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New Developments in the Chemistry of *N*-Acyliminium Ions and Related Intermediates

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1. Introduction

Reactions between *N*-acyliminium ions and nucleophiles—also described as amidoalkylation or Mannich type condensations—have been frequently utilized to introduce substituents at the α-carbon of an amine. Details of these reactions, including methods of generation,[1] preparation of suitable precursors,[2] stereochemical aspects[3] and application in natural product syntheses,[4] have been extensively reviewed while the development of chiral variations[5] has constituted part of a major reference work. Since the appearance of the most recent surveys, however, a substantial number of valuable and pertinent contributions have appeared in the literature covering significant improvements in the accessibility of precursors and generation of the reactive species while remarkable developments have also taken place in the utilization of this technique, especially in the control of diastereo- and enantio-selectivity. It is therefore considered appropriate to summarise these novel and relevant findings, which is the subject of this review. Emphasis will be placed upon the studies pertaining to the core chemistry of the *N*-acyliminium synthetic method which have not been fully covered by other authors in reviews on the synthesis of particular classes of compounds. Discussion of the latter results will be included only insofar as the findings are of relevance to the contents of this survey. These reviews cover synthesis of chiral pyrrolidines,[6] chiral piperidines,[7] chiral bicyclic lactams,[8] pyroglutamic acid derivatives,[9] 1,3-dipolar additions of mesoionic compounds,[10] peptide mimetics,[11] α-cation equivalents of amino acids,[12] benzotriazoles in amidoalkylation,[13] peptide chemistry,[14] silicon compounds in natural product synthesis,[15] Mannich reactions[16] and *N*-sulfonyl imines[17] and all contain essential parts on *N*-acyliminium chemistry. Results of standard procedures which lack new or unexpected findings as compared to previous reviews will be mentioned as references in the appropriate section.

2. General Aspects

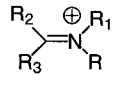
2.1. Structure and reactivity

Throughout the last two decades it has been well-established that substitution with electron-attracting groups at nitrogen renders the Mannich-intermediate **1** considerably more reactive by enhancing its cationic character. Of these modified cations the *N*-acyl derivative **2** and the carbamate **3** have been most widely exploited although the use of other electronegative substituents such as the amide **4** and *N*-tosyl **5** cations have also been examined. Depending on the type of R_1, R_2 and R_3 various cyclic and linear forms can be distinguished and new variations, for example the hydrazonium **6** cation, have been added (Fig. 1).

Since in previous surveys the structural factors have already been discussed in depth only a few comments of a more practical nature will be added. The endocyclic forms **2**—R_1,R_2 or R,R_3 constitute a ring size of 5–7—obviously favor intramolecular bond formation in which the nucleophile is contained in one of the remaining substituents. In the intermolecular application, usually in combination with an (electro)oxidative formation of the precursor molecule, the alkoxycarbonyl form **3** is often selected. In the case of a reductive preparation of the precursor of **3** the nonequivalence of the two carbonyl groups in the starting material should be noted. For the metal-mediated addition of nucleophiles to **2** or **3** the complexation of the metal species with the carbonyl in the *s-cis* form may have a beneficial effect towards stereocontrol. The overall reactivity of **2** and **3** in general is not varying greatly although in some cases noticeable differences in the stereochemistry of the reaction are observed. These will be discussed in the appropriate sections. Use of the tosyl form **5** may offer advantages in terms of stability and crystallinity of the starting materials and/or products. Its reactivity may also slightly differ due to smaller resonance and enhanced inductive effects although its more difficult removal renders its use less frequent. As mentioned in the introduction a recent review covers various aspects of this chemistry.[17]

The question of whether it is possible to have both substituents R and R_1 as electron-withdrawing groups is of interest since the corresponding precursors can be obtained quite easily (cf. Section 3.1.8). So far no examples of these forms have been observed and therefore it is necessary before generating the reactive iminium cation to remove one of the carbonyl groups. It should be noted that for R_2 or R_3=COOX the class of glycine cations is formed with numerous synthetic applications.[12] The use of intermediates **4** and **6** is mentioned in the Sections 3.1.5. and 4.2.2.1.

Whereas theoretical considerations and ab-initio calculations[18] already provided ample support for the experimentally



1 R = H, alkyl **4** R = $CONR_2$
2 R = acyl **5** R = Tos
3 R = COOR **6** R = NR_2

Figure 1.

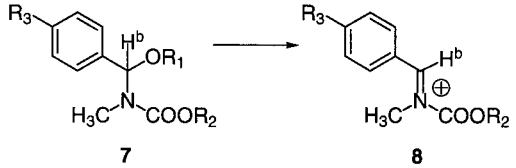
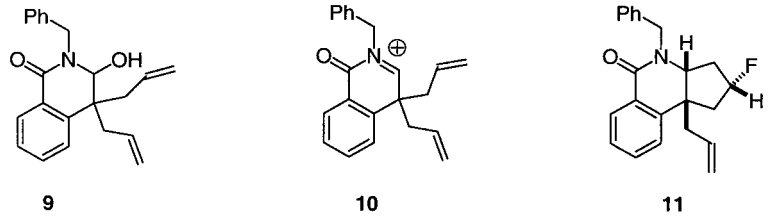


Figure 2.



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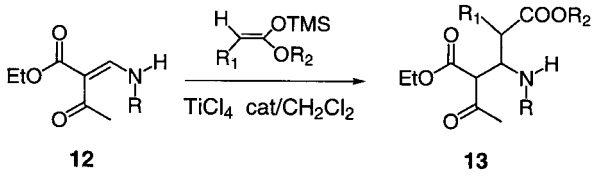


Figure 4.

found reactivity differences between **1** and the cations **2**–**6** and ^{13}C NMR data of stable salts were also determined,[19] the observation of a transient *N*-acyliminium intermediate in dynamic NMR has been reported only twice. In a specially designed experiment it was shown that the alkoxycarbamate **7** at −55°C in the presence of Tf_2O produced a clean ^{13}C NMR of the intermediate **8** (Fig. 2) upon treatment with a Lewis acid.[20]

Recently it was found[21] that treatment of the bis(homoallyl) hydroxylactam **9** with $BF_3{\cdot}OEt_2$ at 25°C produced the ^{13}C spectrum of the *N*-acyliminium ion **10**. This intermediate was slowly (1 h) converted to the fluoro compound **11**. The reasons for this unexpected stability are not entirely clear although the spectral data show the greater withdrawing ability of the amide carbonyl as compared to the carbamate (Fig. 3).

Presumably the allyl groups may also stabilize the cation by a dynamic process of π-participation. It has also been experimentally demonstrated that *N*-acyliminium ions possess a higher reactivity profile as compared to the iminium species. A recent intermolecular example is found in the ketene acetal addition[22] to **12** which proceeds rapidly to **13** in case of R=Cbz. An acyl group on the nitrogen atom is crucial for the reaction to take place since *N*-alkyl versions are inert under the given reaction conditions (Fig. 4).

The difference in reactivity between oxycarbenium and *N*-acyliminium intermediates as established earlier[23] was confirmed in a special study which also included the stereochemical aspect. Upon treatment of **14** (R=H) with allyltrimethylsilane and BF_3/MeCN at −40°C the allyl group was introduced at the α-carbon next to oxygen (Fig. 5).

For R=Me or R=Et the reaction at −15°C produced the rearranged product **15** which is the result of an alkyl transposition due to a favorable geometry allowing the observed shift and implicitly suggesting a higher stability for the *N*-acyliminium form. A special example relating to an alkyl shift is found[24] in the NBS treatment of **16** thereby promoting a cation-induced rearrangement ultimately leading to the *N*-acyliminium form which after capture of methanol leads to **17**.

2.2. Structural modifications

The effects of structural changes can markedly influence the mode of reaction and its stereochemical course. Well-known in this respect is the reversal of stereochemistry in allylsilane additions to *O*-benzyl and *O*-acetyl malic acid precursors which was recently extensively studied for a variety of catalysts and nucleophiles.[25] Incorporation of heteroatoms into the ring leads to modifications such as the oxazolidinium **18a**,[26,27] the imidazolinium **18b**,[28] morpholinium **19a**[27] and pyrazinium **19b**[29] derivatives while vicinal attachment of a second nitrogen introduces

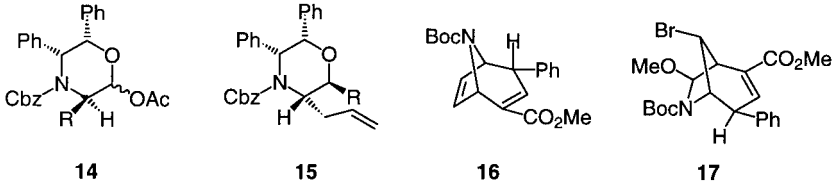


Figure 5.

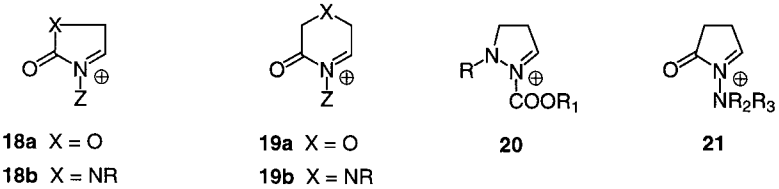


Figure 6.

22 **23a** **23b**

Figure 7.

the hydrazine moiety. In this case the pyrazolinium forms **20**[30] are formed in the endocyclic mode while the exocyclic variant **21** is used as a vehicle for asymmetric transformations (Fig. 6).[31]

2.3. Experimental conditions

Protic acids—formic acid—as well as Lewis acids have been used to effect bond formation. Evidently for sensitive nucleophiles such as enol ethers, alkenylsilanes or organometallic derivatives, e.g. organocuprates, the use of a protic acid is only possible if the rate of bond formation is sufficiently high as compared to the alternative nucleophilic decomposition which in practice limits the reaction to the intramolecular variant. In the Lewis acid mode a number of studies are concerned with the effects of different catalysts. From these data it is inferred that in the majority of reactions $BF_3{\cdot}OEt_2$, $SnCl_4$ and $TiCl_4$ are superior in terms of convenience and results. In a few cases metal halides such as $FeCl_3$, $ZnBr_2$ and $MgBr_2$ or $LiClO_4$ are used. For enol ethers trimethylsilyl triflate (TMSOTf) is often appropriate. Due to its different coordinating ability $TiCl_4$ sometimes leads to adverse and unexpected results especially in relation to stereochemistry.[32] Of added interest is the change in reaction pathway by intramolecular acylation of imines with $TiCl_4$ complexes of *t*-butylcarbamates and ensuing alkene addition.[33] While the use of any particular combination of Lewis acid and nucleophile often dictates the experimental conditions some results have been reported in which the work-up technique determines the type of product formed.[34] The adaptation of a particular combination of solvent and Lewis acid may additionally strongly influence the outcome of the reaction.[23,25,35] Finally a remarkable influence of the type of protic acid has been reported in the reaction of β,γ-alkenamides with aldehydes to form lactams (Fig. 7).[36a]

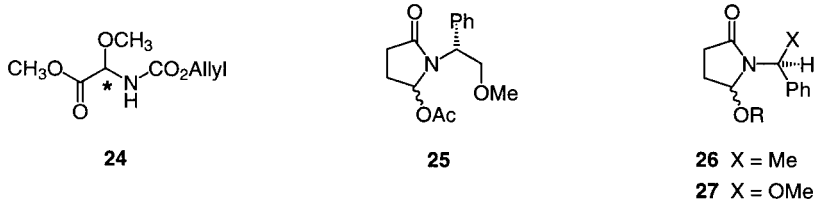
Whereas the γ-lactam **22** is obtained in P_2O_5–$MeSO_3H$ at 35°C upon condensing (*E*)-3-pentenamide with benzaldehyde, the isomeric δ-lactam **23a** is the product upon treatment with polyphosphoric acid (PPA). Alternatively the latter material is also formed upon reaction of **22** with PPA. Other condensation products are obtained depending on the type of starting material, acids used and the temperature. In this manner the δ-ene-lactam **23b** is formed as the sole product.[36b]

2.4. Stereocontrol

The mechanistic pathway for *N*-acyliminium reactions does not allow direct control of the desired stereochemistry. As discussed in the foregoing sections the S_N1-type intermediate has been detected directly in NMR studies and is also chemically proven by experimental observations. A recent example is found in the reaction of optically pure (+)-**24** with three types of nucleophiles, in all cases the completely racemized products being obtained.[37] Moreover upon mixing **24** with $BF_3{\cdot}OEt_2$ without a carbon nucleophile present, the starting material had almost completely racemized within 24 h at room temperature. Thus any desired effect should be brought about via indirect techniques such as the use of chiral pool starting materials or with the aid of chiral auxiliaries.

Within the latter group, remarkable alterations can be brought about by changing the Lewis acid from $SnCl_4$ to $TiCl_4$, as demonstrated by the reaction of **25** with allyltrimethylsilane to induce opposite diastereoselectivities.[38] Alternatively changing the auxiliary to an oxygen containing analog may also reverse the face-differentiating effect, as shown by the TMSOTf catalyzed reactions of **26** and **27** with a vinyl sulfide.[39] A useful method to influence the stereochemistry of the bond-forming process is the incorporation of the leaving group into a fused ring. The first general variant of this type has been studied in great detail by Meyers in the chemistry of chiral bicyclic lactams. Since the latter results have been reviewed elsewhere[8] no further discussion is given. Additional examples of this effect will be presented in other sections of this survey (cf. Section 3.1.6) (Fig. 8).

Two very promising techniques describe the generation of chiral precursors from *meso*-type imides and cyclic amines. In the reductive process impressive results have been obtained in the oxazaborolidine catalyzed conversion of a variety of symmetric cyclic imides to chiral hydroxylactams[40] with ee's >90%. The use of other catalysts in this type of reduction is possible albeit with less efficacy.[41]



24 **25** **26** X = Me **27** X = OMe

Figure 8.

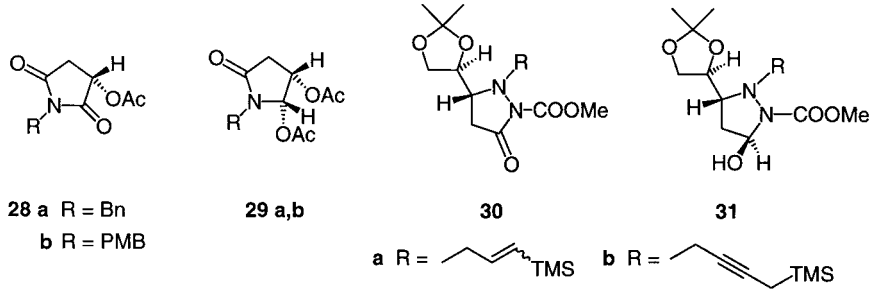


Figure 9.

In a complementary way it is also possible to oxidize a cylic *meso*-amine with PhIO using a (salen)manganese(III) complex in ee's up to 64%.[42] Examples of these procedures will be given in the corresponding sections (cf. Sections 3.1.1.1 and 3.1.3).

3. Synthesis of Chiral and Achiral Precursors

3.1. Cyclic precursors

The controlled preparation of a suitable cyclic precursor for generating an endocyclic iminium is discussed in this section. A great variety of structures have been described including various types of substituted and heterocyclic variants of the imide system. These substrates will not be reviewed separately but all of the results will be discussed in the appropriate section. Of the nearly 400 references in the period 1992–1999, only those adding relevant material to the existing documentation will be discussed.

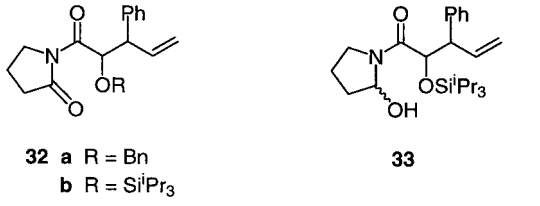


Figure 10.

3.1.1. Hydride addition to C=O of lactams and imides. Selective hydride reduction of one of the carbonyl groups in a cyclic imide marked the beginning of the rapid expansion of the *N*-acyliminium field in the last 25 years. Since the stereochemistry of the so-formed oxylactam is usually not important in the next step the mixture of stereoisomers can be used as such. New developments with regard to chiral applications are discussed in Sections 3.1.1.1 and 3.1.9. Depending on the substrate, high stereoselectivity is observed in some cases notably with malic acid imide, tartarimide and chiral pyrazolones. The almost exclusive formation of the *cis*-isomer **29a** from the $NaBH_4$ reduction of **28a** depends strongly on the work-up. Careful neutralization at −23°C with MeOH–HCl and acetylation affords the almost pure isomer (*cis*/*trans* 19:1), while addition of HCl at room temperature gives a 1:1 mixture of epimers.[43] Similarly **28b** produces **29b** in 82% yield.[44] Comparable results have been obtained in reductions of dibenzyl[45] or diTBS[46] tartarimide. The pyrazolones **30a** and **30b** afford the reduced **31a**,**b** ($NaBH_4$–EtOH, 2 M H_2SO_4, −25°C) as single stereoisomers (Fig. 9).[47]

The importance of the steric factor is clearly demonstrated in the reduction of acylpyrrolidones **32**.[48] While in **32a** only the *exo*-carbonyl is reduced, exchange of the benzyl group for the bulky tri-*i*-propylsilyl leads to reduction of the ring

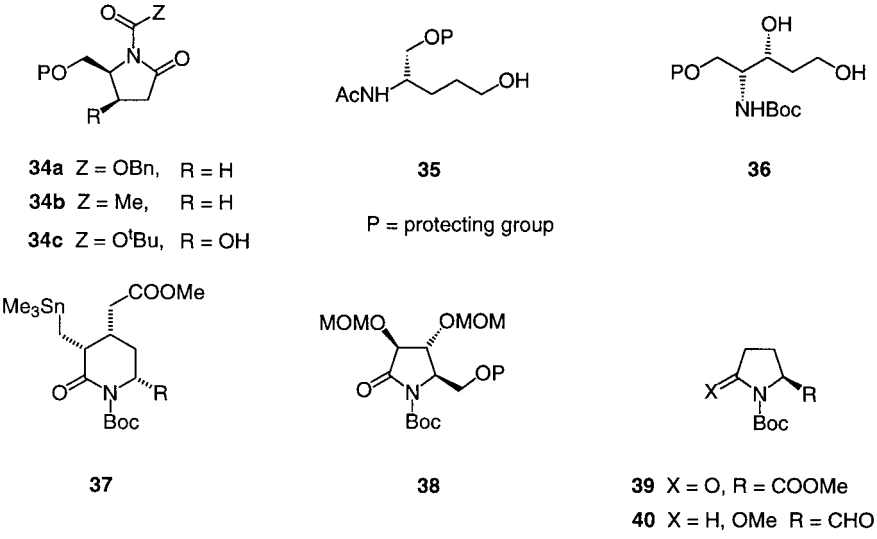


Figure 11.

carbonyl in **32b** and subsequently to the acyclic hydroxy amide. Upon Swern-oxidation the latter is converted to the *N*-acyliminium precursor **33** (Fig. 10).

A comparable effect is observed[49] in the reduction of the pyroglutamate derivatives **34a** and **34b**. Whereas the benzylcarbamate **34a** underwent clean *endo*-reduction the *N*-acetyl lactam **34b** gave presumably a mixture of *exo*- (not isolated) and reduced ring-opened *endo*-product **35** which was reoxidized—TPAP/NMO—to the hydroxylactam (Fig. 11).

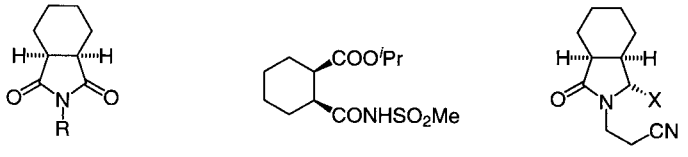
Interestingly, the presence of an extra hydroxy substituent in **34c** led under analogous conditions[50] exclusively to the ring-opened *endo*-product **36**. Usually the reduction of pyroglutamate derivatives can be carried out with a variety of reducing agents and leads to mixtures of stereoisomeric hydroxylactams. $NaBH_4$,[51] $LiEt_3BH$[52,53,55] and DIBAL-H[54,56,57] have been used. The choice of other hydride reagents allows the use of different solvents. In some studies $LiEt_3BH$ proved very effective, e.g. the reduction[58] of lactam **37** and the conversion of the highly-substituted lactams **38**.[59] The application of DIBAL-H may be advantageous in particular when *N*-tosyl lactams are the starting materials.[60–62] The selectivity aspect in the conversion of **39** to **40** is also remarkable. In THF–CH_2Cl_2 as a solvent the lactam carbonyl is solely reduced to the *endo* OH whereas after the exchange of this OH to OMe the ester is transformed to the aldehyde **40** upon use of CH_2Cl_2 as the solvent in the DIBAL-H reduction.[54] Of practical value (cf. Section 6.1) is the virtually complete and selective DIBAL-H reduction of a biotin precursor.[63]

3.1.1.1. Enantiocontrolled reduction of *meso*-imides. Whereas the reduction of ring substituted cyclic imides is subject to diastereoselective control C_2 symmetric *meso*-imides only give racemic products. Earlier work to solve this problem[5] has now been followed by the introduction of several new methods which show substantial progress in the control of enantioselectivity. Use of an excess of (*R*)- or (*S*)-BINAL-H gave good yields (up to 94% ee)[64] of chiral hydroxylactams starting from the *N*-aryl imide **41**. For R=benzyl or methyl the yields were much lower. Similar results were obtained[41] in the catalytic reduction of **41** (R=Ar) with a thiazazincolidine complex and an excess of bis-(2,6-dimethylphenoxy)-borane while for R=benzyl less satisfactory results were found. The *N*-sulfonyl derivative **42** was reduced with a slight excess of a TADDOLate and in a slow reaction (28 days/−50°C/THF–Et_2O/85% ee) a good yield of enantiopure **43** was obtained.[65] A marked improvement was attained upon use of the catalytic oxazaborolidine method.[66] Not only *N*-arylimides **41** but also *N*-benzyl and *N*-alkyl derivatives could be converted[40] while also the variation in the imide structure, e.g. *N*-benzyl-diacetoxytartarimide, was reduced with an ee of 87%, widened the scope of the method. In this manner the useful product **44** was obtained which on conversion into the sulfone **45** by reaction with benzenesulfinic acid in the presence of $CaCl_2$[67] gave the optically pure material upon crystallization (Fig. 12).

3.1.2. Addition of RMgBr or RLi to imides. Addition of organolithium or Grignard reagents to imides leads to tertiary hydroxylactams. These compounds are far less stable than the secondary reduction products and are often isolated as mixtures of cyclic and linear tautomers.[5] The practical value is mostly connected with the intramolecular cyclization under acid catalysis and the tautomer mixture is therefore used as such. Grignard additions have been carried out with achiral and optically active imides at ambient[68,69] or low temperature.[70,71] Et_3SiH–$BF_3{\cdot}OEt_2$ reduction of the tertiary hydroxylactam affords the alkylated lactam which can be also prepared in a stereochemically complementary way by intermolecular addition to a secondary hydroxylactam with an activated nucleophile (cf. Section 4.2.2.1). An increase in the synthetic flexibility is possible by using lithiated reagents since exchange methods allow the preparation of a variety of RLi derivatives[34] while the factors influencing the tautomeric equilibrium could also be evaluated in greater detail. Finally if R contains an activated group—e.g. an allylsilane moiety—consecutive cyclizations to spirocyclic products are possible.[72]

3.1.3. Chemical oxidation at α-CH in cyclic amines and lactams. Ruthenium catalyzed oxidation of carbamates as developed by Murahashi[73] constitutes a versatile method to generate precursors for the *N*-acyliminium species. Recent examples are found in Stemona alkaloid synthesis[74] and in studies on actinomycin.[75] Hypervalent iodine oxidations have been used to introduce the azide moiety in *N*-acylated pyrrolidines and piperidines.[76] An interesting observation[77] relates to $Mn(OAc)_3$ oxidations of enamides. Oxidation of the β-keto ester **46** forms a radical, thereby triggering a cyclization which is terminated by further oxidation to the cation and capture of methanol to afford **47**. Using an analogous pathway[78] in which Cu^{2+} is the oxidative reagent methoxylactams **49** are formed from amines **48** through the sequence: diazotation→Cu(I) generation of the radical→1,5 hydrogen atom transfer→Cu(II) oxidation.

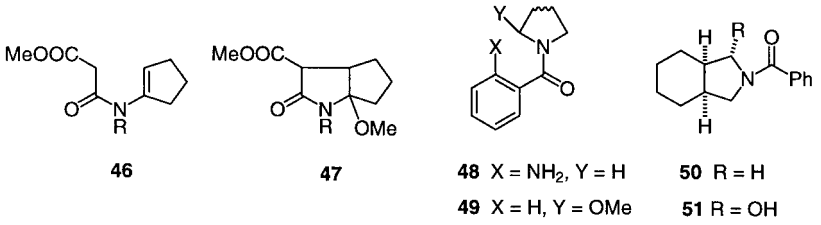
As an alternative to the enantiocontrolled reduction of *meso*-imides (Section 3.1.1.1) a catalytic oxidative dissymmetrization of *N*-benzoyl-*meso*-pyrrolidines **50** has been reported which makes use of a (salen)-manganese(III)



41 R = Ar, CH_2Ph, Me **43** **44** X = OEt

42 R = SO_2Me **45** X = SO_2Ph

Figure 12.



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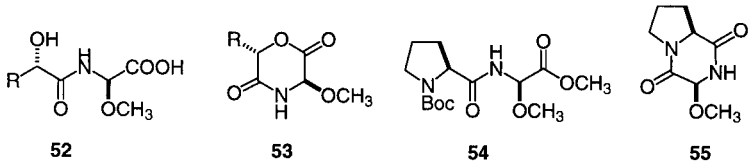


Figure 14.

complex and PhIO as the terminal oxidant.[42] Ee's up to 64% of **51** were found which could be raised to 76% by using C_6F_5IO and the *N*-phenylacetyl derivative (Fig. 13).

3.1.4. Electrochemical oxidation and decarboxylation at α-CH in cyclic amines and lactams. Since the pioneering work of Shono[79] this method has been applied frequently in the following general cases: (i) a variety of oxylactams of different types can be obtained from readily available amine precursors; and (ii) oxidation products allow the use of amino acids as cationic synthons. Well studied in the first category is the oxidation of proline derivatives which is the complementary form of the hydride reduction of pyroglutamates. Amongst the numerous recent examples are the preparation of precursors for peptide mimetics,[80–82] condensed heterocycles[83,84] and other biologically interesting targets.[85–88] In the second category the work of Steckhan describes a number of interesting results. Starting from enantiopure α-hydroxy acids the methoxy amide **52** is formed by condensation with dimethyl aminomalonate, electrochemical oxidation and hydrolysis/decarboxylation. Upon heating in vacuum the morpholinediones **53** were formed.[89] The selectivity of the oxidation is illustrated in the reaction of the proline derivative **54** which affords the piperazine **55**, albeit that in the process a dimethoxy by-product of **54** is also formed (Fig. 14).[90]

The tertiary methoxylactams **57** and **59** are the oxidation

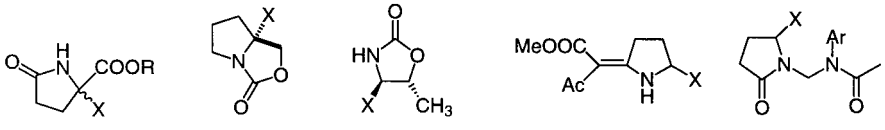


Figure 15.

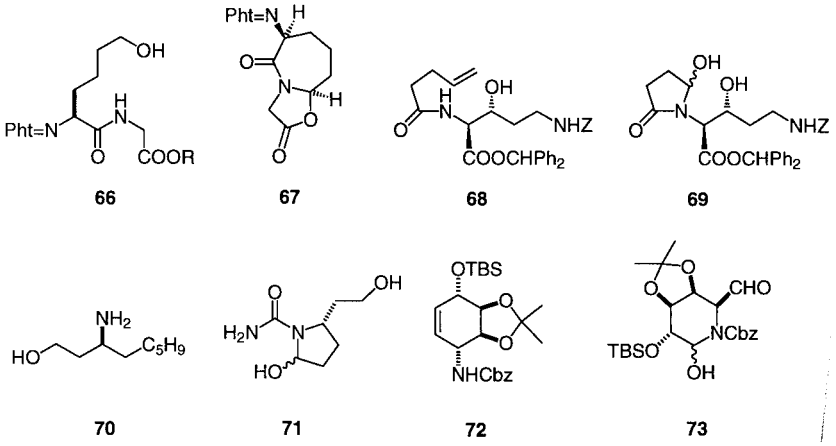


Figure 16.

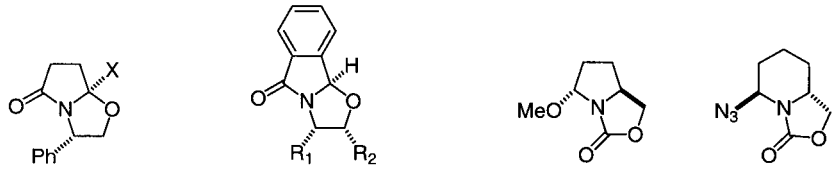


Figure 17.

products of the pyroglutamate **56** (R=menthyl)[91] and the bicyclic **58**.[55] Anodic oxidative decarboxylation of *N*-acyl amino acids offers alternative possibilities for regiocontrol as exemplified by the conversions **60→61**,[26] **62→63**[92] and **64→65**[93] (Fig. 15).

3.1.5. Ring closure of linear amides. As discussed in Section 3.1.1, linear amido aldehydes may cyclize to hydroxylactams. Enantiopure starting materials affording amido aldehydes have been reviewed in part[11] and the additional studies are now discussed. Starting from the *N*-phthaloyl amide **66** upon Swern-oxidation and reflux in TFA–$CHCl_3$ **67** was formed in a diastereomeric ratio of 93:7.[93] Similarly the γ-lactam analog of dihydroclavaminic acid **69** was obtained[94] upon oxidation—$NaIO_4$, OsO_4—of the alkene **68**.

In the synthesis of (−)-ptilomycalin A[95] the amine **70** was converted—KOCN, HCl, 70°C; O_3, MeOH −78°C—to the (*S*)-ureido aldehyde **71** while in the synthesis of azasugars[96] the hydroxylactam **73** was formed upon ozonolysis of cyclohexene **72**. Other studies relate to the use of aspartate[97] and tartrates.[59] From these few examples it will be clear that a variety of structurally different precursors are available by this technique (Fig. 16).

3.1.6. Bicyclic oxylactams. In the preceding sections some examples of this type of precursor have been discussed. For the 5,5 type, Meyers has extensively studied the chemistry of the chiral oxylactam **74a** obtained by condensation of 2-amino alcohol derivatives with γ-ketocarboxylic acids.[8] Additional examples **74b**, **75** and **76** aiming at tandem type cyclizations have been reported.[98,99] As discussed in Section 4.2.2.1, the rigid structure of oxazolidinones **77** may influence the stereochemical course of the addition of a nucleophile as compared to the open (*S*)-pyroglutamate precursor.[100,55] A further example of this effect is found in L-lysine derived **78** (Fig. 17).[101]

3.1.7. Additions to enamide and pyridinium type compounds. Cyclic *N*-acylenamines can be obtained by treatment with acid of the amine through the intermediacy of the *N*-acyliminium species or by direct electrochemical oxidation. In a few cases other methods have been used such as the Pd-catalyzed isomerisation of 3,4-dehydropiperidines,[102] the ring closure of an *N*-benzyl-*N*-tosylamide acetal[103] or the preparation of 3,6-dihydro-2H-1,3-oxazines via (4+2)-cycloaddition.[104] The possibility of oxidizing the enamide with MCPBA,[105] OsO_4-NMO,[106] DMD (dimethyldioxirane)[107] or halomethoxylation[108] allows the introduction of a new functionality at the β-C atom. An asymmetric variant using an (*S*,*S*)-salenMn(III) complex with the oxidant PhIO was also reported.[109] Some examples of this type of structure are **79**, **80** and **81**. A special subclass is formed by the addition of organometallics to chiral *N*-acylpyridinium salts[110] to afford compounds of type **82** which have recently been reviewed[111] (Fig. 18).

3.1.8. Additions to enantiopure unsaturated alkoxylactams. A special category of chiral precursors is constituted by the enelactams **83** (X=^{i}Pr). The convenient synthesis of this lactam from L-malic acid[112] could be

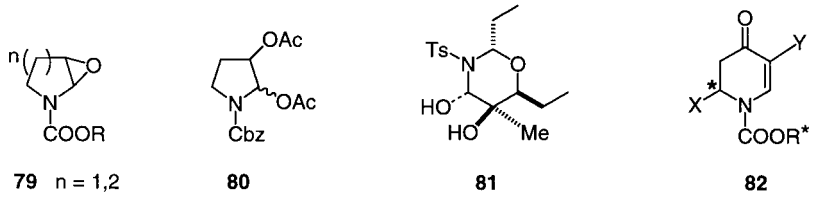


Figure 18.

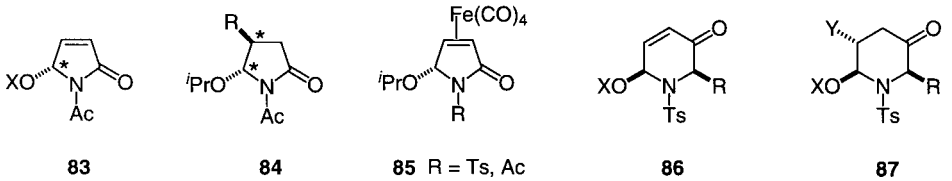
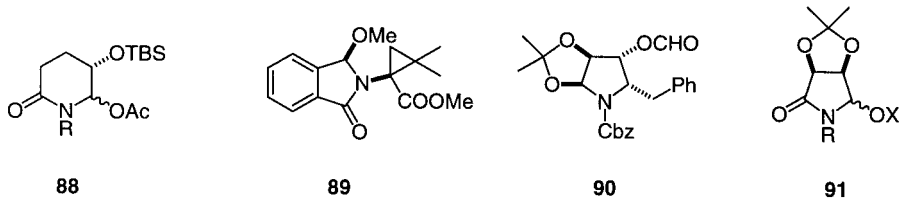


Figure 19.



88 89 90 91

Figure 20.

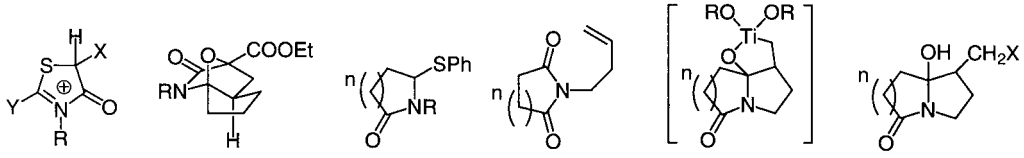
markedly improved by an enzyme-catalyzed transformation of the corresponding acetate **83** (X=Ac) allowing a facile multigram preparation.[113]

The conversion of **83** into alkoxylactams **84** offers the added possibility of preparing various chiral precursors for further applications.[114–116] The synthesis of $Fe(CO)_4$ complexes **85** is also of interest since direct stereocontrolled substitutions of the alkoxy substituent can be carried out.[117] The related chiral[118] and achiral[119] piperidinones **86** have been synthesized starting from furan derivatives. Cuprate additions provide the substituted **87** (Fig. 19).[120]

3.1.9. Sugar and amino acid type starting materials. Throughout the preceding sections a variety of chiral starting materials have been described and in this section only additional results are discussed. Recent surveys on some compound classes are available. The conversion of carbohydrates into azasugars by the useful hydride reductions of *N*-acyliminium type intermediates has been reported.[121] A review of recent applications of amino acid α-cation equivalents has also appeared.[12] The following examples are only indicative of the diversity of potential applications. L-glutamic acid has been used as the chiral source[122] to prepare the homolog malic acid lactam **88** while (*S*)-leucine[123] was transformed into **89** as a (*S*)-2,3-methanovaline precursor. Some examples in the carbohydrate field are the D-mannose derived **90**[124] and the D-ribose intermediate **91**.[125] Other references include the use of a pyranose in the synthesis of (−)-antirhine[126] and D-fructose in a synthesis of an aza-analog of (+)-hydantocidine (Fig. 20).[127]

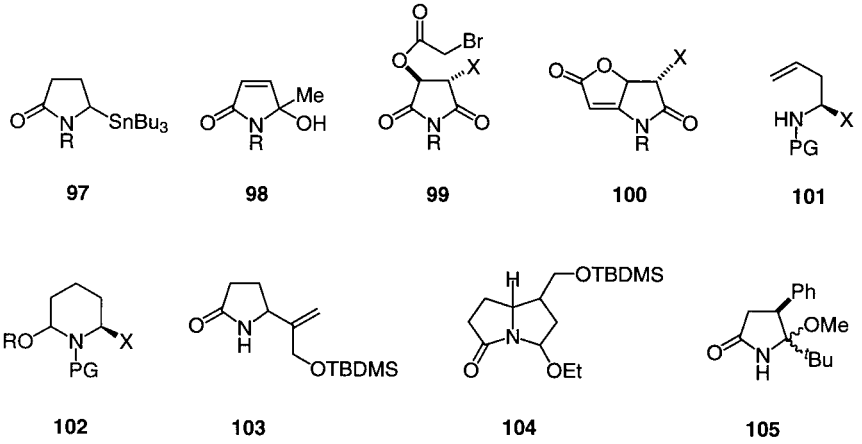
3.1.10. Other methods. Several new types of precursors have been developed which constitute interesting routes to the *N*-acyliminium species although their synthetic utility may vary considerably. Examples of a subclass comprising sulfur-containing derivatives have been studied by Padwa.[128] Thioamides react with bromoacetyl chloride to generate thio-*N*-acyliminium ions **92** which may cyclize in an intramolecular fashion onto a tethered (aromatic) nucleophile.

The bridged oxylactam **93** can be obtained by Rh(II)-catalyzed cyclization of diazo-imides.[129] Making use of a silicon Pummerer reaction amide sulfoxides are converted



92 93 94 95 95a R = ^{i}Pr 96a X = H b X = OH

Figure 21.



97 98 99 100 101

102 103 104 105

Figure 22.

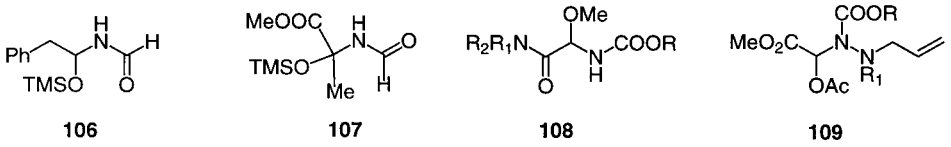


Figure 23.

to thio substituted lactams **94**.[130] A useful reaction to obtain tertiary hydroxylactams is the organotitanium-induced cyclization of alkenylimides **95** to intermediate **95a** which can be hydrolyzed to **96a** or oxidized to **96b** (Fig. 21).[131]

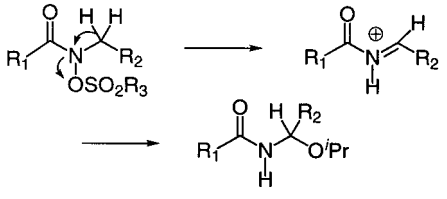
A sulfone leaving group may be advantageous in terms of purification of the crystalline lactam as discussed in Section 3.1.1.1 and in some additions of organometallics.[67] Organostannanes have been studied as linear[132] or cyclic forms **97**.[133] By electrochemical or chemical oxidation—CAN—it is possible to generate the *N*-acyliminium intermediate thus allowing reactions under neutral conditions. A different method, albeit of less practical value, is the photolactamization[134] of γ-keto-α, β-unsaturated amides to 5-hydroxypyrrolin-2-ones **98**. The conversion of malic (X=H) or tartaric (X=OTBS) imide **99** into the enamide **100** by an intramolecular Wittig reaction generates a tertiary precursor.[135] A different method has its origin in the catalytic hydroformylation of olefins. Ojima has studied the (regioselective) cyclohydrocarbonylation of amides **101** (X=COOR) which under influence of $Rh(acac)(CO)_2$ (1.0 mol%) in presence of BIPHEPHOS (2.0 mol%) and $CO–H_2$ (1/1; 4 atm; 65°C) are converted to oxylactams **102** in good yield.[136]

Depending on the solvent the corresponding enamide could also be obtained. Furthermore the stereocentre in **101** was not affected. Under slightly different conditions the bicyclic lactam **104** was formed from the lactam **103**[137] while it proved equally possible to selectively formylate[138] the corresponding bisallyl systems **101** ($X=CH_2CH=CH_2$) to the cyclized form **102** ($X=CH_2CH_2CH_2CHO$). Nonsymmetrical amidodienes **101** ($X=CH=CH_2$) also reacted regioselectively to form the piperidine derivatives. Of added interest is the (4+1) cycloaddition of 3-TMSO-2-aza-1,3-butadienes with certain types of Fischer carbene complexes leading to a mixture of tertiary oxylactams **105** (Fig. 22).[139]

3.2. Linear precursors

Since the early development of the amidoalkylation reaction the majority of applications has been of the linear type. Although in nearly all cases the precursor could not be isolated due to the highly acidic medium the outcome of the reactions is fully consistent with the in situ formation of the *N*-acyliminium species.[140] The rapid advancement of methods to obtain the cyclic precursor in a pure form has also stimulated work on the acyclic variant. Indirect methods such as the acid halide addition to imines,[32,141] the use of stable biscarbamates[142,143] and the reduction of imidates[144] has been known for some time while the acid-catalyzed addition of an aldehyde to a carbamate directly generates the cation.[145] By a related process it is also possible to obtain *N*-(alkoxyalkyl)formamides upon TMSOTf-catalyzed addition of bis(TMS)formamide (BSF) to aldehydes as exemplified by the formation of crystalline **106** from phenylacetaldehyde and BSF. Other examples include *N*-acetyl, *N*-methyl and *N*-hydroxy variants.[146] Upon using the reactive pyruvate the precursor **107** for the synthesis of α-substituted α-amino acids can be obtained.[147] The carboxamides **108** have also been prepared by conventional methods[37] while peptide analogs can be obtained from $Pb(OAc)_4$ oxidation of the corresponding L-serine derivative.[148] A recent account of α-cation equivalents of amino acids covers the extensive developments in this field.[12] A further example of this type of stable aldehyde amide precursor suitable for synthesizing hydrazine type analogs is represented by **109** (Fig. 23).[149]

Newer methods to exploit the synthetic possibilities of the linear *N*-acyliminium form include the role of the benzotriazole moiety as a leaving group[150] and the use of *N*-triflyloxyamides. Upon heating in 2-propanol the latter compounds are transformed into the linear isopropoxyamides **110** according to Eq. (1) in which process the intermediate can also be directly trapped with an allylsilane.[151]



(1)

Direct reduction with DIBAL-H of acylcarbamates affords the linear hemiaminals **111** as quite stable compounds which can be subsequently cyclized onto the aromatic nucleophile.[152] A remarkable DABCO-catalyzed addition

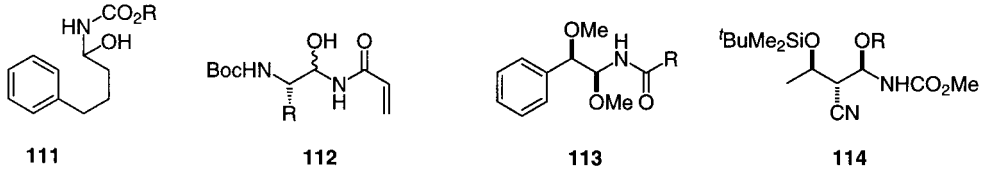


Figure 24.

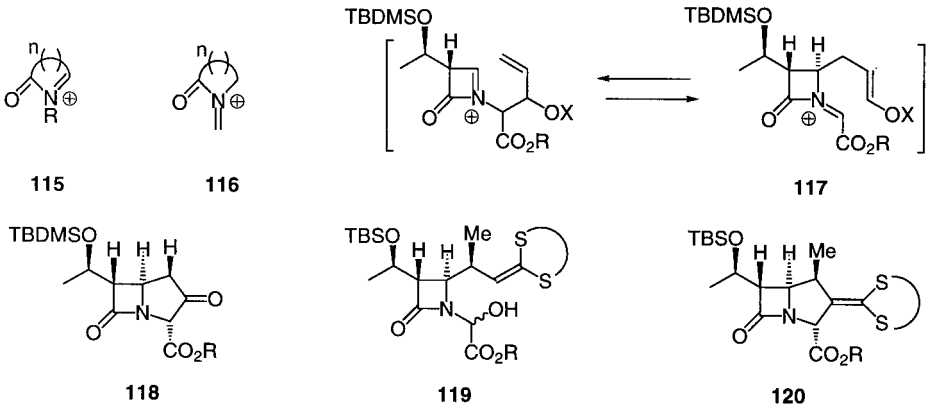


Figure 25.

of α-aminoaldehydes onto acrylamide affords the stable hemiaminals **112** which is the opposite of the usual instability of this type of hydroxyamide and may be explained by an extra stabilization through an intramolecular hydrogen bonding network.[153] Other methods to obtain linear precursors are the $(PhO)_2PON_3$ conversion of suitable α-OMe carboxylic acids the in presence of TMS–ethanol to afford the Teoc amide which subsequently can be converted to the amide **113** via acylation and deprotection[154] and the unprecedented cleavage of the β-lactam ring leading to chiral β-amido cyanides **114** (Fig. 24).[155]

It should be emphasized that several in situ reactions have also been reported in which the linear reactive intermediate is generated by acid-catalyzed coupling of formaldehydes and amides.[156–158]

4. Carbon–Carbon Bond Formation of Cyclic *N*-Acyliminium Intermediates

4.1. Intramolecular C–C bond formation

The synthesis of fused ring systems starting from a cyclic *N*-acyliminium precursor is discussed in this section. Both endocyclic **115** as well as exocyclic **116** variants will be described, the ring size of the starting precursor being the sole criterion for classification of the sections. The type of nucleophile, size of the ring to be formed and positional attachment of the tether are also discussed here.

4.1.1. 4,n Type. Studies in the β-lactam field related to this topic are the assemblies of 4,5 and 4,6 systems. The carbapenem **118** has been obtained[159] by an aza-Cope Mannich cyclization of the intermediate **117**—generated from the chloride upon $AgBF_4$ elimination—while the system **120** can be constructed[160] by the thermal mesylate-acetonitrile ring closure of the thioacetal **119** (Fig. 25). The latter precursor is made by addition of the glyoxylate to the NH-lactam which is also a method to form the 4,6 system. Starting from an azetidinone[161,162] or an optically active form,[163,164] carbacephems are obtained upon treatment with Lewis acid. The length of the nucleophile containing chain requires activation as the enol derivative **121** to give **122**. The methyl alkyne **123a** can be cyclized to **124** in a 6-*exo* process. The 7-*endo* form **125** is the product upon starting from the silyl derivative **123b**. The more difficult formation of the reactive intermediate requires the use of moderately strong Lewis acids of the SnX_4 type and elevated temperature (0°C). The latter type reactions are also carried out in an asymmetric fashion in a synthesis of Loracarbef (Fig. 26).[163]

4.1.2. 5,n Type. Since the introduction of the *N*-acyliminium method as a versatile synthetic tool the succinimide derivatives have prominently figured in the field of

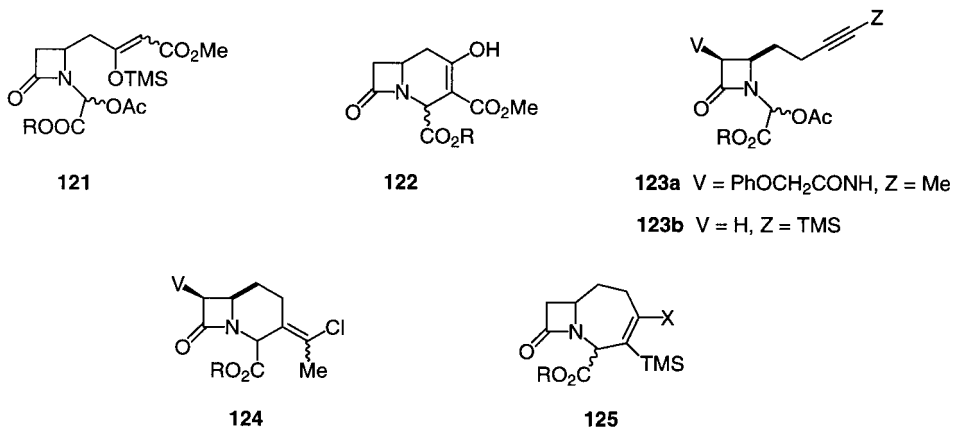


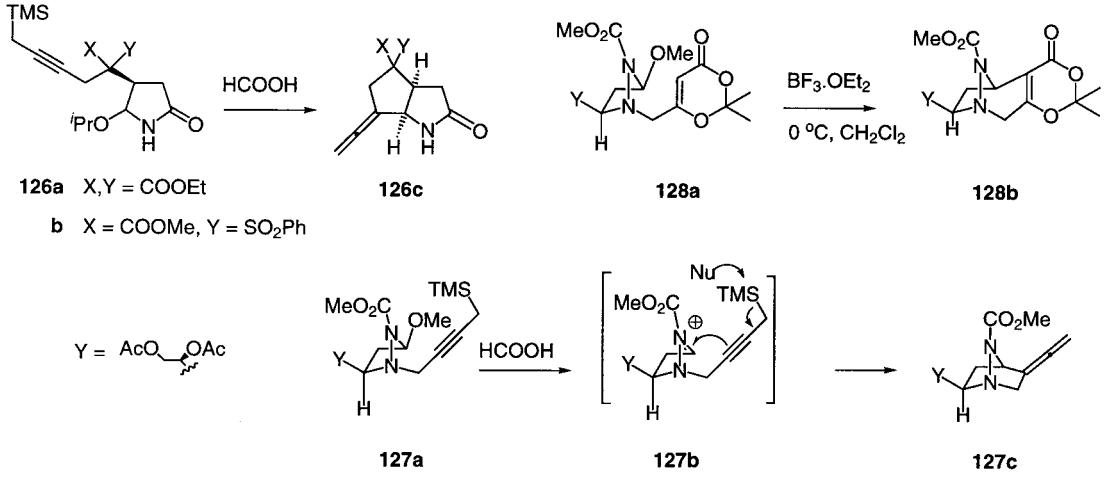
Figure 26.

Table 1.

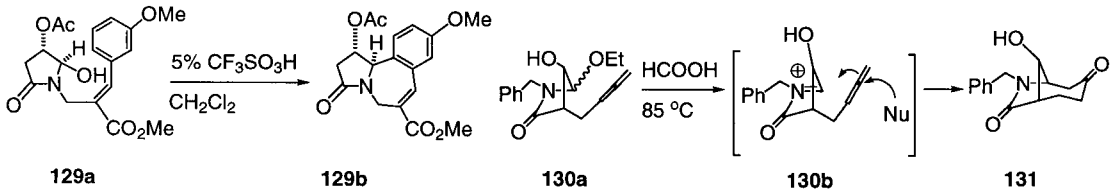
Entry	1	2	3	4	Reference
1	ArN-5, N-5	5, (6)	C≡CBr	HF or TFA	165
2	ArN-5, ArN-5 (t)	5, (6)	Thiophene	$TiCl_4$ or TFA	166
3	N-5* [N]	5, (6)	C=CMe_2	HCOOH	47
4	5* [N,N] {2,5}	5	C≡CH_2TMS	HCOOH	47
5	5* spiro	5, (6)	C=CR	HCOOH	69
6	5* spiro	5, (6)	Ph	TFA	68
7	N-5 [N] exo	5	C=CMe_2	HCOOH	167
8	N-5	5 [N]	C=CCH_2TMS	BF_3OEt_2	168
9	5 spiro	5	C=CCH_2TMS	Et_3N–MsCl	72
10	N-5*	6	Ph	$TiCl_4$	115
11	N-5*	6 (S)	Ph	$TiCl_4$	114
12	5 [N,N] {2,5}	6	C=CH_2	$TiCl_4$	30
13	N-5 (t)	6	Ar	TFA	72
14	N-5	6	C=CBr	BF_3–AcOH	130
15	ArN-5	6 [N], (7[N])	Ar	TFA	169
16	ArN-5	6*	Ph	TMSOTf	99b
17	N-5	6	Imidazole	HCOOH	170
18	N-5, N-5 [O]	6	Cyclohexene*	HCOOH, BF_3	171
19	N-5* (t)	6	Ar	TsOH	135
20	N-5*	6	Ph	BF_3OEt_2	172
21	N-5 (t)	6	Ph	TFA	34
22	N-5 (t) [S]	6	Ar	$BrCH_2COCl$	128
23	N-5	6 [N]	Ph	$SnCl_4$	93
24	N-5*	6	C=CTMS	BF_3OEt_2	45
25	ArN-5, N-5	6	Pyridine	TsOH	173
26	N-5 (t)	6, (7)	2-OTMS-furan	$LiClO_4$–Et_2O	35
27	5* [N,N] {2,5}	6	See text	See text	174
28	N-5*	6, (7)	$(CH_3)C$–C=CH_2	$TiCl_4$	175
29	N-5*	6, (7)	HC–C=CH_2	$TiCl_4$	176
30	N-5*	6	Cyclohexene	$TiCl_4$	177
31	5 {2,5}	7	Enone	HCl	60
32	5 {2,5}	7	Enone	HCl	178
33	5* {3,5}	7	Allene	HCOOH	179
34	ArN-5	7	Ph	TFA	180
35	N-5*	7	Ar	CF_3SO_3H	181
36	N-5	7	C=CH_2	$TiCl_4$	48

intramolecular applications. In this section the recent results will be summarized in tabular form with the exception of a few selected examples incorporating some novel features. The synthesis of natural targets and other molecules of biological interest will be discussed in Section 6.

The following notation and symbols are used in Table 1. For the starting hydroxylactams in the first column (**1**) the terms ArN-5 or N-5 used are derived from phthalimide or succinimide, respectively. The position of the tether is represented by N if connected to nitrogen, by atom numbers within { } forming a bridged bicycle or indicated otherwise. A tertiary precursor is symbolized by a (t) while the presence of chiral elements is indicated by an asterisk (*). A number in the second column (**2**) corresponds to the size of the ring formed and the eventual presence of heteroatoms in the ring or chain in columns **1** and **2** is marked by the symbol [ ]. The type of nucleophile and acid used are given



Scheme 1.



Scheme 2.

in columns **3** and **4**. Thus the combination N-5*[O], 6[N], Ph in columns **1**, **2** and **3** would indicate the cyclization of a chiral heterocyclic precursor onto a phenyl nucleophile forming a six-membered ring containing a nitrogen atom.

From the table it follows that half of the examples include the presence of chiral elements mostly in the starting alkoxylactam. Since the formation of 5,5 and 5,7 bicycles is less common a few additional comments will be given. A recent example (Scheme 1) is the conversion of **126a**,**b** into **126c** by treatment with formic acid.[182]

The 5,5 bicyclic hydrazines can be obtained by making use of a stabilizing terminating nucleophile such as the *gem*-dimethylalkene (entries 3 and 7) or a silylalkene. The propargylsilane nucleophile allows access to the bridged bicyclic form (entry 4). In the latter reaction an exchange of the acetal **30** (Section 3.1.1) into the diacetoxy form **127a** is a prerequisite to carry out the acid-catalyzed cyclization through **127b** to the allene **127c**. A similar strategy has been followed (Scheme 1) in the aza-tropane series to cyclize the dioxinone **128a** to the bridged **128b** (entry 27).

The 5,7 tricyclic system **129b** can be obtained (Scheme 2) from the corresponding malic acid precursor **129a** (entry 35) while the gelsedine fragment **131** is smoothly formed upon ring closure of the allene **130a** via the intermediate **130b** (entry 33).

The 5,7 bicycle **133a** is the product upon cyclization of the alkene **132** (entry 29) when R=H. For R=Me (entry 28) only the 5,6 system **133b** is obtained due to an alkyl shift in the initially formed cation, which is also the case in the disubstituted series (entry 30, cf. Scheme 25). An application enforcing a necessary (*Z*)-conformation onto the reacting *N*-acyliminium ion is the cyclization of an oxazole derivative. Whereas the linear glycine cation **134a** does not form the bicyclo[3.3.1] system presumably due to an unfavorable *E*-type transition state the cyclic **134b** now locked into the *Z*-form leads to the desired ring closure (Fig. 27).[183]

Upon use of furan as a nucleophile[184] two types of cyclizations are possible, i.e. the 3-to-2 mode **135a→135b** and the 2-to-3 mode **136a→136b** of which the former is electronically favored. Thus while in the former for m=2, a 5,7 or 6,7 bicylic system is obtained, this ring closure fails for **136a** (m=2) (Fig. 28).

A 5,6 spirocyclic variant corresponding to the Erythrinane skeleton has been obtained by the application of the already discussed Pummerer reaction (cf Section 3.1.10) to generate the intermediate cation.[185]

4.1.3. 6,n Type. The reactive intermediate has been generated both directly from reduced glutarimide–allylsilane cyclic substrates[186] and indirectly from linear precursors to afford 6,6 and 6,7 bicyclics. Examples of the linear type are found in the work leading to the synthesis of Aspidosperma alkaloids[187] and in the synthesis of peptidomimetics.[188] In the latter study the enamide **137** (n=2) generated from protected allylglycine, gave upon successive treatment with trifluoromethanesulfonic acid, diazomethane and sodium iodide 59% of the iodide **138** accompanied by

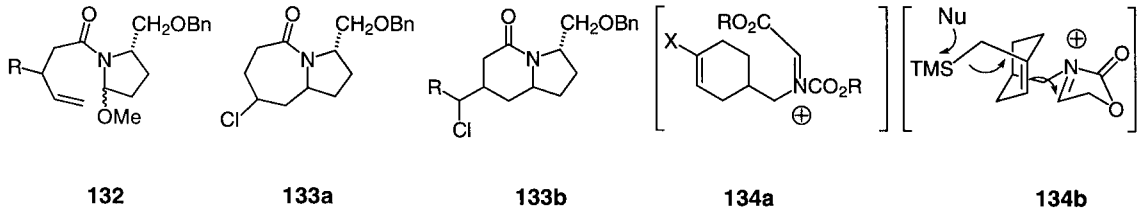


Figure 27.

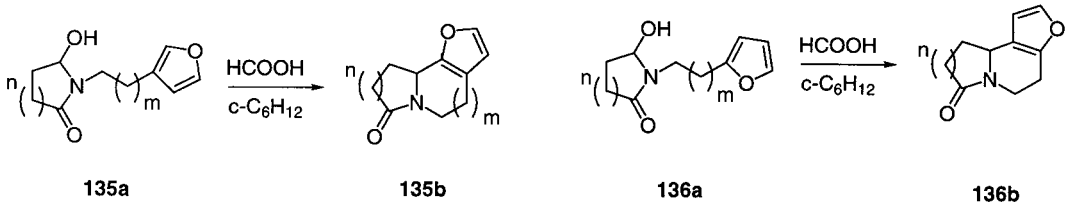
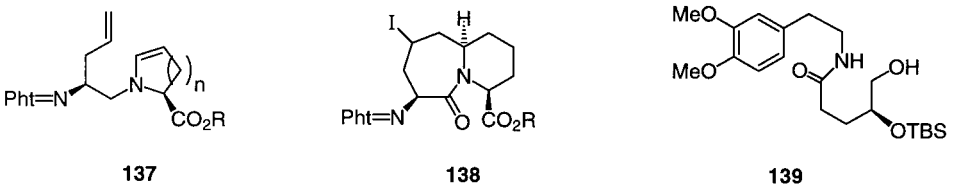
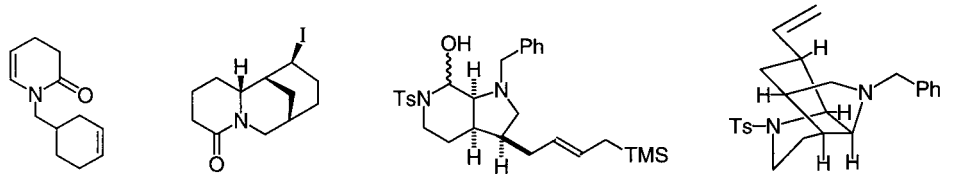


Figure 28.



137 138 139

Figure 29.



140 141 142 143

Figure 30.

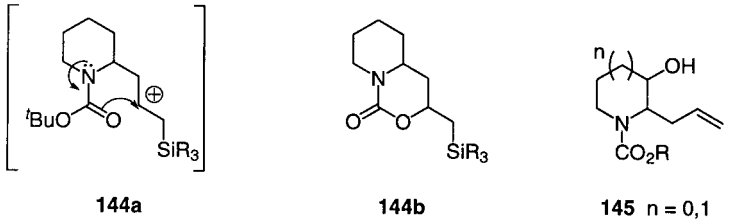
14% of elimination products. In a similar way starting from **137** (n=1) the 5,7 system was prepared. From L-glutamic acid the linear amide **139** was obtained which after pyridine–SO_3 oxidation and acetoxylation could be cyclized with $BF_3{\cdot}OEt_2$ (Fig. 29).[122]

In the 6,6 bicyclo[3.3.1.]nonane precursor **140** the high regioselectivity in the formation of the iodide **141** was noted upon use of the Overman conditions[189] for preventing the competitive 1,2 hydride migration in the intermediate cation. The synthesis of the condensed 6,6 bicycloderivative **143** shows the remarkable potential of the *N*-tosyliminium species since other N-protecting groups do not lead to cyclization. On the other hand the delicate balance between the types of nucleophile in the precursor **142** is also to be noted only the use of the allylsilane leading to the desired product.[62] Attempts to use the corresponding silylenolether in situ have remained unsuccessful.[190] Lastly a 6,6 system has been obtained via a bromoalkyne (–C≡CBr) ring closure (Fig. 30).[165]

4.2. Intermolecular C–C bond formation

As already indicated in Section 2.4 the last decade has witnessed substantial progress in expanding the synthetic usefulness and stereocontrol of the intermolecular *N*-acyliminium variant. Both with respect to the types of precursors and activated nucleophiles (i.e. organometallics) as well as the experimental conditions, a large number of new studies have been published. Chiral applications will be discussed in Sections 4.2.1 and 4.2.2. In this introductory part a non-exhaustive list of references is given dealing with newer achiral results in this field in which a cyclic precursor is coupled with the following nucleophiles using the indicated Lewis acid. 3-Trimethylsilylpropene-1, here abbreviated as allylTMS, in combination with $TiCl_4$ has been used frequently[78,191] with newer results dealing with tertiary precursors.[91,192,193] Of interest is the observation of a reaction path in the initial adduct **144a** leading to complete formation of the bicyclic **144b** instead of the allylated piperidine upon use of the bulky allyltri-*i*-propylsilane (R=^{i}Pr) (Fig. 31).[194]

Use of 1-TMS-2,4-pentadiene/$BF_3{\cdot}OEt_2$ allows the introduction of the diene substituent.[195] The reaction of allylTMS with an epoxidized enecarbamate—e.g. **79** in Section 3.1.7—leads to mixtures of *syn*- and *anti*-diastereomers **145** the ratio of which is slightly dependent on the type of Lewis acid.[107] Propargylsilane/$TiCl_4$[196] gives rise to a [3+2] annulation, the latter condensation type also being observed with the tandem reagent 2-chloromethyl-3-TMS-propene/$TiCl_4$.[197] 1-Propynyltributylstannane/$BF_3{\cdot}OEt_2$[198] and propadienyltributylstannane/$BF_3{\cdot}OEt_2$[199] have been used to introduce acetylene and allene substituents. A vinyl group has been attached by reaction with lithium divinylcuprate/$BF_3{\cdot}OEt_2$.[200] 3-TMSO-2-butenoate/TMSOTf with 5-ethoxy-pyrrolid-2-one leads to introduction of the β-ketoester[201] while *N*-Boc-2-OEt-piperidine reacts with 2-TMSO-butadienes/TMSOTf in a tandem addition of the Michael type to quinolizidines **146**.[202] 2-TMSO-furan/$BF_3{\cdot}OEt_2$ at −78°C has been used in several chiral applications (cf. Section 4.2.2.3). Upon condensing *N*-Boc-2-OEt-pyrrolidine under



144a 144b 145 n = 0,1

Figure 31.

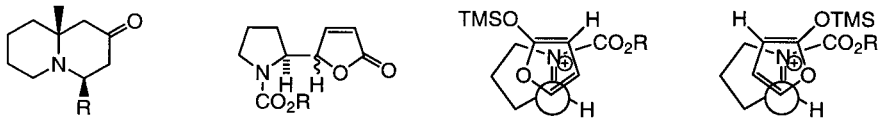


Figure 32.

these conditions a 5/1 mixture of *threo*- and *erythro*-isomers **147a** and **147b** was obtained thus presumably favoring a TS of the type **148a** over the alternative **148b** (Fig. 32).[203,204]

4.2.1. Auxiliary control. Some results of the foregoing introduction can be extended in an asymmetric mode by simply attaching a chiral auxiliary onto the reacting system (cf. Section 2.4). In a study by Polniaszek[205] it was found that (*E*)- or (*Z*)-crotylsilanes upon $SnCl_4$ reaction with **149**, X=OH gave mixtures of all four diastereomers, the ratio of which was markedly dependent upon the type of Ar-substituent. For Ar=Ph and (*E*)-crotyl-TMS the 5*S*,6*R* *syn*-isomer **150a** proved to be the major product. Of added interest was the observation that $ZnBr_2$ reaction of the hard allylMgBr nucleophile with the lactam **149**, X=OTs, Ar=2,6-diClphenyl, gave a complete change in stereocontrol producing mainly the C-5 diastereomer of **150b** in a 95:5 ratio. The TMSOTf catalyzed reaction of (alkylthio)allyl silyl ethers as studied by Kuwajima[39] complemented these findings, the 5*S*,6*S* isomer **151a** being formed in 84:16 ratio as the major product upon reaction of **149**, X=OBz, Ar=Ph. A remarkable reversal of stereochemistry occurs upon exchange of the methyl group for a OMe substituent in **152**, X=OBz (cf. **27** in Section 2.4). Now the 5*R*,6*R* isomer **151b** is obtained with 95:5 diastereoselectivity. This effect may be due to a reversal in face-differentiation resulting from a dipole attraction between oxygen and cationic site in **153** (Fig. 33).

Similar effects are also observed depending upon the type of Lewis acid catalyst. Whereas $BF_3{\cdot}OEt_2$, TMSOTf and $TiCl_4$ in the reaction of **152**, X=OAc (cf. **25** in Section 2.4) with allylTMS favor the formation of the 5*S* isomer **154**, the use of $SnCl_4$ completely reverses this ratio and the 5*R* diastereomer is the main product.[38] An adequate explanation for this exceptional behavior has not been given albeit it is likely that some type of tin-complexation disrupts the stabilizing dipole effect in **153**. The influence of the size of the Ar moiety is also demonstrated[206] in the addition of pentadienylTMS to **149**, X=OMe. Higher (4:1) selectivity is observed for Ar=naphthyl as compared to Ar=Ph (3:1). A different type of auxiliary is the chiral hydrazine of type **155**. Interestingly in the C_2 symmetrical series **155** (X=R) the observed stereoselection is not as high as in the mono-substituted **155** (X=H) series. Furthermore in the six-membered lactams **156** (*n*=2, Nu=–CH=CH_2 or COAr) the *syn*-selectivity is almost complete irrespective of the size of R and the eventual presence of oxygen atoms in R. Nucleophiles used are allylTMS and TMS enol ethers with $BF_3{\cdot}OEt_2$ as Lewis acid and give comparable degrees of induction. The observed *syn*-selectivity is rationalized favouring the intermediate ion **157** for the six-membered form (Fig. 34).[31]

Of continuing interest are the results obtained by Wanner in the piperidine[102] and quinoline[207] series possessing a chiral bulky *N*-acyl substituent based on (+)-camphoric acid. With nucleophiles such as $ZnEt_2$, $AlEt_3$ and RMgBr selectivities of >90:10 can be obtained.

The $Fe(CO)_4$ moiety as a non-chiral auxiliary has already been mentioned (cf. Section 3.1.8) in compounds **85** (R=Ac).[208] Such types of unsaturated *N*-acyl-oxylactams undergo substitution with a variety of nucleophiles including

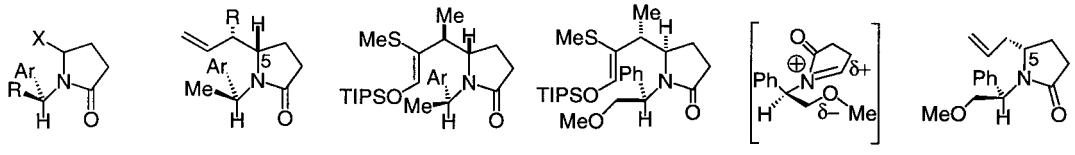


Figure 33.

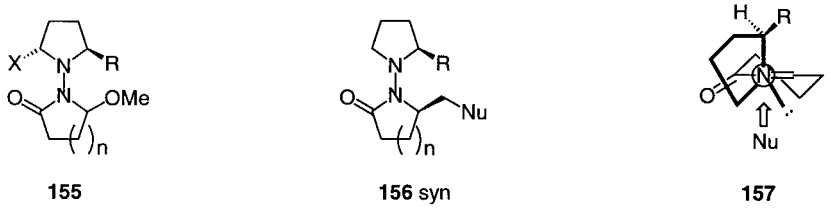


Figure 34.

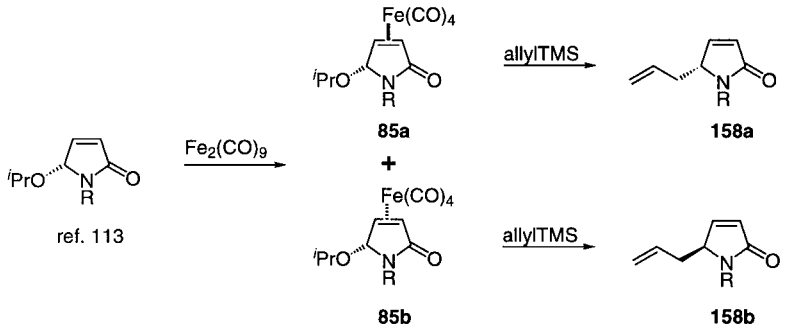


Figure 35.

allylTMS/BF_3·OEt_2 with retention and ee >95% for the *trans*-isomer **85a→158a** and inversion for the *cis*-isomer **85b→158b** (Fig. 35).

The results have been explained on the basis of a chiral π-allyliron complex as an intermediate. Remarkably, change of the N-substituent not only favored the formation of the *cis* **85b** (R=Ts) complex but also controlled the allylation to the enantiopure (*S*)-**158b** (R=Ts) in 88% yield.[117]

4.2.2. Inherent stereocontrol. Since the majority of intermolecular applications deal with (chiral) substituted precursors a number of studies have been aimed at the optimization of the factors determining the stereocontrol. Rather than separately discussing various types of combinations the reactions are grouped around the type of nucleophile and common trends if present will be signaled.

4.2.2.1. Alkenyl silanes and stannanes. Allylsilanes and related metallo-unsaturated derivatives constitute a principal subclass of this type of nucleophile. As a cheap chiral source pyroglutamic acid has been frequently used. Highest *cis*-selectivity has been found in the $TiCl_4$/allylTMS reaction to **159** for Y=COOMe, Z=COO^{t}Bu (or Z=CO^{t}Bu). Interestingly in the case where Y and Z are connected as in **160** (*n*=1, R=allyl) high *trans*-selectivity is observed, cf. Section 3.1.6.[209] These observations have been confirmed and extended by Lhommet[55,210] for a series of other nucleophiles and also for the piperidine **160** (*n*=2, R=allyl). For TMSCN as a nucleophile a generally lower selectivity is observed, the cyanide **160** (*n*=1, R=CN) being formed in a *trans/cis* ratio of 70:30. Again in the piperidine **160** (*n*=2, R=CN) virtually complete *trans* stereocontrol is found. For the open analog a high preference for the *trans* product **161** (X=H,[56] X=TBS[51] or X=Bn[57]) has also been established albeit with lower control (*trans/cis* ca. 2:1). That the ester group in a pyroglutamate is mainly *cis*-directing is also found in the corresponding (4*S*)OAc-proline[87] which upon allylation again favors the *cis*-product. Change of the nucleophile to allyltributyltin leads also to *cis/trans*

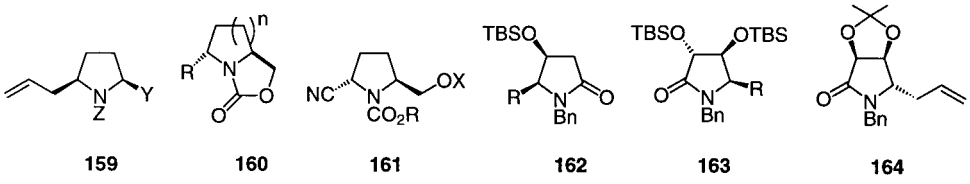


Figure 36.

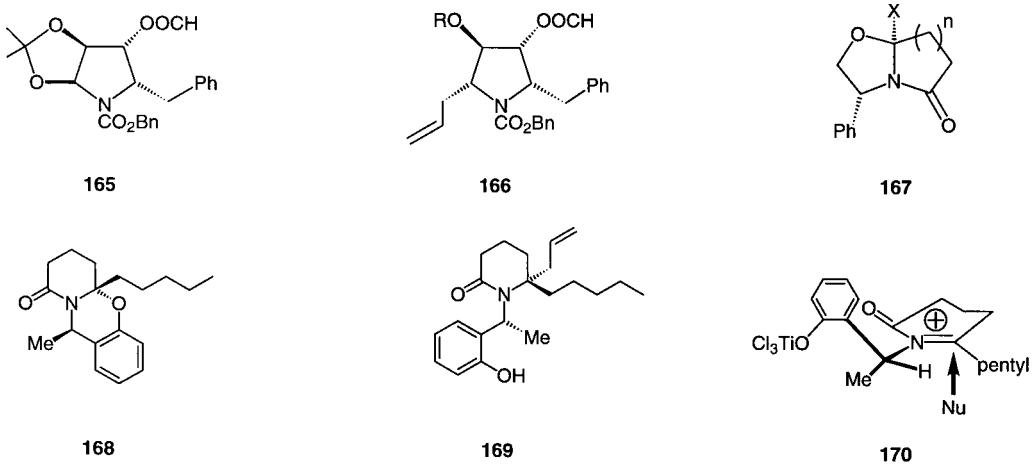


Figure 37.

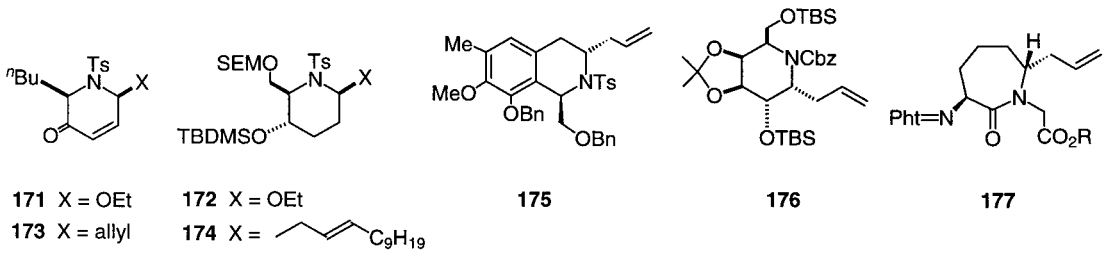


Figure 38.

mixtures favoring the *cis* product.[53] Highly selective C4–C5 *cis* addition to iminium ions derived from *S*-malic acid[25] and L-tartaric acid[46,70] of allylTMS, allyltin, propargyltin and allenyltin nucleophiles in CH_2Cl_2 or toluene with $MgBr_2$ as a catalyst are also reported. Thus good yields of **162** and **163** (R=allyl, propargyl and allenyl) are found (Fig. 36).

These results are in marked contrast to the observations[125] on the addition of allylTMS/BF_3·OEt_2 to a cyclic acetal which due to preferred approach from the convex side solely affords *trans*-**164**. A similar C4–C5 *trans* selectivity was observed in the allylation of the acetal **165** which gave a 62% yield of **166** (DS >95:5). Here the bulky acetal–BF_3 complex may provide enough steric barrier to change the usual *cis*-addition.[124]

Intermolecular additions of allylTMS/$TiCl_4$ to tertiary precursors **167** (*n*=1, X=Me) have been studied extensively by Meyers[211] and are highly sensitive to the size of the substituent on nitrogen in regard to the bulky alkoxy-titanium intermediate complex. A further example is the synthesis of (−)-adalinine as described by Kibayashi.[212] While the pentyl substituted **167** (*n*=2, X=pentyl) did not react, the phenoxy derivative **168** underwent clean allylation to a 16:1 *R*/*S* mixture of diastereomers **169** upon warming in a sealed tube at 50°C. It is assumed that the reaction proceeds through the TS **170** favoring the formation of the *R*-isomer (Fig. 37).

In the piperidine series also a few studies deal with the stereocontrol at the cationic site. Piperidones **171** (cf. **86** Section 3.1.8)[119] and **172**[118,213]—only one ethoxy isomer given—react with alkenylsilanes to afford exclusively the *cis*-2,6-disubstituted products **173** and **174** as the result of a preferred axial attack of the silane. Remarkably, upon a relatively small change of the substitution pattern such as in the isoquinoline **175**[103] or the fully substituted **176**[96] derived from **73** (cf. Section 3.1.5) only *trans*-addition is observed. Again steric approach control may be involved allowing addition from the convex side. In the azepine series[93] the high selectivity and yield (95%) in the formation of **177** from the bicyclic precursor **67** (Section 3.1.5) should be noted (Fig. 38).

With heterocyclic precursors a high selectivity is also observed. The imidazoline **178**[28] undergoes exclusive *cis*-addition of allylTMS/$ZnBr_2$ to **179** which again relates to the conformational factors described before. A quantitative study of these and other effects has been described by Seebach.[214] In the oxazolidin-2-one series a high selectivity is also encountered in the allylation to the *trans*-product **180**.[215,216]

The cationic glycine equivalents in the morpholine[89] and piperazine[90] series undergo *anti*-1,4 addition to **181** (selectivity 86.5:13.5) and **182** (>99% *anti*) upon allylTMS/$TiCl_4$ reaction. A rather uncommon *anti*-1,4 addition is the allylTMS/BF_3·OEt_2 catalyzed addition to a

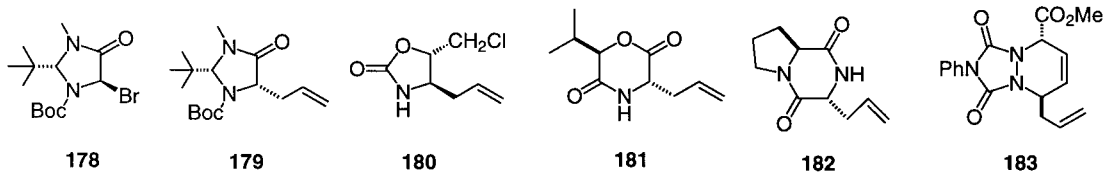


Figure 39.

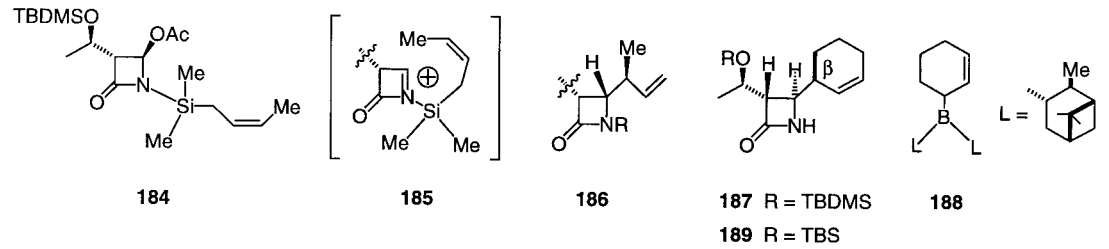
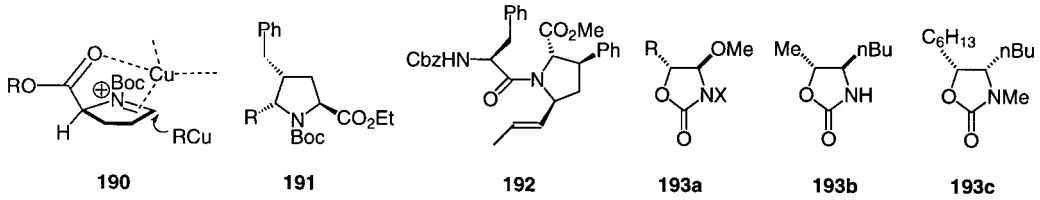


Figure 40.



190 191 192 193a 193b 193c

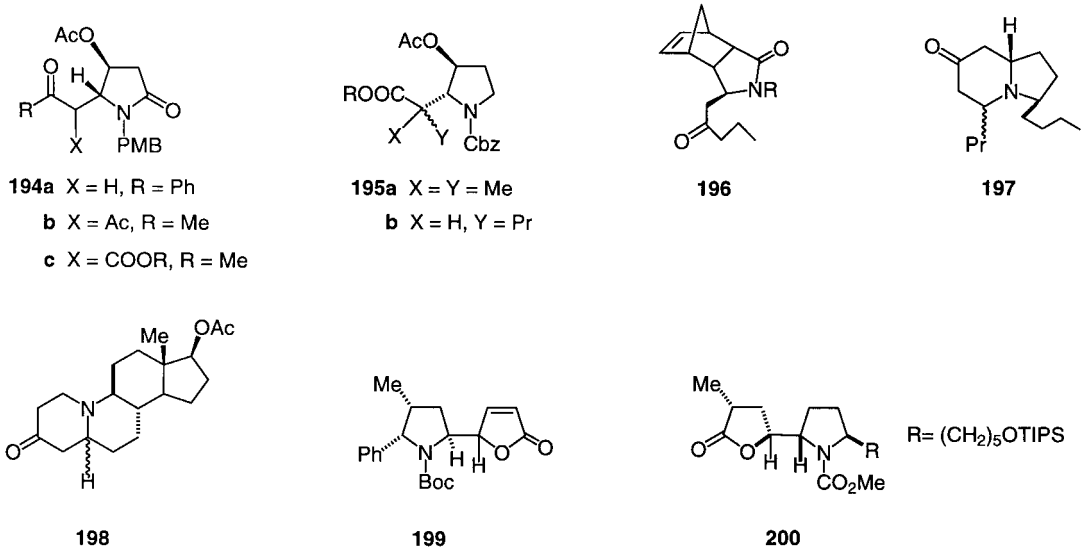
Figure 41.

chiral hydrazine bicyclic system[217] producing the allylated **183** (Fig. 39).

By a Sakurai-type process a β-lactam precursor[218] reacts with a chlorosilane to the N–Si intermediate **184** which upon treatment with TMSOTf undergoes an intramolecular substitution/rearrangement via **185** to afford in a stereocontrolled way the carbapenem precursor **186**. In the same manner the cyclohexenyl N–Si analog gave rise to the predominant formation of the desired β-epimer **187**[219a] obtained in a 4:1 β/α ratio in 50% yield upon TMSOTf treatment in MeCN at 0°C. In a related type of reaction in which a chiral allylic borane **188** was condensed with the azetidinone it was possible to obtain a 95:5 β/α ratio in 95% yield upon use of the mild Lewis acid Et_2Zn. The preferred formation of the β-isomer **189** is proposed to proceed by a 'closed' TS in which the boron atom coordinates with the imine nitrogen (Fig. 40).[219b]

4.2.2.2. Organocuprates. In contrast to the previously discussed *cis*-addition in pyroglutamate type precursors the organocopper nucleophiles favor a high *trans*-selectivity.[220] This reversal of stereocontrol is explained on the basis of an RCu-complex **190** effectively shielding one face of the molecule. Even in the presence of a relatively large benzyl substituent at C-3 almost exclusively *trans*-product **191** (R=Bu, Ph) is formed.[52] The cuprate is usually generated from the corresponding RMgBr or RLi reagent and the substitution occurs under Lewis acid—$BF_3{\cdot}OEt_2$—catalysis. Among the various applications, methylations of pyrrolidines,[86,221] butylation of a pipecolate,[136] hexenylation of a L-proline precursor[178] and introduction of a (*Z*)-Me-vinyl moiety[82] are recorded. In a related example[55] high *trans*-selectivity in the synthesis of **192** again illustrates the dominant influence of the Cu-ester complex vs. the hindrance of a 4-Ph substituent in determining the outcome of the substitution. In a few studies it was found beneficial to introduce a different leaving group, e.g. a SPh,[222] a SO_2Ph[67] or a SO_2Tol moiety.[191] In the latter substitutions it proved also possible to use the RMgBr reagent itself, albeit with lesser yields. Of mechanistic interest are the results obtained with the oxazolidinone **193a**. For X=H clean *trans* introduction to **193b** ($Bu_3Cu_2Li/BF_3{\cdot}OEt_2$) was observed and a series of structurally different alkyl and aryl cuprates gave similar results as established by Kunieda[223] and also by Steckhan.[26] On the contrary as reported by Yamamoto[27] for **193a** X=Me the *cis*-product **193c** was formed and this result was also independently confirmed.[26] The different stereocontrol is rationalized by assuming a S_N2 mechanism to be operative in the N–Me series though other types of nucleophiles, e.g. allylsilanes, afford the expected *trans*-products (Fig. 41).

4.2.2.3. Enol derivatives. As already indicated in Section 4.2 silyl enol ethers in combination with TMSOTf or $BF_3{\cdot}OEt_2$ as Lewis acids are excellent nucleophiles for the intermolecular C–C bond formation. In some cases silyl enol ether derivatives were studied next to the discussed nucleophiles, e.g. **156**[31,208] in Section 4.2.1. In the first report it is remarkable that the reaction of the *N*-tosyl enelactam **85b** required the use of enolacetates as



194a X = H, R = Ph
b X = Ac, R = Me
c X = COOR, R = Me

195a X = Y = Me
b X = H, Y = Pr

196 197

198 199 200

Figure 42.

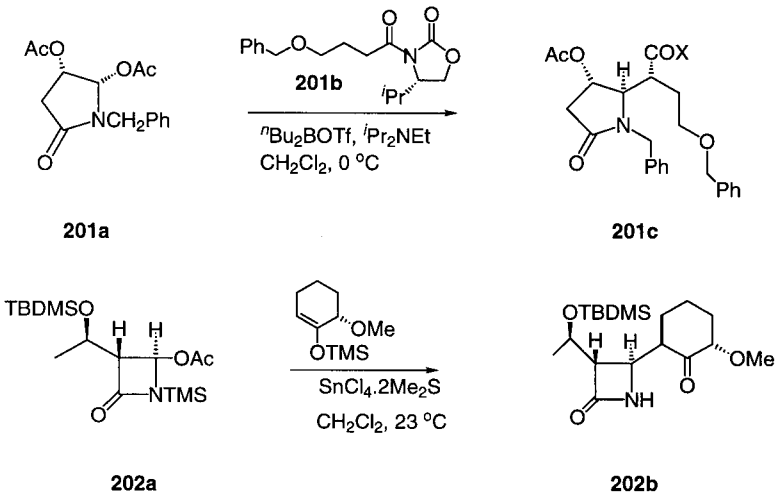


Figure 43.

nucleophiles, the silyl enol ether virtually failing to produce any coupled product.[117] Reactions of N-PMB protected malic acid precursors provided the substituted **194a**,**b**,**c** with high *trans*-selectivity.[44] In a related study silyl ketene acetals were reacted with proline derived precursors to provide again exclusively the *trans*-pyrrolidines **195**.[106] Other additions follow similar patterns, the steric outcome being predictable on the basis of conformational arguments. The cyclic acetal **91** (Section 3.1.9) gave with the TMS enol ether of pinacolone/$BF_3{\cdot}OEt_2$ 88% of the *trans*-adduct.[224] In a chiral norbornene (**261b**, Section 6.1.1), 91% of the *exo*-adduct **196** was obtained[225] while in the bicyclic piperidine series the *trans*-selectivity as given for **160** (Section 4.2.2.1) oxazolidinone[100] and the corresponding oxazinone[226] was also observed. 2-OTMS-4-Pr-butadiene/TMSOTf (cf. **146** Section 4.2) provides the *trans*-adduct **197** as a 3:2 mixture of *n*-propyl stereoisomers[227] on reaction with a chiral butylpyrrolidine. The reaction of the parent diene with a tricyclic lactam precursor afforded a 1.2:1 mixture of *trans* and *cis* isomers **198** of a 10-azasteroid, while the 1-OMe-3-OTMS-butadiene gave only the C_2–C_3 unsaturated *trans*-adduct albeit in moderate yield.[228] A number of studies have dealt with the use of the cyclic ketene acetal 2-OTMS-furan.

As discussed in Section 4.2 (structures **147** and **148**) a high *threo*-selectivity is observed which is also confirmed in pyrrolidines **199**[204] and **200** (Fig. 42).[74] The *threo*-isomer is the preferred (5:1) isomer formed in **199** while the product **200** which is an intermediate in studies related to the synthesis of Stemona alkaloids is even obtained in a 9:1 *threo*/*erythro* ratio. Other work relates to the synthesis of a Stemona alkaloid[229] (cf. Section 6.1.2) and the influence of the substituent in the proline-derived starting material.[230,231] The use of a chiral boron enolate in the synthesis of **201c** is of some interest since it allows not only stereocontrol at C-5 of the pyrrolidinone but also in the substituent.

By combining the acetoxylactam **201a** and $^nBu_2OTf$ with the boron enolate of Evans oxazolidinone **201b**, 53% of the single isomer **201c** could be obtained.[43] The high stereocontrol has been explained as an intramolecular chelation effect of the boron. Modulation of the Lewis acid in the addition of the TMS enol ether of (*S*)-(−)-2-OMe-cyclohexanone to the azetidinone **202a** allowed the synthesis of a β-lactam precursor **202b** as a single isomer in 50% yield upon use of $SnCl_4{\cdot}2Me_2S$ in CH_2Cl_2 at 23°C. All other solvents and/or ligands investigated gave less satisfactory results[232] (Fig. 43).

5. Carbon–Carbon Bond Formation of Linear *N*-Acyliminium Intermediates

The availability of stable linear precursors for the acyclic *N*-acyliminium intermediate—as reviewed in Section 3.2—has greatly expanded its synthetic potential. In this section a survey is presented of intra- and intermolecular applications both on achiral and chiral forms.

5.1. Intramolecular C–C bond formation

This type of amidoalkylation as already discussed in Section 2.3 for the cyclization of (*E*)-Me-alkeneamides/benzaldehyde mixtures is often carried out without isolating the hemi-aminals. Thus reaction of **203** with formaldehyde/HCOOH at 55°C gives a mixture of cyclization products among which **204a** and **204b** are formed in 41 and 34% yield, respectively.[158]

An interesting variation is the $FeCl_3$ catalyzed ring closure of the aza-diene **205** to the tricycle **206** and its C_9 epimer which is formed as a 5.7:1 mixture.[233] In this reaction the *N*-acyliminium ion constitutes the terminating cation while the use of other Lewis acids gave inferior results. A reaction corresponding to results described earlier[234] is the cyclization of hydrazoic precursors **207**. For R=H the aza-proline **208** is formed upon $SnCl_4$ cyclization. Remarkably the methallyl homolog **207** (R=Me) affords a mixture of **208** (R=Me) and **209** (X=Cl) with Et_2AlCl and solely **209** (X=OCHO) with HCOOH as protic acid.[149] Other nucleophiles have been studied as well as, for instance, **207** R=CH_2SiMe_3 which gives **210** with Et_2AlCl (Fig. 44). These results are rationalized by invoking a stabilizing interaction of the *N*-Bn moiety and the final cation leading to a bridged aziridinium intermediate. A different 1,3-diaza

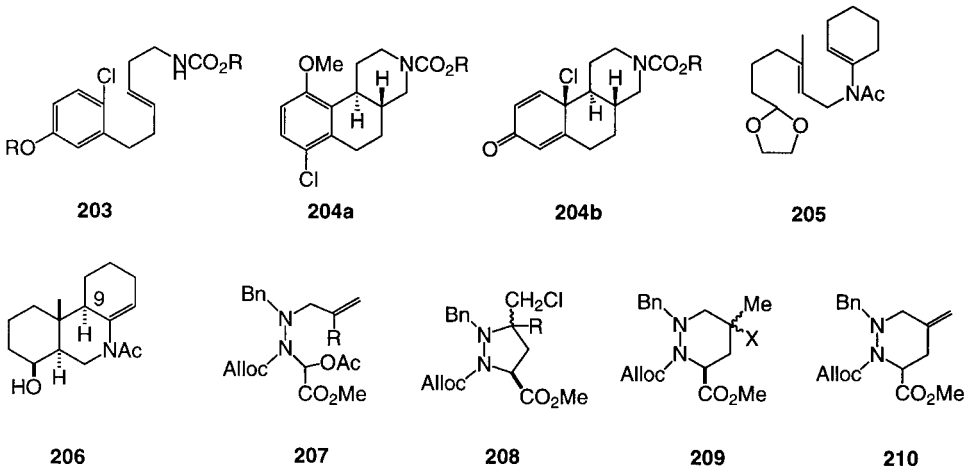


Figure 44.

tricyclic system is formed by the involvement of an imine in the generation of the reactive species.[33] By a $TiCl_4$-catalyzed reaction the *N*-Boc-arylamine **211** is converted into the quinolinium intermediate **212** which cyclized to a >9:1 mixture of α/β chloro-epimers **213**. In case another Lewis acid—e.g. TMSOTf—is used, the Boc group is removed first and the resulting amine follows a different cyclization pathway. A useful variation is described by Panek[235] who synthesized chiral cyclopentanes **214** with high levels of diastereo- and enantioselectivity by forming the *N*-tosyliminium ion in situ from the aldehyde **215**, *p*-$TsNH_2$ and $BF_3{\cdot}OEt_2$. The *cis*-substituted cyclohexane **217** could be obtained by Johnson[236] in 93% yield upon HCOOH cyclization of the formamide **216**—the *cis*/*trans* ratio being 85:15—and hydrolysis and benzoylation. Cyclic products are also formed[237] in the coupling of

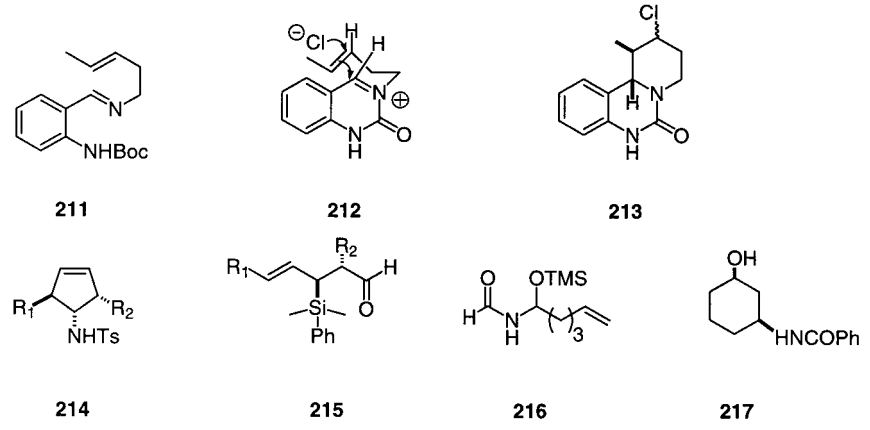


Figure 45.

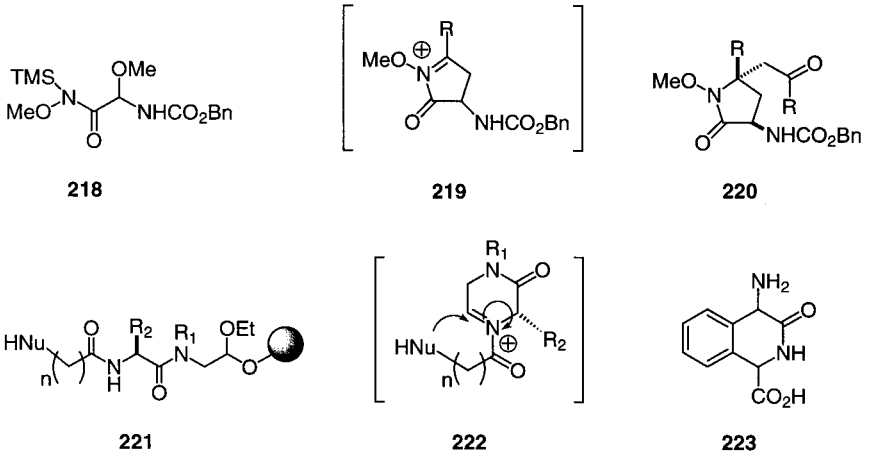
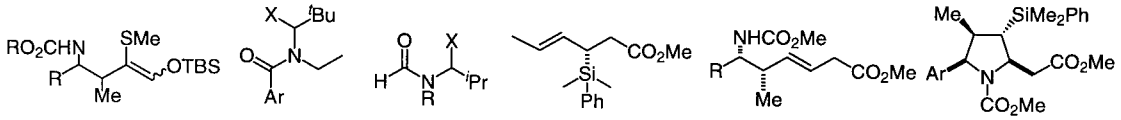


Figure 46.



224 **225 a** X = Cl **b** X = Et **226 a** X = OTMS **b** X = allyl **227** **228** **229**

Figure 47.

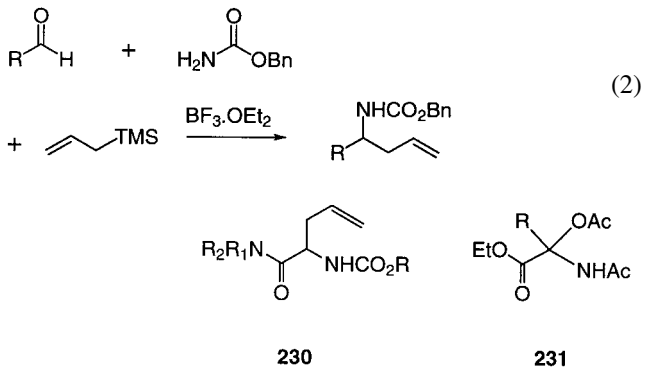
α-methoxyglycinamide **218** with silylenol ethers to produce pyrrolinones **220** (R=Me, ^{t}Bu and Ph) by two-fold coupling through the intermediate **219** (Fig. 45).

Of special interest is the generation of the pyrazinium **222** cation and ensuing cyclizations from solid-phase synthesis[238] of the linear acetal **221**. A final example is taken from the work of Ben-Ishai[239] who synthesized isoquinolone **223** from dipeptide α-OMe-Gly-Phg (Fig. 46).

5.2. Intermolecular C–C bond formation

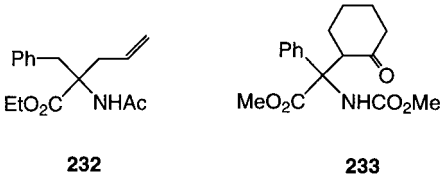
In Sections 2.1 and 3.2, the intermolecular C–C coupling with a particular type of activated nucleophile has already been indicated. Thus a silyl ketene acetal has been reacted with a linear enamide[22] while allylTMS was coupled with *N*-(α-stannylalkyl) amides[132] and *N*-triflyloxyamides.[151] A biscarbamate underwent highly stereoselective addition to 2-(alkylthio)allyl silyl ether with $BF_3{\cdot}OEt_2$ affording **224** in high *syn*/*anti* ratio[240] while EtMgCl reacted in 96% yield with the α-Cl amide **225a** derived from the imine and aroyl chloride to the product **225b**.[141] Although the difference in nucleophilic character between allylsilanes and allylstannanes is usually not manifested in experimental results, the linear **226a** did not add to allylTMS but gave a 93% yield of **226b** upon reaction with allyltributylstannane/$BF_3{\cdot}OEt_2$.[236] The chiral silane **227** coupled in a highly diastereo- and enantioselective manner with the in situ generated iminium intermediate obtained from aldehyde or acetal, methyl carbamate and $BF_3{\cdot}OEt_2$ at −100 to −78°C to the β,γ-ester **228**. The formation of the pyrrolidine **229** by a 3+2 annulation process could be also demonstrated this product being converted to **228** upon renewed treatment with acid[145] (Fig. 47).

A practical one-pot variant of the latter technique affording homoallyl amines has been reported by Veenstra[241] and is represented by Eq. (2).



(2)

230 **231**



232 **233**

Figure 48.

Rutjes[242] has adapted this method into a solid support version whereby the linker was attached to the carbamate, thus introducing one of the first examples of the use of the *N*-acyliminium reaction in combinatorial chemistry. Extensive studies on the use of α-amino carboxamides have led to an array of novel amino acid derivatives, several of which were obtained in optically pure form by a subsequent enzymatic kinetic resolution.[37] By using the precursor **108** (cf. Section 3.2) or **218** (cf. Section 5.1) compounds of type **230** (R_1R_2=H or Me; R_1=H, R_2=OMe) were obtained. Slight modification of the precursor, e.g. **107** (cf. Section 3.2) or **231** (R=Me, Bn or allyl), allowed the synthesis of tertiary derivatives,[147] while the use of the oxidized form of phenylglycine gave the α-phenyl amino acids. Usually allylsilanes or silyl enol ethers were used as nucleophiles. Compounds **232** and **233** are typical examples out of the many new structures (Fig. 48).

Use of chiral auxiliaries gave rise to marked induction. The norbornene derivative **234** (X=OMe) upon reaction with allylTMS afforded the allylation product with 62% de, while butylcuprate/$BF_3{\cdot}OEt_2$ even led to the butyl compound **234** (X=Bu) with 100% de.[243] A high induction was also found upon reaction of the *N*-acyliminium ion **235** which was generated from a diarylamine and *N*,*N*-phthaloyl-*t*-leucine chloride. In the absence of additional Lewis acid coupling with silyl ketene acetal gave >99:1 formation of the addition product **236**. The results have been evaluated for a series of aryl substituents R_1 and R_2.[244] Use of a different type of starting material in which the transfer of the nucleophile occurred in an intramolecular fashion enhanced the degree of stereocontrol in the addition process. In the work of Hioki[144] the chiral allyl silyloxy carbamate **237** underwent almost complete *anti* allyl transfer to **238** thus allowing the stereoselective synthesis of 1,2- and 1,3-*anti*-amino alcohols. High selectivity was also found for the transfer of a phenyl group (instead of an allyl) from the silyloxy starting material (Fig. 49).

6. Applications

In the previous sections, novel and extended pathways were discussed regarding the preparation and reactions of

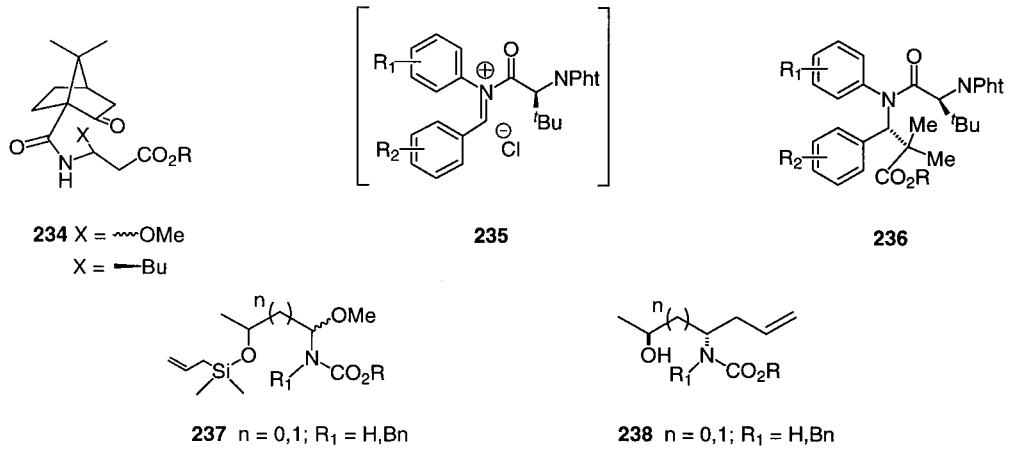


Figure 49.

N-acyliminium precursors. In this section, work on the synthesis of natural products of relatively simple and more complex structures and also on the construction of non-natural molecules of possible biological interest will be summarized. The discussion will not be focused on separate compound classes, rather the elements of structure, type of ring to be formed and stereochemical control, emphasizing the degree of chirospecificity of the chemical transformations are the common factors in this section.

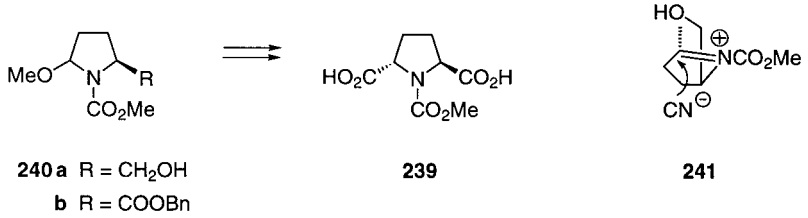
6.1. Alkaloids and related substances

6.1.1. Monocyclic and bicyclic natural compounds. In the past decade the stereocontrolled substitution of monocyclic precursors (cf. Section 4.2) has been a topic of considerable interest in this field. The availability of tools to favor a desired stereochemistry coupled with a practical knowledge on intermolecular substitutions are the main driving factors for this enhanced activity. Interestingly not only the direct synthesis of monocyclic enantiopure alkaloids has been a target but often the stereocontrolled ways of substituting monocyclic precursors has also led to chirospecific syntheses of bicyclic alkaloids. Therefore the two classes of compounds will be reviewed in one section. Since in the Sections 3 and 4 several precursors and reaction methods have already been discussed, back-referring will be used whenever possible.

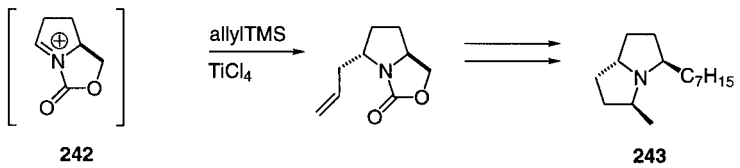
Straightforward synthesis of optically pure compounds from chiral precursors is almost a standard technique and some newer examples in the monocyclic series comprise anisomycin from (*S*)-malic acid,[245] (+)-preussin from D-mannose[124] via the intermediacy of **90** (Section 3.1.9) and of the bicyclic lentiginosine from L-tartrimide.[246] In Scheme 3, the synthesis of (2*S*),(5*S*)-pyrrolidine 2,5-dicarboxylic acid **239** is outlined by addition of TMSCN/$SnCl_4$ to **240**.

Whereas addition of TMSCN to **240a** favors the *trans*-isomer (*trans*/*cis* 65:35), the use of **240b** gives a 70:30 ratio of *cis*/*trans*.[56] It is assumed that this change is caused by the role of the OH in **240a** in stabilizing the preferred conformation **241** of the reactive intermediate.

Making use of the almost exclusive *trans*-addition of various types of nucleophiles to bicyclic *N*-acyliminium ion **242** (cf. **77**, Section 3.1.6) derived from proline, the synthesis of the pyrrolizidine alkaloid (−)-xenovenine **243** has been carried out[55] according to Scheme 4.



Scheme 3.



Scheme 4.

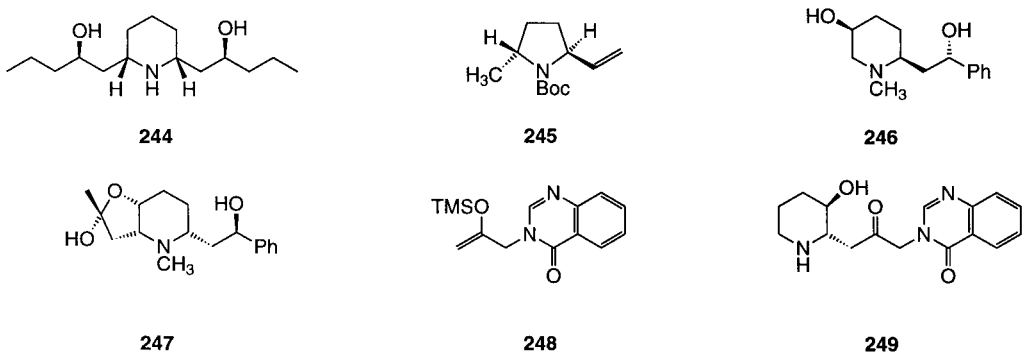
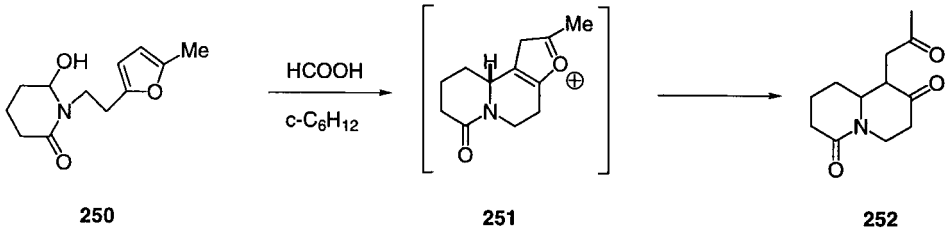


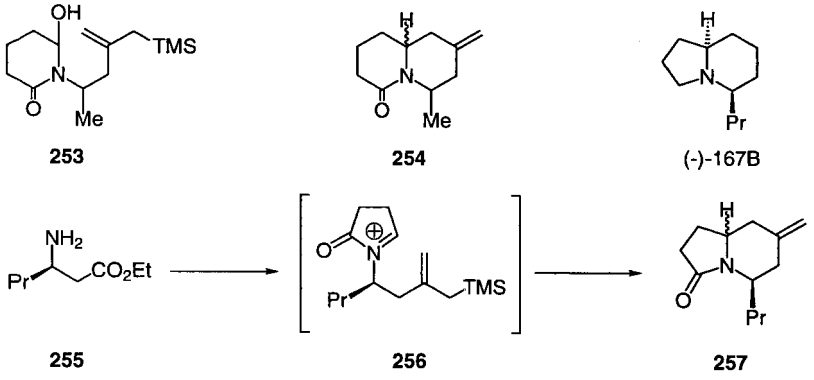
Figure 50.

Other pyrrolizidine and indolizidine alkaloids have been prepared following the same principle of *trans*-addition to a bicyclic precursor. An example in the piperidine series, e.g. andrachamine **244** has also been synthesized.[226] As discussed in Section 4.2.2.2, a different method to achieve highly selective *trans*-addition in α-carboxyl containing precursors makes use of organocuprate chemistry. As studied by Wistrand,[220] chirospecific synthesis of several ant pheromones of the 2,5-dialkylpyrrolidine type has been achieved. In a related application the synthesis of the previously discussed **243** is based on the selective methyl cuprate addition (*trans*/*cis* 9:1) to a pyroglutamate and conversion of the carboxylate into a vinyl substituent to obtain **245**. Hydroformylation of the latter product[221] followed by $C_7H_{15}MgBr$ addition and ring closure then affords the pyrrolizidine. As described in Section 3.1.10, a related method has been developed by Ojima[137] by the amidocarbonylation of suitable precursors to obtain pyrrolizidines, e.g. **104**, which were transformed into (±)-isoretronecanol and other alkaloids of this type. Synthesis of β-hydroxypiperidine alkaloids has been achieved by anodic oxidation and hydroboration of the enecarbamates so obtained.[84] Thus (−)-5-hydroxysedamine **246** and (+)-sedacryptine **247** were obtained in this way.

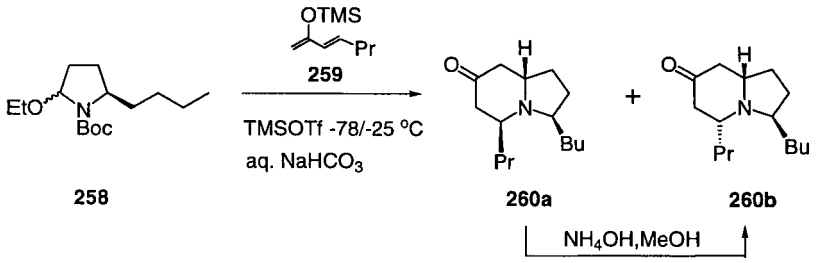
A different type of oxidation of an enecarbamate allowed the synthesis of febrifugine **249**. Upon reacting the epoxide **79** (*n*=2, cf. Section 3.1.7) with the enol ether **248**—$TiCl_4$, CH_2Cl_2, 0°C—separation of the 1:1 mixture of diastereomers and hydrolysis of the carbamate **249** was obtained (Fig. 50).[107] Use of activated nucleophiles also led to the synthesis of various izidine alkaloids. Racemic epilupinine was obtained by ring closure of a bromoacetylene[247] and by applying a furan derivative[184] as presented in Scheme 5. Treatment with acid of the precursor **250** led to an oxocarbenium intermediate which presumably undergoes a [1,5] H-shift giving rise to the new species **251**.



Scheme 5.



Scheme 6.



Scheme 7.

After capture of water the dione **252** is formed which can be transformed to epilupinine by a series of standard conversions.

Other quinolizidine alkaloids, e.g. (+)-myrtine, have been prepared[248] by ring closure of the allylsilane **253** producing a 7:3 mixture of the epimers **254**. Scheme 6 also contains the synthesis of (−)-indolizidine 167B which is made from aminoester **255** by coupling with succinic anhydride/acetyl chloride, $NaBH_4/H^+$ reduction in ethanol and treatment with the cerium reagent derived from trimethylsilylmethylmagnesium chloride and $CeCl_3$.

Upon hydrolysis with 1N HCl the intermediate **256** underwent cyclization to a 4:1 mixture of epimers **257** which was further processed to the title compound. Although the unwanted stereoisomer was formed in excess, this result proved of no consequence since in one of the later steps complete isomerization—presumably through a *retro*-Mannich fragmentation-cyclization process—occurred to give the desired isomer.[249] In an intermolecular fashion (±)-myrtine and related alkaloids have been synthesized by the addition of 2-TMSO-1,3-dienes to cyclic *N*-acyliminium ions[227] (cf. Section 4.2, **146** and Section 4.2.2.3, **197**).

In Scheme 7 the synthesis of (−)-indolizidine 223AB is given in which the lactam **258**—prepared by a cuprate alkylation of a pyroglutamate precursor—is coupled with the diene **259** to obtain a 3:2 mixture of isomers **260a** and **260b** which could be converted to the desired 223AB upon isomerization with ammonia–methanol and removal of the carbonyl group.[227]

As discussed in Section 4.2.1 (cf. **149** and **150**), the use of chiral auxiliaries in intermolecular additions[205] also leads to acceptable levels of stereoselection. By this method the indolizidine alkaloids (−)-205A and (−)-235B were obtained. Flash-vacuum thermolysis has been applied by Koizumi[225] in the synthesis of various indolizidine alkaloids. By condensing the optically active maleimide **261a** with cyclopentadiene, $NaBH_4$ reduction and removal of the sulfinyl moiety the bicyclic precursors **261b** were formed which in both intramolecular and intermolecular additions according to the type of N–R substituent can be further processed to (+)-elaeokanines A and C and other members of this class (also cf. **196** in Section 4.2.2.3), which constitutes an example of an intermolecular application. This thermal *retro*-Diels–Alder process has also been applied by Winterfeldt[250] by using the chiral diene **262a** as

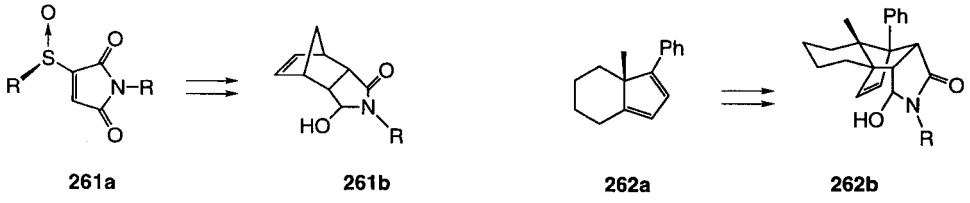
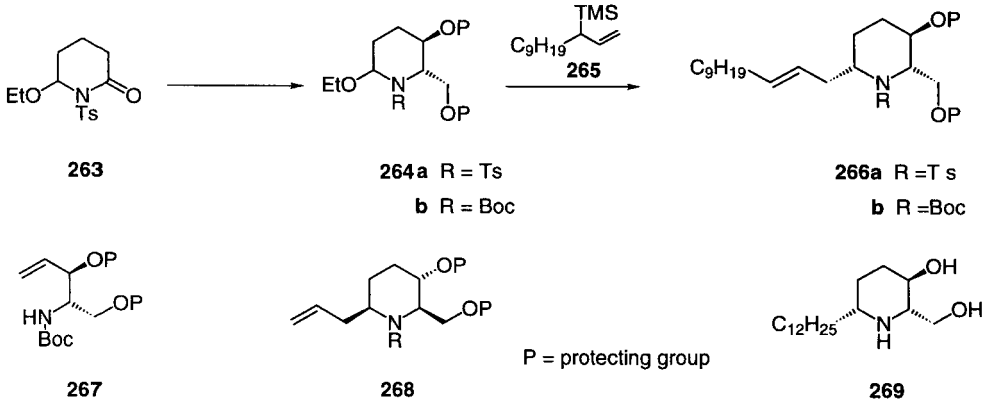
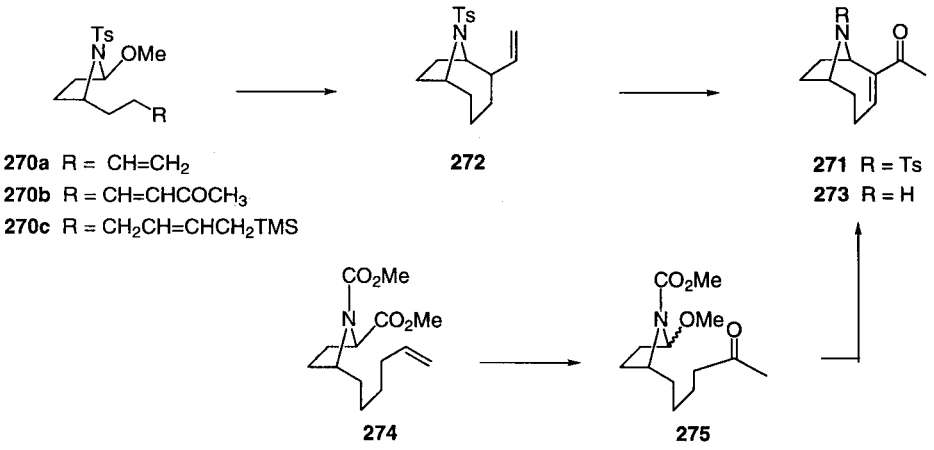


Figure 51.



Scheme 8.



Scheme 9.

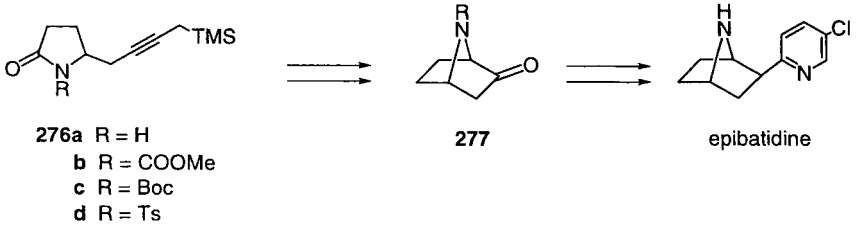
an auxiliary to obtain the adducts **262b** and synthesizing the izidine target alkaloids (Fig. 51).

Finally, by modification of the chiral boron enolate adduct **201**, cf. Section 4.2.2.3, the pyrrolizidine alkaloid (+)-hastanecine has been prepared.[43] In three syntheses of desoxoprosophylline **269**, the final step is based upon the known preference for *cis*-addition at the α′-position of an α-substituted piperidine, cf. **171** in Section 4.2.2.1. These approaches are summarized in Scheme 8. In the first route,[213] the starting piperidine **264a** is made from the piperidone **263** by introducing an ester moiety via an enol triflate and, after reduction of the ester, a subsequent hydroboration of the resulting *N*-tosylenamide.

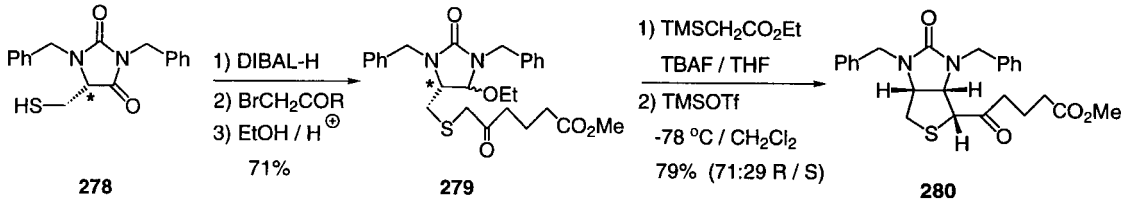
The *cis*-addition of the side chain to form **266** then takes place upon $BF_3{\cdot}OEt_2$ reaction of the alkenyl silane **265** at −78°C→−30°C. Removal of protecting groups and hydrogenation then provides the alkaloid **269**. Interestingly in the second route **264b** is prepared by cyclohydrocarbonylation of the *N*-Boc amine **267** (cf. Section 3.1.10, **101** and **102**) and the side chain was attached as described before.[251] Since the starting amine is optically active (−)-desoxoprosophylline **269** is the final product. In the third method the oxidation of a furan derivative[118] (cf. Section 3.1.8, **86**) has been employed to obtain a piperidone precursor which upon reaction with allylTMS afforded **268**. The allyl substituent was converted to the correct side chain by known methods to produce the *ent*-isomer of **269**. In other work based upon the use of a similar furan starting material a compound of type **264a** carrying a different α-substituent was obtained in which the OEt was removed with $NaBH_4$-HCOOH at 0°C and the remaining piperidine converted into (−)-swainsonine.[252] The use of tertiary *N*-acyliminium ions in piperidine alkaloid synthesis is rather limited. A recent example combines the use of a novel chiral auxiliary and leaving group and this has been discussed in Section 4.2.2.1, cf. compounds **168** and **169** in the synthesis of (−)-adalinine.[212] A similar strategy was employed in the synthesis of (±)-adalinine.[192]

Structurally different forms of bicyclic alkaloids such as the enantiomers of (+)-anatoxine **273** and (−)-epibatidine have been also synthesized. Whereas the former was obtained earlier in a racemic form,[5] the latter had not been reported through the use of *N*-acyliminium chemistry. Starting from L-pyroglutamic acid the alkene **270a** has been prepared[60] (Scheme 9) which was converted to the enone **270b** and the silane **270c** by standard methods. Ring closure of **270b**—HCl/MeOH—gave the bicycle **271** while application of a Lewis acid on **270c**—$TiCl_4/CH_2Cl_2$/−78°C—led to **272**. Both compounds were finally processed into **273**. A second pathway[178] proceeded from L-proline and made use of the *trans*-addition of an organocuprate to obtain **274** which, after Wacker oxidation, was oxidatively decarboxylated to **275**. Final ring closure and further transformation produced **273**.

The synthesis of (−)-epibatidine has been carried out through the ketone intermediate **277c** which was synthesized according to the procedure given in Scheme 10. Proceeding from the known (*R*)-(+)-5-(iodomethyl)pyrrolidin-2-one[253] an acetylenic iodide was coupled via the zinc reagent[254] to afford **276a**. After protection of the nitrogen as a carbamate **276b**,**c** or the tosylamide **276d** and $NaBH_4$ reduction, the cyclization was carried out via the



Scheme 10.



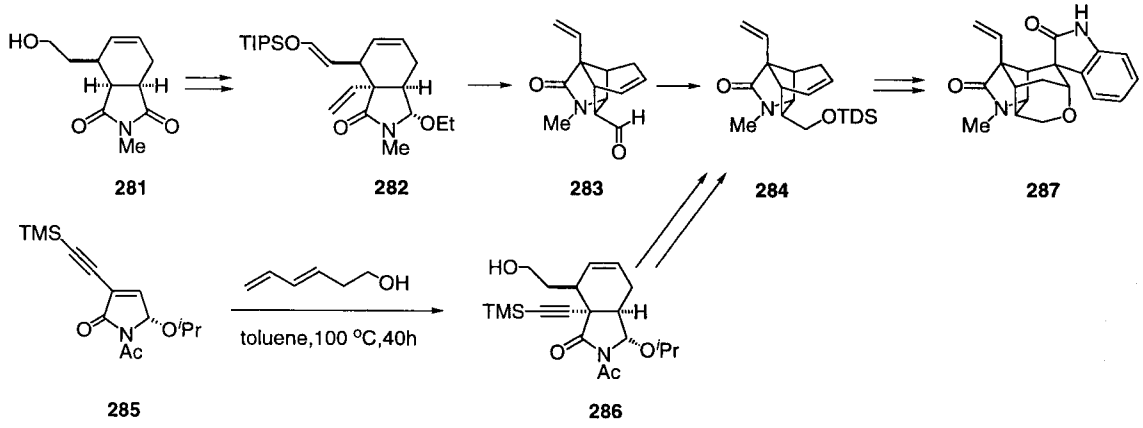
Scheme 11.

methoxylated derivative to afford an allene which after oxidation with ozone gave the known bicyclic ketone **277b** (R=COOMe).

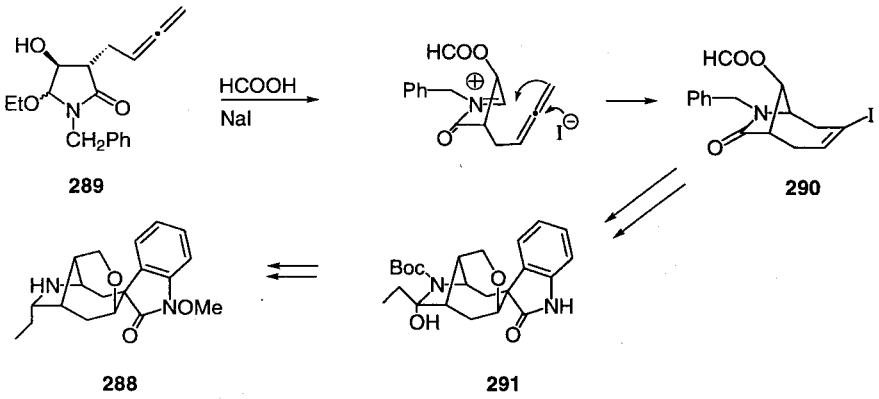
Since the allene ring closure with the *N*-Boc derivative **276c** gave variable results the pyrrolidinone **276d** was also investigated[255a] which afforded **277d** (R=Ts)[255b] in reproducible yields of >80%. The ketone **277c** has been converted to (−)-epibatidine following a known procedure.[256]

A notable example of a bicyclic system is the nutritional cofactor (+)-biotin. Its synthesis[63] proved remarkably efficient by applying a regioselective in situ silylenol ether/cyclization technique as exemplified by the transformation **279→280**. In Scheme 11 one of the routes is given which afforded **280** in an overall yield of 56.5% (40% of the *R*-isomer). Starting from the L-cysteine derived imidazolidinone **278** the synthesis proceeded by selective reduction of a carbonyl group, coupling with an α-bromo ketone and exchange of the OH into the OEt. After the preparation of the silylenol ether for which other alternatives were also developed the ring closure was effected with TMSOTf.

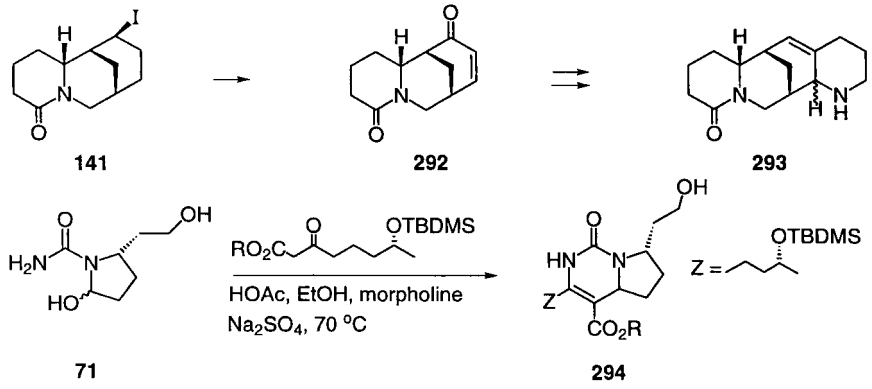
6.1.2. Polycyclic natural compounds. As has been reviewed previously[2,4] the *N*-acyliminium method has been used with great success in the synthesis of a variety of simple and complex alkaloid structures. In the last decade several examples of the usefulness of this method have been reported. Amongst these are the syntheses of the *Gelsemium* alkaloids (±)-gelsemine,[257] (+)-gelsemine[258] and (+)-gelsedine,[259–261] the indole alkaloid (−)-ajmalicine,[157] the Stemona alkaloid (+)-croomine,[229] the guanidinium alkaloid (−)-ptilomycalin,[95] the marine derived anti-tumor agent ecteinascidin 743[262] and the antibiotic (+)-streptazolin[45] in addition to a number of less complex structures.



Scheme 12.



Scheme 13.



Scheme 14.

Intramolecular cyclizations of a silylenol ether and an allene onto *N*-acyliminium intermediates are among the key steps of the syntheses of *Gelsemium* alkaloids which are outlined in Scheme 12.

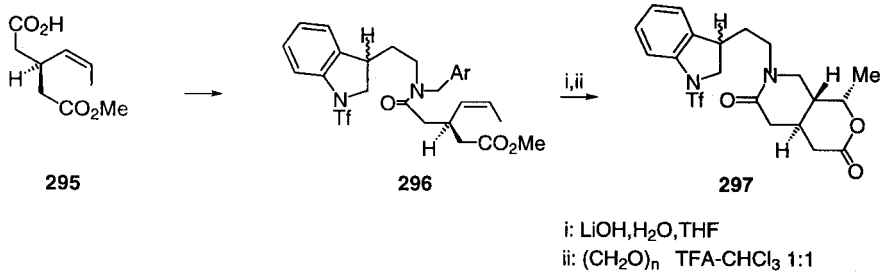
In the synthesis of (±)-gelsemine the bicyclic imide **281** was converted into the appropriate cyclization precursor **282** which, due to the favorable—ratio *E*/*Z* 3:1—(*E*)-enol ether geometry, cyclized to a separable 3:1 mixture of the required aldehyde **283** and its *endo*-isomer in 70% yield. After chromatographic separation, **283** was converted to the TDS-protected alcohol **284**. By slightly varying this route and using a different bicyclic precursor the ring closure proceeded with even better selectivity. Thus, upon Diels–Alder reaction of (*S*)-pyrrolinone **285** with 3,5-hexadien-1-ol, the lactam **286** was formed which by similar operations could be transformed into the cyclized **284** and its *endo*-isomer in a 4:1 selectivity. After a series of other steps (±)-gelsemine **287**[257] and (+)-gelsemine **287** were obtained.[258]

The synthetic sequence to (+)-gelsedine **288** made use of a novel variation of an allene cyclization. This route is summarized in Scheme 13. emphasizing the regioselective iodo-alkene formation **289→290** upon use of the iodide anion in the allene ring closure.[259,260] The cyclization (viz Scheme 2) of **130a** affording ketone **131** discussed earlier cannot be applied since the formation of the enol proceeds in a non-regioselective manner.

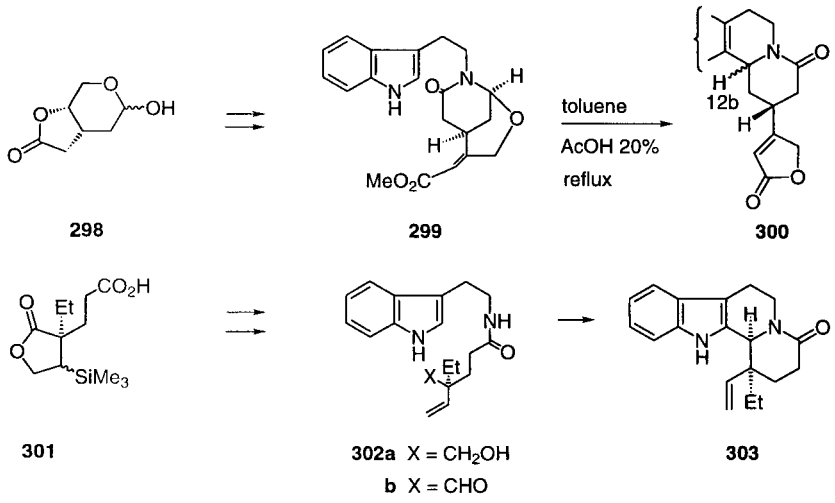
Following the attachment of the oxindole via a Pd-catalyzed aminocarbonylation reaction and formation of the ether ring the tertiary hydroxylactam **291** may be prepared and the corresponding *N*-acyliminium intermediate reduced in a stereoselective way by the TFA/Et_3SiH method after which the synthesis of **288** is completed upon introduction of the *N*-OMe moiety.[261] The variant of addition of iodide as developed by Overman has been discussed in Section 4.1.3, cf. **140→141** and this was used in the synthesis of the two stereomers of aloperine **293** in Scheme 14. By converting the iodide **141** into the enone **292** and attachment of the last ring the title compound was formed.[189]

In work towards the enantioselective synthesis of the guanidinium alkaloid (−)-ptilomycalin, the Biginelli reaction[262] of the enantiopure hydroxylactam **71** (cf. Section 3.1.5) was used to obtain the pyrimidine **294** (Scheme 14) as the key intermediate for the synthesis of the natural product.[95] The synthesis of the indole alkaloid (−)-ajmalicine is also of interest.[157] Whilst in principle both the iminium and the *N*-acyliminium methods could be applied to obtain a central bicyclic intermediate, for strategic reasons the *N*-acyliminium route was selected (Scheme 15). Biscyclization of the amide **296** prepared from the glutarate monoester **295** gave via the linear cation the lactone **297**. The *N*-triflylindoline moiety was chosen to prevent unwanted side reactions with the highly nucleophilic indole.

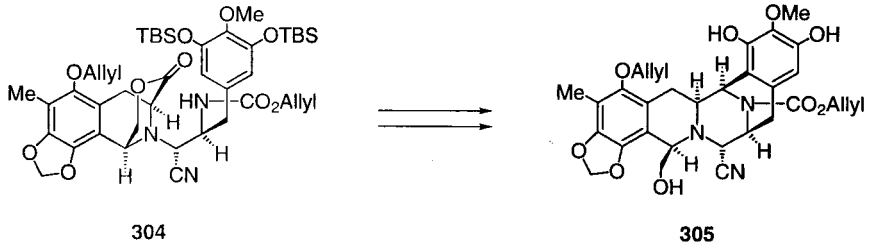
It was necessary to protect the amine with a 2,4-dimethoxybenzyl group to avoid racemization of the starting ester in the hydrolysis step (i) to the carboxylate via the transient formation of a glutarimide. Trifluoroacetic acid serves to firstly remove the protecting dimethoxybenzyl group and then to promote the methyleneiminium biscyclization step (ii) in which the carboxylate proved the best acceptor. Lastly the (*Z*)-geometry of the alkene controlled the configuration of the methyl substituent. The synthesis of the



Scheme 15.



Scheme 16.



Scheme 17.

title alkaloid was completed by a small number of additional steps.

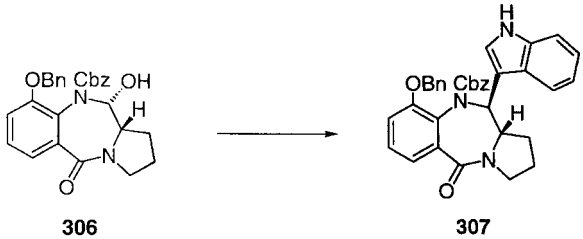
Of the many indole alkaloid syntheses those of (−)-antirhine[126] and (−)-eburnamonine[187] also include *N*-acyliminium steps. Starting from the pyranose **298** (cf. Section 3.1.9) and tryptamine the amide formed was converted to the ester **299** which cyclized to a 70:30 mixture of H_{12b} α- and β-epimers **300** (Scheme 16).

After separation of the α-isomer the synthesis of (−)-antirhine was completed by conventional transformations. The synthesis of (−)-eburnamonine included the ring closure of the enantiopure indole amide **302a** which was obtained through coupling of the lactone acid **301** with tryptamine, $LiBH_4$ reduction of the lactone and KH elimination of the silyl moiety. TPAP–NMO oxidation of the alcohol gave the aldehyde **302b** which cyclized diastereoselectively via the aminal (cf. Section 3.1.5) upon treatment with TFA/−55°C/CH_2Cl_2 into a 18:1 mixture of **303** and its β-H epimer. (−)-Eburnamonine was prepared from **303**.

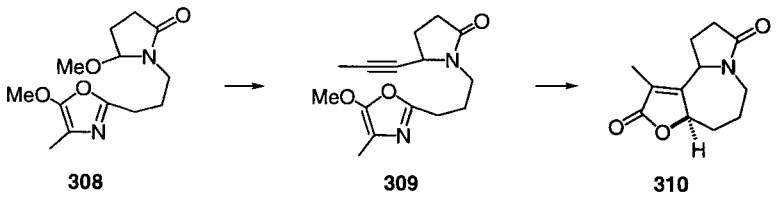
An illustrative example of the aminal method is found in the synthesis of ecteinascidin 743 by Corey.[263] The lactone **304** was reduced with DIBAL-H at −78°C, the silyl protecting moiety removed with $KF{\cdot}2H_2O$ and the hemiacetal treated with CH_3SO_3H/molecular sieves to promote the formation of the *N*-acyliminium ion and subsequent ring closure onto the aromatic nucleophile to form **305** (Scheme 17).

Additional examples of intramolecular cyclizations are the synthesis of (±)-glochidine by a site-selective ring closure of a tertiary *N*-acyliminium ion onto an imidazole[170] and the improved enantiocontrolled synthesis of (+)-streptazolin via a modified sequence[45] of the earlier reported route.[2] As discussed in Section 3.2 linear precursors (cf. **106**) can also be prepared and cyclized in an intramolecular mode. An example of this variant is the synthesis of *N*-formylpavine[264] in which 3,4-dimethoxyphenylacetaldehyde is coupled with BSF-TMSOTf[146] to produce a bis-adduct which cyclized in a twofold manner upon treatment with HCOOH to the pavine alkaloid. Intermolecular applications have also been reported. Coupling of an isatoic anhydride with (*S*)-proline and $NaBH_4/H^+$ reduction of the adduct gave the precursor **306** which was condensed with indole in acetic acid to produce the metabolite (+)-tillivaline **307** in a stereocontrolled way[265] (Scheme 18).

Two additional examples of this type of reaction are described in the syntheses of members of the *Stemonaceae* alkaloid class. As reported by Jacobi, (±)-stemoamide was



Scheme 18.



Scheme 19.

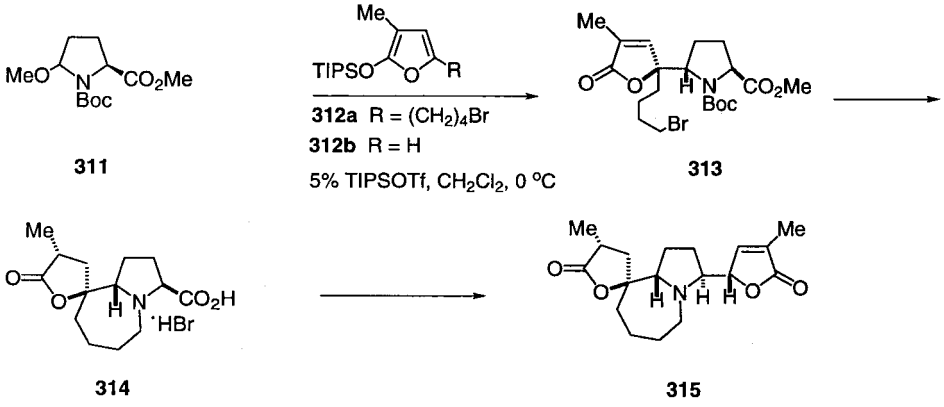
synthesized by following a [4+2] strategy.[198] The required precursor is the acetylene-substituted pyrrolidone **309** which is synthesized by condensing the methoxylactam **308** with (1-propynyl)tributylstannane/BF_3·OEt_2. Intramolecular Diels–Alder (*retro*-Diels–Alder) at 182°C then afforded the skeleton **310** of the title alkaloid (Scheme 19). The synthesis of (+)-croomine[229a] is also an elegant example of the synthetic potential of the enantiocontrolled intermolecular addition to an achiral furan precursor.

The pyrrolidine **311** reacted with remarkable *threo*-selectivity with the furanone **312a** to afford **313** in 32% yield and <1% of the other *threo*-isomer was formed. After transforming **313** to the azepine **314** a second condensation with furanone **312b** was carried out with the iminium intermediate obtained from the acid **314** upon $POCl_3$–DMF treatment to form a 2:1 mixture (47%) of *threo* and *erythro* coupling product **315** of which the former after separation was finally hydrogenated as the hydrochloride salt to (+)-croomine (Scheme 20). A recent example of this addition described the synthesis of pumiliotoxin 251D.[229b]

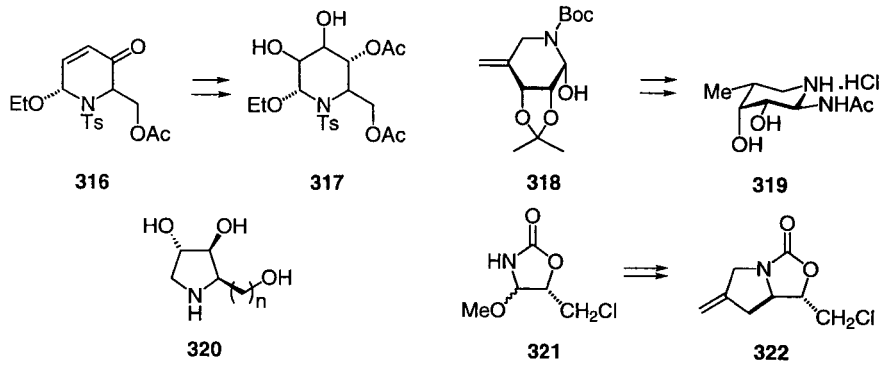
6.2. Other target molecules of biological interest

Throughout the preceding sections, methods and techniques have been described which relate to the synthesis of molecules possessing (potential) biological activity. In this section a short survey of the previously discussed classes of compounds is presented in addition to a few related applications.

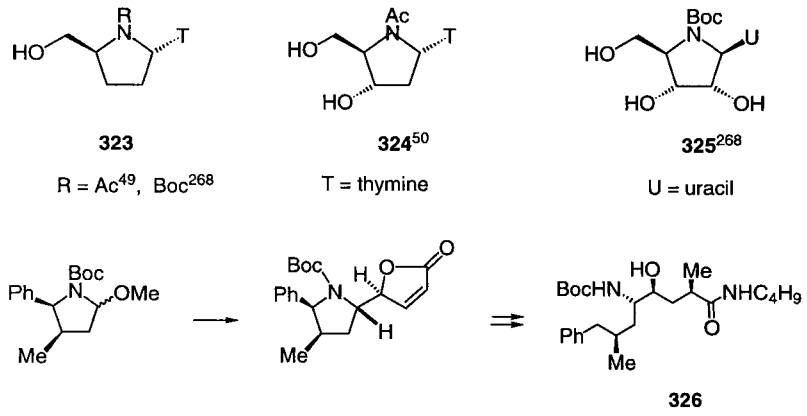
In the β-lactam field, carbapenems,[159,160] carbacephems,[161,164] loracarbacef,[163] trinem antibiotics[218,219] and γ-lactam analogs of claviminic acid[94] have been prepared by *N*-acyliminium chemistry. A different class of bioactive molecules—the azasugars—have also been synthesized by this type of reaction. In addition to the reduction of modified carbohydrates via *N*-acyliminium intermediates[121] the following azasugars and analogs were referred to:



Scheme 20.



Scheme 21.



Scheme 22.

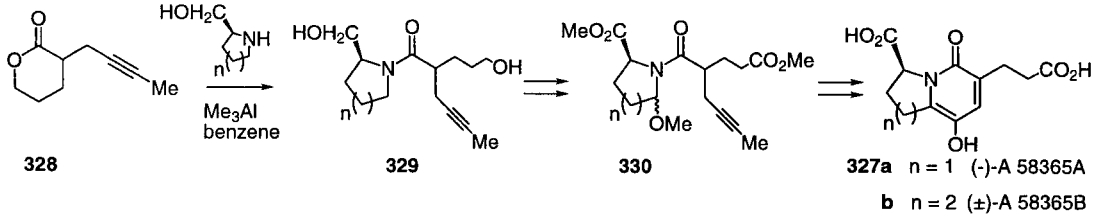
1-deoxygalactonojirimycin[96] (cf. **72→73**, Section 3.1.5) mannonojirimycin[266] (Scheme 21, **316→317**) and swainsonine, all of which have been prepared by application of the earlier discussed pyridone route (cf. **86** Section 3.1.8). The α-L-fucosidase inhibitor **319**[267] has been synthesized from D-ribono-γ-lactone which was first transformed into the hydroxylactam **318** after which the α-amino substituent was introduced while the analogs **320**[46] were derived from tartrimide. Precursors for pyrrolidine azasugars have also been obtained from **321** which in turn is prepared from *S*-malic acid and can be converted to **322**[216] (cf. also **180**, Section 4.2.2.1).

The synthesis of some azasteroids has been discussed[158,228] in previous sections, cf. **198** in Section 4.2.2.3 and **203**, **204** in Section 5.1. In relation to the interest in antisense oligonucleotides a number of nucleoside analogs have been prepared[49,50,268] based on thymidine and uracil derivatives. Some structures, e.g. **323**, **324** and **325** are presented in Scheme 22 (cf. **34** and **35** in Section 3.1.1) which clearly emphasize the potential of the method in this novel area.

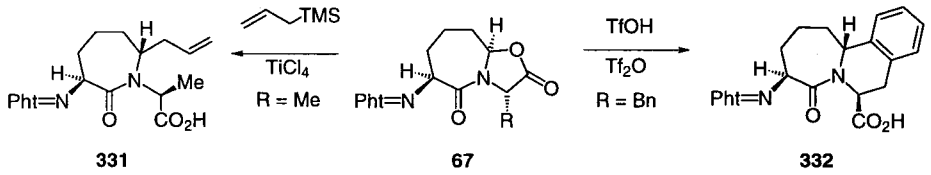
Other stereoisomers have been obtained in the condensation of the bissilylated nucleobase with the *N*-acyliminium precursor under $SnCl_4$ catalysis. In the synthesis of other bioactive materials some interesting results have been reported. As referred earlier (cf. **199** in Section 4.2.2.3) a 2-methoxyfuran derivative served as a useful nucleophile to induce stereocontrol in intermolecular additions. Hanessian[204] applied this method to synthesize the non-peptidic inhibitor model **326** as a hydroxyethylene isostere of part of the proteolytic enzyme renin. Its synthesis is illustrated in Scheme 22 and serves as a fine example of the degree of stereocontrol which can be reached in this type of addition. The *threo–erythro* ratio was 6:1 and the principal isomer was obtained in a crystalline form. The stereochemical result was in part predicted by the *syn*-disposition of the methyl and phenyl substituents thus ensuring the *anti*-approach of the furan nucleophile and an (*S*)-configuration at the center α to the nitrogen atom.

The ACE inhibitors (−)**327a** and (±)**327b** were obtained by Moeller[175] by a route described in Scheme 23. By adding (*S*)-(+)-2-pyrrolidinemethanol or 2-piperidinemethanol to the lactone **328** and anodic amide oxidation of the resulting adducts **329**, the acetylenes **330** were intramolecularly cyclized with $TiCl_4$, CH_2Cl_2 at −78°C and the resulting bicyclic lactams converted to the target compounds.

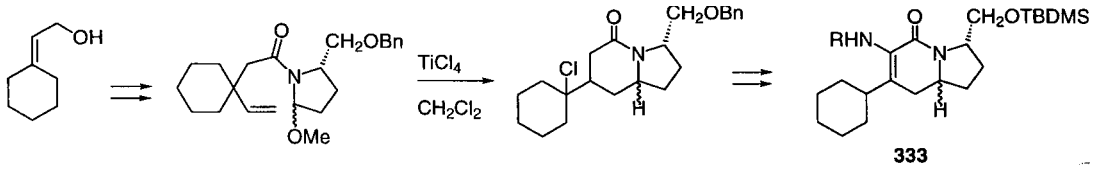
In a related field the synthesis of peptidomimetics, notably the so-called conformationally restricted peptide mimetics,



Scheme 23.



Scheme 24.



Scheme 25.

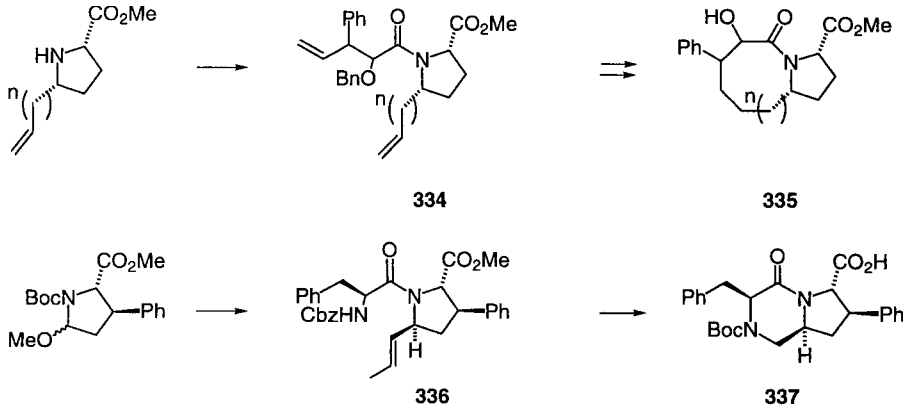
has received considerable attention. The focus of this work was aimed at the synthesis of azepinones[93] and 5,6- 5,7- and 6,7-fused bicyclic lactams[176,177,188] as more rigid analogs for the Ala-Pro or Leu-Pro part of the peptide backbone. As discussed earlier (cf. **66**, **67** in Section 3.1.5 and **177** in Section 4.2.2.1) the synthesis of the azepinone type lactam is relatively facile and proceeds with high stereocontrol[93] to afford the target compounds. As a further example, Scheme 24 shows the conversion to the substituted **331**, while introduction of a benzyl substituent leads after ring closure to the tricyclic **332**.

In Section 4.1.3 (cf. compounds **137** and **138**) the approach to 5,7 and 6,7 bicyclics was discussed[188] in which the seven-membered ring had been attached to a pyrrolidine or piperidine enamide by ring closure of an appropriately substituted side chain. In a different strategy, Moeller[176] discovered the facile rearrangement (cf. **132** and **133**, Section 4.1.2) to synthesize the 5,6 bicyclic system. This work was later extended[177] to a flexible approach towards this class of differently-substituted TRH analogs amongst which the cyclohexyl-substituted **333** (Scheme 25) is an example. The bicyclic lactam **333** was obtained as a 1.3:1 mixture of isomers which, after separation and substitution at the amine, gave the desired analogs.

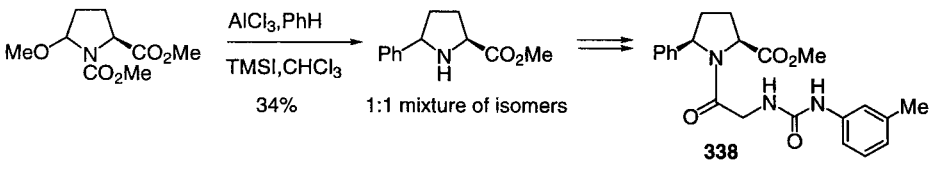
Since in this route only the 6,5 bicycles could be obtained, a different strategy[80] incorporating a metathesis ring closure based upon the preparation of vinyl or allyl substituted prolines **334** afforded (Scheme 26) highly substituted 5,7- and 5,8 systems **335**. The synthesis of a substance P analog possessing a similar bicyclic skeleton in which a nitrogen atom replaced a carbon is also outlined in this scheme. Again a substituted proline undergoes anodic oxidation and is substituted by a vinyl cuprate[81] in a stereocontrolled manner to afford after *N*-acylation the precursor **336** which is further converted into the piperazine bicycle **337**. The latter heterocyclic system has also been the target of other work as in the synthesis of Praziquantel[29] and a combinatorial library synthesis (cf. **221** and **222**, Section 5.1) of 1-acyl-3-oxo-piperazines.[238]

The synthesis of the non-peptide agonist **338** (Scheme 27) is a rare example of an intermolecular phenylation.[85] Although the reaction under the conditions employed gave a modest yield and showed no stereocontrol, the separation of the diastereomers proved facile and the (*R*,*S*)-isomer could be converted in a straightforward manner to the desired compound.

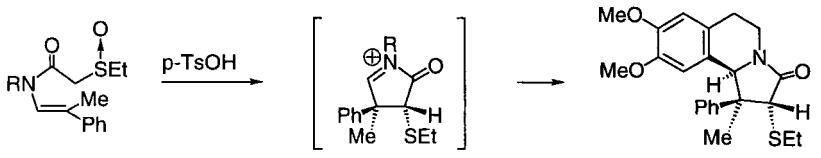
Finally it should be emphasized that in other projects towards enzyme analogs natural amino acids have been replaced by substitutes obtained through the chemistry discussed so far. It falls outside the scope of this review to fully cover these ongoing developments.



Scheme 26.



Scheme 27.



Scheme 28.

7. Outlook and Update

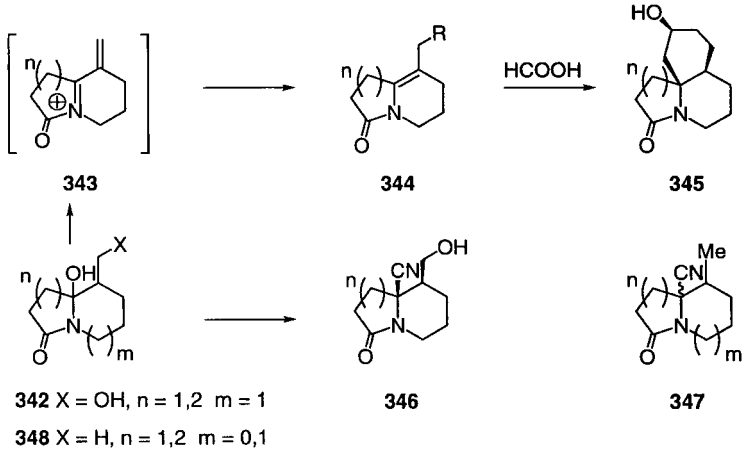
A century of developments in cationic carbon–carbon bond coupling by the use of *N*-acyl substituted carbocations has provided the organic chemist with a plethora of methods to achieve a desired transformation. The question may therefore be posed whether this technology has now reached a state of maturity and the reader of this and other reviews will have no doubts about answering in an affirmative way. Yet both in the further extensions of this method as well as in the area of current developments in biological application a steady accumulation of highly relevant data can be observed. Such new results have been partly included in the review wherever possible although a few others will be taken up in the sequel.

In a new variant (Scheme 28) of the thionium-*N*-acyliminium cascade (cf. **94**, Section 3.1.10) Padwa[269] reported the conversion of **339** to isoquinolines **341** through the intermediacy of the α-acylthionium ion formed in a Pummerer-type reaction which by way of a Nazarov 4π-electrocyclic ring closure leads to the intermediate *N*-acyliminium species **340**.

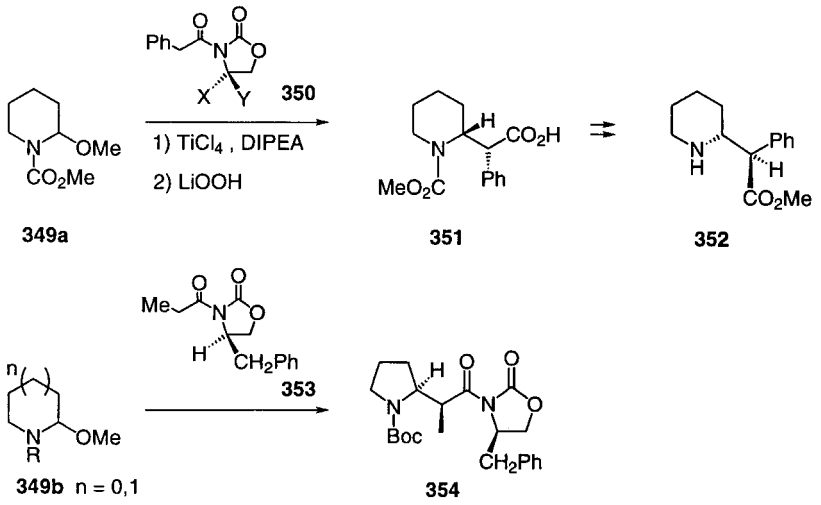
Organotitanium chemistry has been developed to synthesize precursors for tertiary *N*-acyliminium species (cf. **96**, Section 3.1.10). This type of hydroxylactam proved suitable to arrive at tertiary substitution products as has been described by Ollero.[270] Moreover a practical route (Scheme 29) towards polycyclic structures possessing a quaternary carbon atom such as the alkaloid lepadiformine by two consecutive *N*-acyliminium reactions considerably extended the scope of this work.

After oxidative generation of the diol **342** the intermolecular substitution of the primary alcohol by allylsilanes or silylenol ether/Lewis acid through the intermediacy of **343** as a vinylogous cation afforded enamides of the type **344** which for R=allyl could be cyclized to the spiro tricyclic **345** upon treatment with formic acid. Interestingly reaction of **342** (n=1) with TMSCN/TMSOTf gave solely the cyanide **346** resulting from coupling of the tertiary cationic intermediate. The latter type of substitution to form the cyanide **347** has been also found for the tertiary hydroxylactam **348** obtained by hydrolysis of the organotitanium complex (cf. **96a**, Section 3.1.10). Thus depending on the work-up method of the latter complex some useful new precursors for other types of *N*-acyliminium type bond construction are now available.

High stereocontrol in enol ether coupling was reported by Matsumura[271] by application of the titanium enolate method. Upon reacting piperidine **349a** (Scheme 30) with the Evans oxazolidinone **350a** (X=^{i}Pr,Y=H) a high ratio of *threo*/*erythro* of 94.7:5.3 could be attained thus affording the 2*R*,2′*R* isomer **351** in almost pure form and constituting an efficient route to *threo*-methylphenidate **352** (drug name Ritalin). With the oxazolidinone **350b** (X=H,Y=Ph) the 2*S*,2′*S* product possessing the opposite configuration was formed (*threo*/*erythro* 98.4:1.6). These results were explained on the basis of a tricoordinated intermediate involving the enolate oxygen and the carbonyl groups of carbamate and oxazolidinone. In a separate study by Pilli[272] analogous findings were also reported reacting the slightly different enolate **353** albeit with somewhat lesser efficacy. With both pyrrolidine and piperidine starting materials **349b** the best result was obtained in the pyrrolidine



Scheme 29.

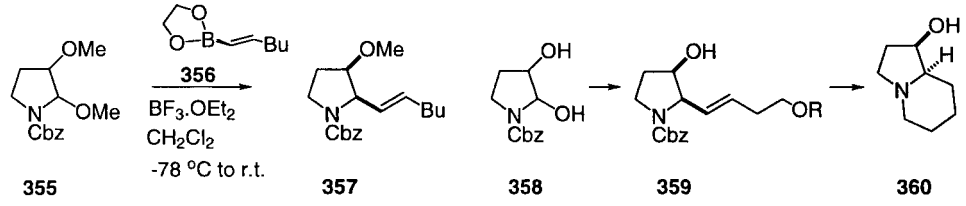


Scheme 30.

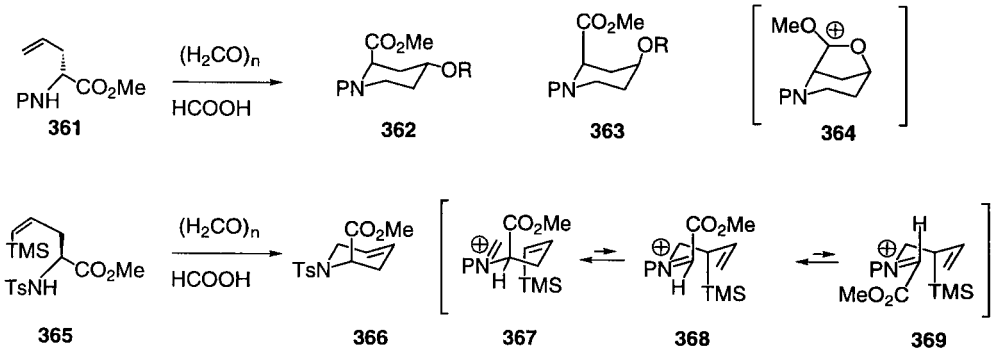
series producing the 2*S*,2′*S* methyl isomer **354** (*threo*/*erythro* 9:1). An examination of the effect of the N–R in **349b** viz R=Boc, Cbz and COOMe indicated some influence of the type of substituent R also suggesting the involvement of the carbonyl in the formation of the intermediate titanium complex (Scheme 30).

As a novel type of nucleophile in this type of substitution the use of boronates has been described by Batey.[273] In Scheme 31 the addition of the hexenyl boronate **356** to the di-OMe pyrrolidine **355** (cf. **80**, Section 3.1.7) is shown which produces the *cis* product **357** as a single diastereomer in 84% yield. The reaction was investigated for a number of different boronates and was shown to be greatly promoted by the presence of the 3-oxy substituent, thus implying some form of coordination between boron and oxygen. Furthermore the exclusive formation of *cis* substitution products in the pyrrolidine series allowed a stereocontrolled synthesis of the indolizidine **360** by carrying out the addition to the di-OH pyrrolidine **358** with the appropriate boronate to form the substituted pyrrolidine **359** (Scheme 31).

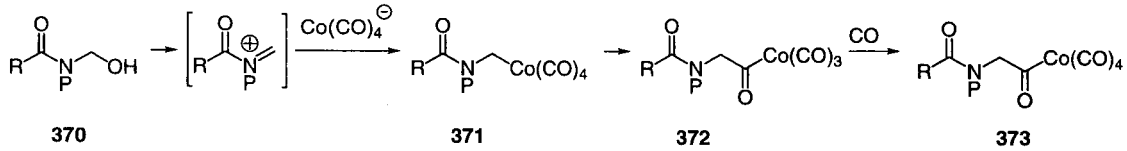
Cyclization of linear precursors derived from optically pure amino acids aiming at the synthesis of enantiopure pipecolic acids using alkenes and vinylsilanes as nucleophiles has been described by Rutjes.[274] It was found that alkenes reacted without racemization of the C-2 ester moiety, while for the vinylsilanes some loss of enantiopurity occurred. Apparently the vinylsilane is not as good as a nucleophile as the unsubstituted olefin. Thus for P=COOMe, Fmoc and Ts the ester **361** gave rise to approximately 1:1 mixtures of *trans* and *cis* products **362**



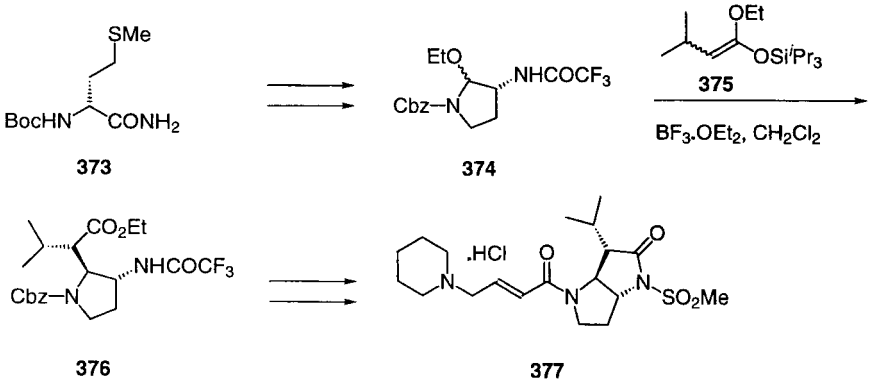
Scheme 31.



Scheme 32.



Scheme 33.



Scheme 34.

and **363** by way of the intermediate **364**. For the vinylsilane **365** a single isomer **366** was formed of which the enantiopurity amounted to 88%, indicating some isomerization via the aza-Cope pathway **367→368→369** (Scheme 32).

The examples discussed in the update clearly show a continuous accumulation of data on new extensions and applications of this synthetic method. Yet also indirectly the *N*-acyliminium intermediate has been shown to function in seemingly unrelated areas. Thus in the amidocarbonylation raction with $CO_2(CO)_8$ as a catalyst a sequence of steps was proposed[275] part of which is given in Scheme 33.

Upon condensing an aldehyde with an amide the alcohol **370** is formed which in acid reacts with the cobalt reagent via the cationic species to **371**. After insertion of CO in the chain to **372** and taking up CO the cobalt intermediate **373** is formed which gives rise to the final products. Such a process once again emphasizes the versatile character of the intermediate.

A novel class of serine protease inhibitors was developed based upon the C-3 aminopyrrolidone moiety which could be converted into the pyrrolidine *trans*-lactam as present in the target compound **377**.[276]

While earlier results on the preparation of suitable precursors for cyclizations of this type were obtained by either reduction of an appropriate C-3 aminosuccimide[277] or addition of an amine[114] to the optically pure enelactam **83** (cf. Section 3.1.8) ring closure of the latter endocyclic precursors afforded solely *cis*-fused bicyclics. Therefore the application of the exocyclic variant of the *N*-acyliminium intermediate allowed a stereoselective *trans* introduction of the enol ether nucleophile. Thus in Scheme 34 the synthesis is outlined starting from (*R*)-methionine. From the amide **373** the *N*-Cbz pyrrolidone was prepared which upon $LiBH_4$-EtOH reduction and exchange of the *N*-Boc for the trifluoroacetyl protective group afforded the precursor **374**. In a comparative study of different ketene acetal/Lewis acid combinations the isopropyl/BF_3 variant **375** gave the highest ratio of the *trans* addition product **376** and its (*R*)-isopropyl enantiomer as a 3:1 mixture which was further processed to **377**.

Finally, in recent work the reactions of 2-methoxy-1,3-oxazolidines formally derived from 1,2-amino alcohols[278] viz nor-ephedrine[279] have been described. Although the chemistry of these intermediates is strongly related to the topic of this report (cf. Section 2.2) it has not been included in the discussion and the interested reader is referred to the original references.

Acknowledgements

The contributions of Professor Henk Hiemstra to various parts of this report are highly valued.

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Biographical Sketch

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