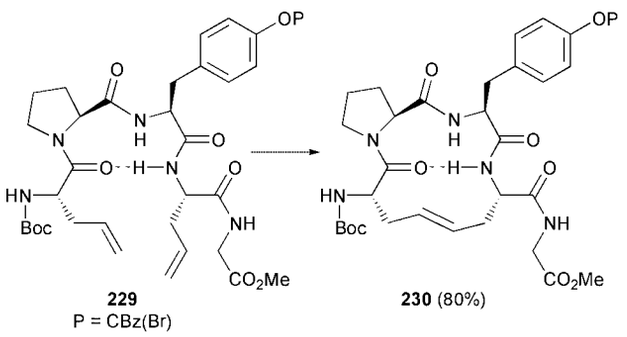


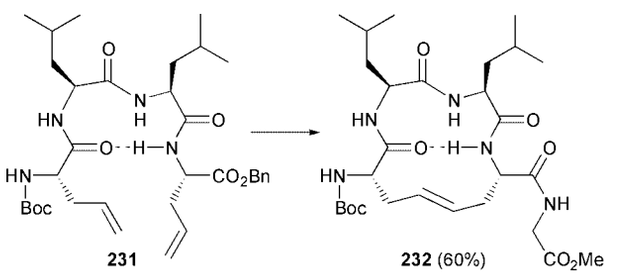
Scheme 51

In the quest for synthesising stable β-turn mimics, the combination of unsaturated amino acids and RCM appeared extremely useful. The Grubbs group was the first to recognise the potential of RCM in the synthesis of covalently stabilised β-turns by substituting the relatively weak disulfide bridges by carbon bridges.[67] The approach is depicted in Scheme 52. Substitution of two cysteine residues by allylglycine residues in a known β-turn precursor led to diolefin **227**. Interestingly, incorporation of racemic allylglycine moieties followed by RCM provided the turn mimic (*S*,*S*,*S*)-**228** as the only cyclisation product (out of four diastereoisomers) in geometrically pure form as well as non-cyclised starting material. Alternatively, subjection of (*S*,*S*,*S*)-**227** to identical conditions gave the desired target compound **228** in 60% yield. More recently, it was shown by the same group that induction of a cyclic conformation prior to the cyclisation is not *per se* necessary.[86] Replacement of the 2-aminoisobutyric acid (Aib) residue with a protected tyrosine (*viz*. **229**) and even replacement of both turn amino acids by two leucine residues (*viz*. **231**) resulted in facile cyclisation in very reasonable yields (Scheme 53). Moreover, this group demonstrated the viability of such cyclisation reactions on the solid support (Scheme 54) *via* the conversion of the immobilised oligopeptide **233** into its cyclic counterpart followed by cleavage from the resin to give **234** in good yield. This is a very useful extension of the protocol, since the starting materials can be readily prepared *via* standard solid phase peptide synthesis techniques, after which the compound can be directly cyclised with the Ru-catalyst. Blechert and co-workers elaborated this strategy even further (Scheme 55).[48] Instead of using standard solid phase peptide methodology, the RCM precursor molecules **237** were attached to the resin *via* one of the two olefinic moieties. In order to obtain the starting materials, the immobilized allylglycine derivatives **235**, the cross-metathesis approach reported earlier by this group was utilised (Scheme 18). Coupling with the appropriate tripeptides provided the metathesis precursors **237**, which were subjected to the Ru-mediated RCM conditions. In this case, the cyclo-release reaction occurred, leading to cyclisation and concomitant

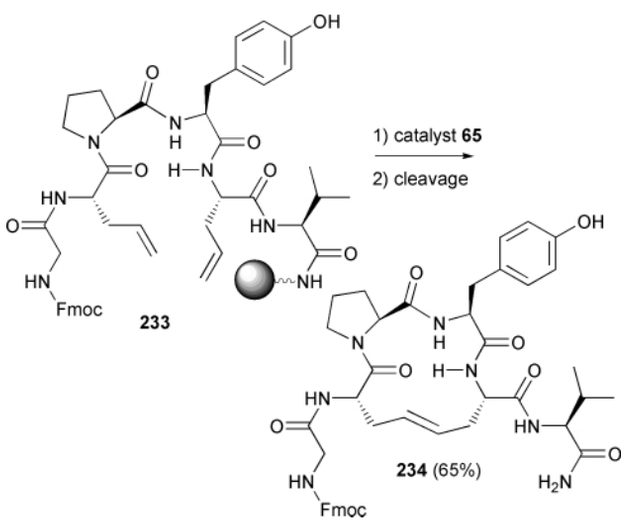


Scheme 52





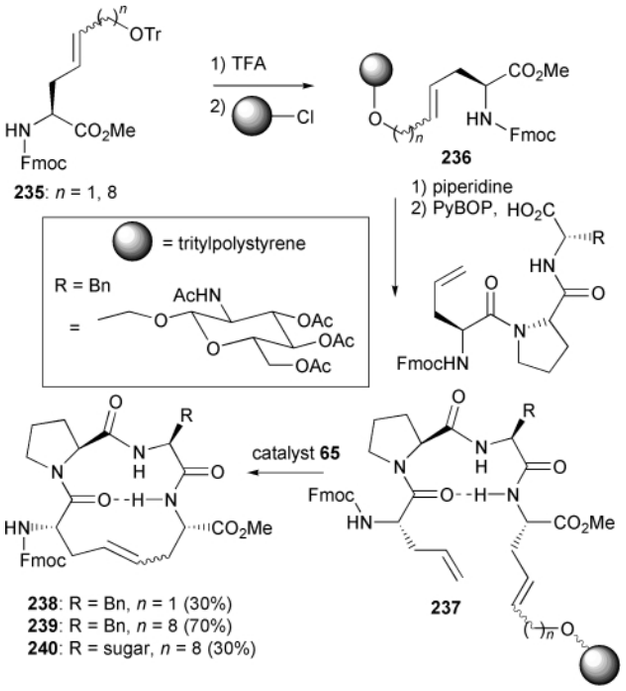
Scheme 53



Scheme 54

cleavage of products **238**–**240** from the resin in variable yields. In contrast with the results of Grubbs, where only the (*E*)-isomer was formed, a mixture of geometrical isomers was obtained.

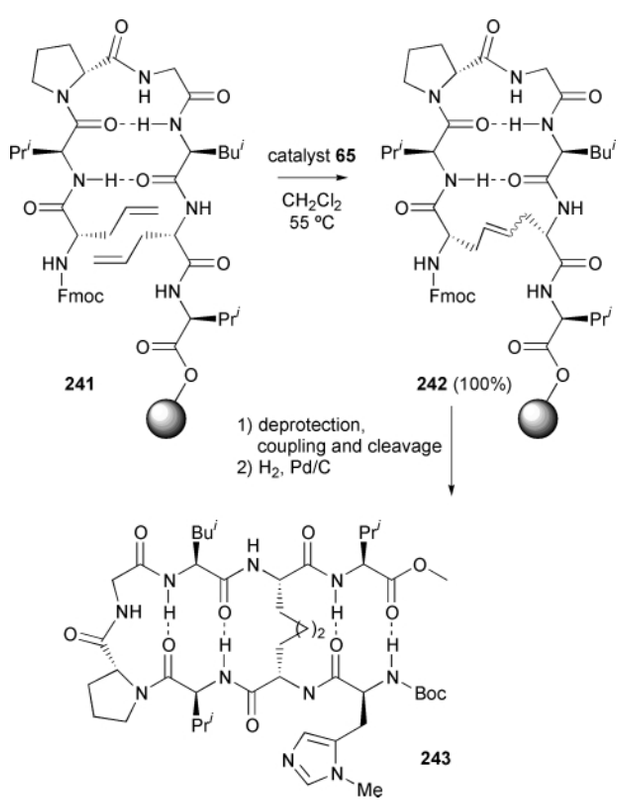
The group of Miller was involved in studying which fragments and structural motifs in peptides are important for controlling asymmetric catalysis.[87] In this research, small peptides that contain modified histidine residues were prepared and evaluated in asymmetric acyl transfer reactions. After it was found that an octapeptide β-hairpin structure catalysed such a reaction with relatively good selectivity, it was concluded that this conformationally rigid structural motif could be a basis for design of more selective catalysts. In order to further rigidify the β-hairpin structure, compound **243** was synthesised in



Scheme 55

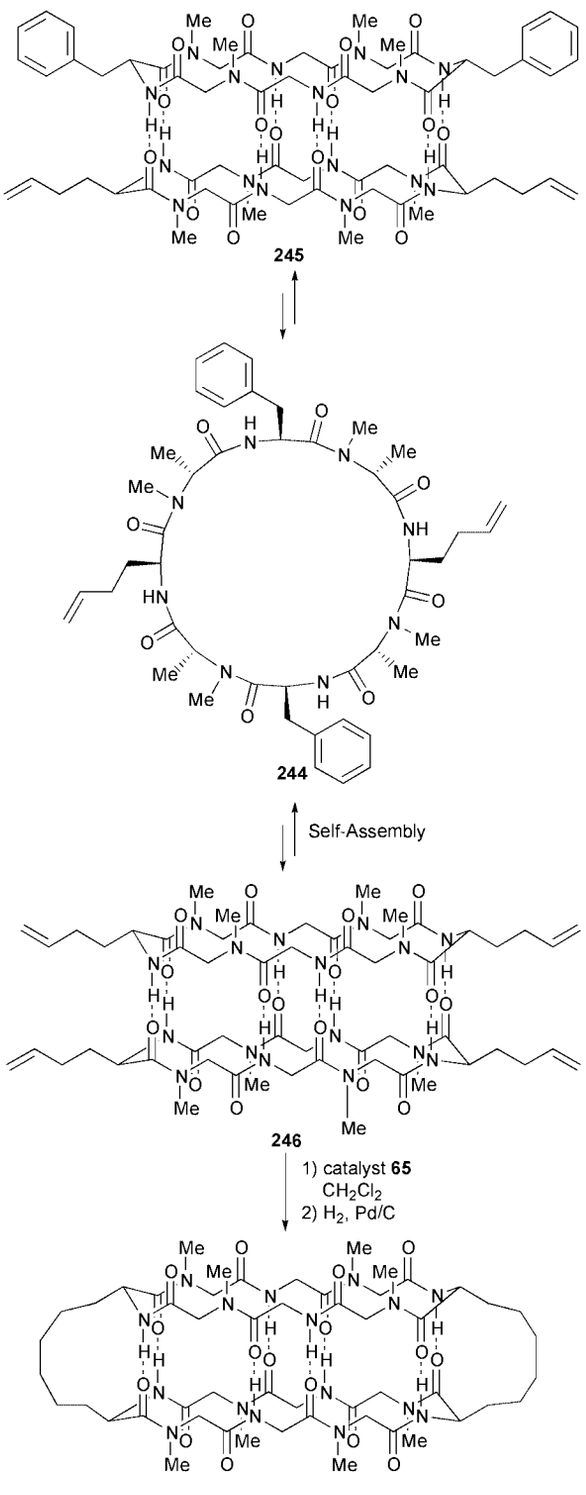
which the two opposing strands are covalently linked to each other (Scheme 56). This compound was prepared *via* solid phase synthesis of **241**, which contains two allylglycine residues, suitably located to undergo an RCM reaction. Indeed, treatment with catalyst **65** afforded in essentially quantitative yield the cyclic structure **242**. Further elaboration to the octapeptide unit and hydrogenation of the double bond eventually yielded the covalently stabilised β-hairpin **243**. Unfortunately, this rigidified structure appeared less selective than the initially studied non-covalently bound β-hairpin.

Beside the formation of β-sheets that *via* pre-organisation facilitate the formation of C–C cross-links through the side



Scheme 56

chain of the amino acids, cyclic structures were also proven to display similar features. An interesting example of pre-organisation by self-assembly, followed by covalent stabilisation of the resulting structure was reported by Ghadiri and Clark (Scheme 57).[88] A suitably designed cyclic 8-mer (**244**), existing of alternating (*R*)- and (*S*)-amino acid residues, partly capped with methyl groups, self-assembled in a dynamic process to (amongst others) the non-covalently bound dimeric structure **246**. Subjection of this dynamic mixture to the Grubbs catalyst **65** led in 65% yield to the corresponding covalently stabilised dimeric structure. Initially, a mixture of all possible geometrical isomers was obtained, which was readily hydrogenated to the saturated compound **247** in quantitative yield.

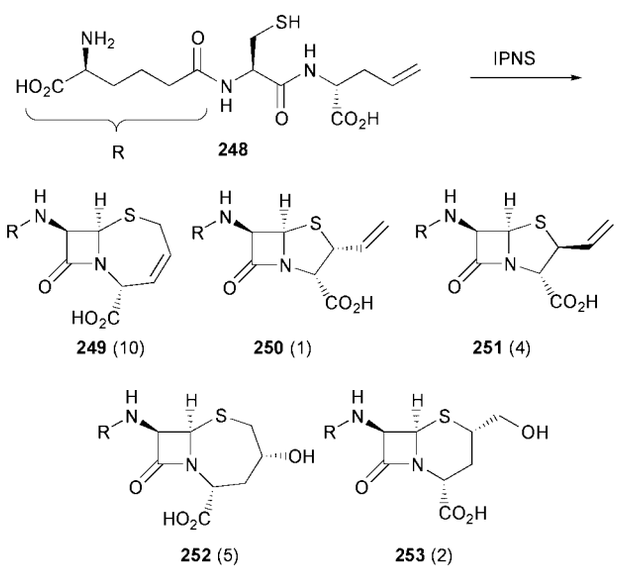


Scheme 57

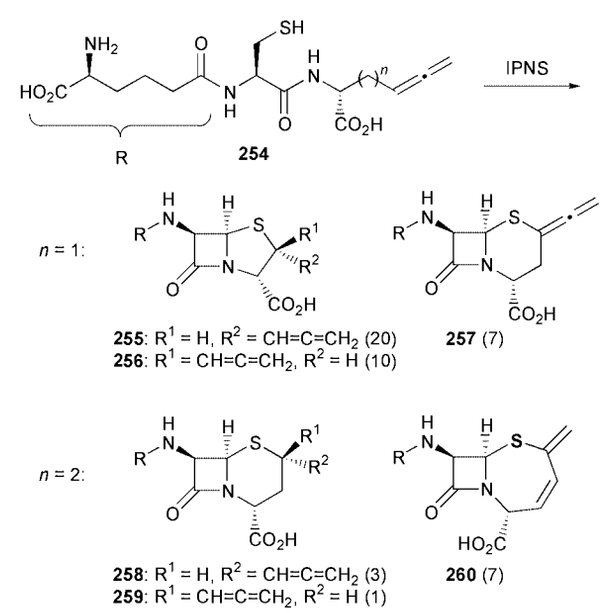
5 Biosynthetic applications

In a biosynthetic strategy aimed at the production of novel β-lactam type antibiotics, the group of Baldwin studied the substrate specificity of the enzyme isopenicillin N synthase (IPNS). Instead of using natural substrates, highly purified IPNS from *Cephalosporium acremonium* CO 728 was incubated with substrates containing olefinic, allenic and acetylenic amino acids. The first example is shown in Scheme 58,[89] where the tripeptide **248**, containing an (*R*)-allylglycine moiety, was subjected to the enzyme IPNS. This gave rise to a number of different β-lactam-like compounds **249**–**253**, which were isolated in a ratio of 10 : 1 : 4 : 5 : 2, respectively. In a similar fashion, both allene-substituted tripeptides **254** ($n = 1, 2$) were incubated with the same enzyme to give rise to the unusual β-lactams **255**–**260** in the ratios shown (Scheme 59).[90] Finally, the (*R*)-propargylglycine-derived tripeptide **261** was expected to lead to a similar result (Scheme 60). In this case, however, incubation under identical conditions as before gave rise to essentially a single product in a high yield, namely, β-lactam **262**.[91] This compound displayed biological activity comparable to isopenicillin N against both *S. aureus* and *E. coli*.

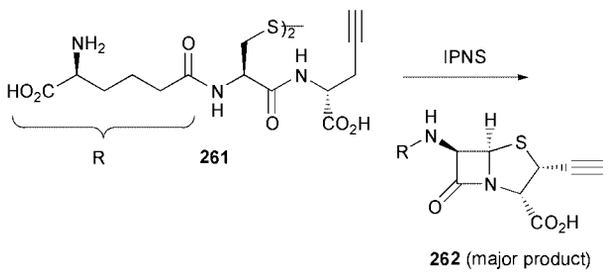
There is a strong interest in incorporating non-proteinogenic amino acids into peptides in order to alter the properties of the



Scheme 58



Scheme 59



Scheme 60

peptide. For example, the enzymatic activity might be improved or adjusted to other substrates, specific labels could be introduced or reactive functionalities may be installed. Beside the conventional synthetic means to incorporate non-proteinogenic amino acids in peptides, recently biosynthetic methods emerged that can accomplish this as well. The first of two *in vitro* methods for site-specific incorporation of non-proteinogenic amino acids in peptides was developed in the group of Schultz.[92] In this approach, the codon encoding the amino acid of interest is replaced with the nonsense codon UAG by oligonucleotide-directed mutagenesis. A suppressor tRNA that recognizes this codon is generated by run-off transcription and then chemically aminoacylated with the desired non-proteinogenic amino acid. Addition of the mutagenised gene and the aminoacylated suppressor tRNA to an *in vitro* extract capable of supporting protein biosynthesis then generates the mutant protein containing the non-proteinogenic amino acid at the specified position. In this way, a wide variety of amino acids, including unsaturated ones, have been incorporated with good efficiency.

Sisido *et al*.[93] developed the so-called 'frameshift method' as an alternative strategy to incorporate non-proteinogenic amino acids in peptides. A four-base codon AGGU was translated into a non-proteinogenic amino acid by chemically aminoacylated frameshift suppressor tRNA, containing the complementary four-base anticodon ACCU. This frameshift strategy overcomes the limitation of the 64 genetic codes and provides, in principle, many extended codons that may be assigned to non-proteinogenic amino acids.

In the group of Tirrell, an *in vivo* method was developed which utilises the wild-type *E. coli* translational system of the cell to incorporate different types of non-proteinogenic amino acids into proteins.[94] The straightforward method and the capacity of the system to provide relatively large quantities of engineered proteins render this a method that may be especially well-suited to producing new biomaterials. They showed that by using cells that were depleted of methionine, but with methionine surrogates present, efficient incorporation of the surrogates took place. Examples of good methionine analogues were homoallylglycine (**1**, $n = 2$) and homopropargylglycine (**2**, $n = 2$), but other non-proteinogenic amino acids could also be incorporated.

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