# Chiral Heterocycles by Iminium Ion Cyclization†

Jacques Royer,* Martine Bonin, and Laurent Micouin

*Synthèse et Structure de Molécules d'Intérêt Pharmacologique, Faculté des Sciences Pharmaceutiques et Biologiques, UMR 8638 (CNRS-Université Paris-5), 4 avenue de l'Observatoire, 75270 Paris Cedex 06, France*

*Received September 25, 2003*

## Contents



## 1. Introduction

Among the different possible cyclizations leading to nitrogen-containing heterocycles, iminium ion cyclization is a widely used process exemplified by some very famous, and old, reactions such as Mannich[1] or Pictet−Spengler[2] reactions. Numerous examples of iminium ion cyclizations can be found in the asymmetric total synthesis of complex structures where, very often, they represent the key step. For example, the asymmetric synthesis of aspidophytine reported by E. J. Corey is a good illustration of the usefulness of the method: two consecutive iminium ion cyclizations leading to a pentacyclic structure and the formation and control of three stereogenic centers were described in this synthesis.[3]

Iminium ion cyclization is probably the most powerful method to form nitrogen-containing heterocycles since it offers several advantages over the other possible cyclization modes. Thus, iminium ions are very reactive intermediates allowing a large range of nucleophiles to be used. They are easily available through several well-established methods. Although iminium ions have been isolated and well charaterized, they are sensitive compounds and are typically prepared immediately prior to use without any purification, or may be stored as known stable precursors, for example, as amino ethers or as aminonitriles. Iminium ions are quite often prochiral species and thus offer the possibility of the construction of new stereogenic centers during the cyclization process. This is an important feature with regard to the preparation of chiral heterocycles.

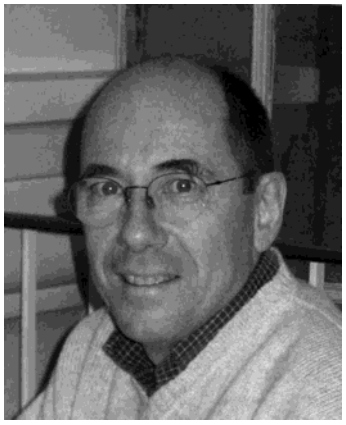
The purpose of this review is to show the importance of the iminium ion cyclization in the enantioselective synthesis of various heterocycles. This survey will focus on iminium ions which formally can arise from the condensation of an aldehyde (or ketone) and a secondary amine (for alkyliminium ions), amide, sulfonamide, or carbamate (for acyl- or tosyliminium ions) (Figure 1). Cyclizations of imines (or protonated imines) or haloiminium ions will not be covered. Only cyclization reactions leading to the creation of a stereogenic center resulting in chiral nonracemic compounds will be considered.

Since a huge variety of heterocycles can be constructed via iminium ion cyclizations, only different suitable and representative examples of cyclizations owing to the size of the formed ring, the type of nucleophile, and the mode of cyclization (*endo*- or *exo*-mode as depicted in Figure 2) will be presented. In the case of cyclizations leading to the creation of more than one cycle, the size of the smallest ring formed will be taken into account.

† Dedicated to Prof. Henri-Philippe Husson as a mark of gratitude and in recognition of his important contributions in the fields of iminium ion and alkaloid chemistry.

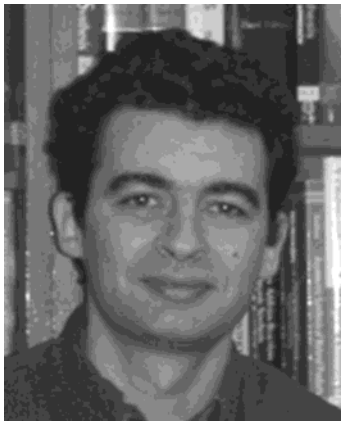
* To whom correspondence should be addressed. Phone: 33-(0)1 53739749. Fax: 33-(0)1 43291403. E-mail: jacques.royer@univ-paris5.fr.

10.1021/cr020083x CCC: $48.50 
Published on Web 03/03/2004



Jacques Royer was born in 1947. He graduated from the University Paris-XI (Orsay), where he also received his Ph.D. prepared under the supervision of Professor Michel Vilkas. After one year (1981) working as a postdostoral fellow at Delalande Research Center (a French pharmaceutical company, now Sanofi-Synthelabo), he joined the group of Professor Henri-Philippe Husson at the Institut de Chimie des Substances Naturelles (CNRS at Gif-sur-Yvette), where he developed new methods for the asymmetric synthesis of alkaloids. In 1999, he moved to the Faculty of Pharmacy in Paris, where he became in 2002 the Director of a CNRS-University laboratory (UMR 8638). Since 1990, he has been Research Director at the CNRS. His main research interest is concerned with the asymmetric synthesis of nitrogen-containing compounds: alkaloids, amino acids, and amino alcohols.

Martine Bonin was born in 1957. She trained as a pharmacist at the University of Bordeaux (1979), and obtained her Ph.D. in chemistry from the University of Paris-Sud (Orsay) in1986 on the total synthesis of piperidine alkaloids. Enlisted as a researcher at CNRS in Professor Henri-Philippe Husson's group (1983), she began a collaboration with Dr. J. -C. Quirion on aminonitrile and oxazolidine synthons and followed that with a one-year postdoctoral stay in Orsay (Drs. G. Balavoine and F. Guibe, organometallic and radical chemistry, 1992). Since 1998, she has worked with Dr. Laurent Micouin; their main research interests are the development of new diastereoselective routes giving access to polyfunctional nitrogen derivatives for medicinal or pharmacological applications.



Laurent Micouin was born in Clermont Ferrand in 1968. He studied at the Ecole Nationale Supérieure de Chimie de Paris, where he obtained an engineering diploma in 1990. He obtained his Ph.D. in the laboratory of Professor Henri-Philippe Husson (University Paris-V) under the guidance of Professor J.-C. Quirion in 1995. After a postdoctoral stay in Marburg (Germany) as a Humboldt Fellow under the direction of Professor Paul Knochel, he obtained a permanent position at CNRS in 1996 and turned back to Paris (Faculty of Pharmacy, Paris-V) as Chargé de Recherche. His scientific interests include the development of new methods in the field of asymmetric synthesis of nitrogen compounds, using diastereoselective dipolar cycloadditions, enantioselective desymmetrizations, or organoaluminum chemistry, as well as the synthesis of bioactive compounds or tools for biological investigations.

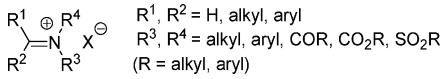



**Figure 1.**

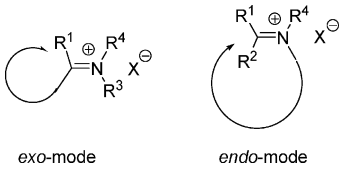



**Figure 2.**

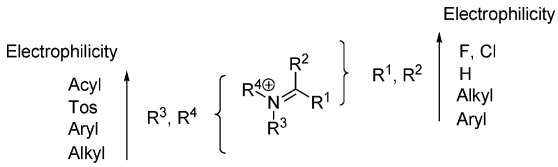



**Figure 3.**

Several aspects of this survey have been reviewed. References to these accounts will be given in the specific sections.

## *2. Generalities*

### 2.1. Iminium Reactivity

Numerous reactivity studies have been performed on iminium ions, including spectroscopic investigations, X-ray structure analyses, and theoretical calculations.[4] The general cationic character of such species is highly dependent on their substitution pattern (Figure 3).

These reactive species can be divided into two main categories: alkyl- and acyliminiums. The electrophilicity of unsubstituted alkyliminiums ($R^1 = R^2 = H$) has been evaluated by NMR measurements and calculations. *N*,*N*-Dialkyliminium ions ($R^3 = R^4 = i$Pr or Me) have an electrophilicity similar to that of *N*-methylacridinium ions, whereas less stabilized systems ($R^3 = Ph$, $R^4 = Me$, $R^1 = R^2 = H$ or $R^3 = R^4 = Me$, $R^1 = Cl$) have a reactivity comparable to that of the tropylium ion.[5,6]

Introduction of electron-withdrawing groups on nitrogen leads to a more electrophilic species. In the case of *N*-acyliminium ions, and to a lesser extent for tosyliminiums, the electron density on nitrogen is less available for cation stabilization, leading to more reactive systems. In a comparative NMR study

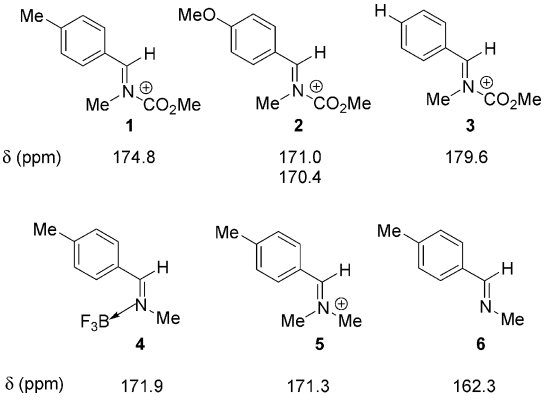



**Figure 4.**

on acyclic activated imines based on $^{13}C$ chemical shifts, the following order of electrophilicity has been assigned: acyliminium ion **1** > alkyliminium ion **5** > imine−$BF_3$ complex **4** > imine **6**.[7] Even though acyliminiums are highly electrophilic species, they are however less electrophilic in comparison with the corresponding aldehydes or oxoniums (Figure 4).[8] A stabilizing effect by OMe and Me groups has also been noted on such species.

The intrinsic gas-phase electrophilic reactivities of cyclic *N*-alkyl- and *N*-acyliminiums with allylsilane nucleophiles have been compared by mass spectrometry experiments and charge density calculations.[9] This study indicates that, toward nucleophile addition, and in the absence of major solvent or counterion effects, five-membered ring *N*-acyliminiums with endocyclic *N*-carbonyl or exocyclic *N*-alkoxycarbonyl, followed by their six-membered ring analogues, are the most reactive *N*-acyliminium ions.

Not only do acyliminium and alkyliminium ions have different electrophilic character, but the presence of electron-withdrawing groups on nitrogen also has a dramatic influence on their behavior toward nucleophiles. Acyliminium species generally react in a fast and irreversible manner, whereas the addition to alkyliminiums can be reversible. In this case, nitrogen's forming lone pair favors fragmentation processes (Grob, retro-Mannich) which further play an important role in the stereochemical outcome of the reaction.[10]

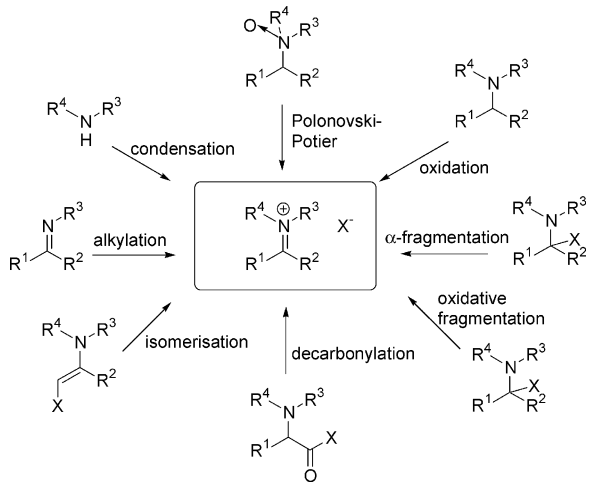
## 2.2. Preparation of Iminium Ions

Numerous routes to iminium ions have been devised (Scheme 1).[11]

Condensation of amines with aldehydes is a classical entry to alkyliminiums. This reaction generally occurs under acidic conditions, in protic solvents. Condensation with ketones is hampered by the reaction's reversibility. Intramolecular reactions leading to cyclic intermediates or the intramolecular trapping of the final iminium can in some cases circumvent this problem. In some other cases, the use of orthoformate esters can also help to remove the water formed, and the use of perchlorate or fluoroborate salts of amines can improve the yield of condensation.

Amines bearing electron-withdrawing groups are usually less efficient in condensation reactions.

**Scheme 1**




Acyliminiums can however be prepared from secondary acylimines and acetals with acidic catalysis, and are generally trapped in situ.

Alkyliminium salts are readily produced from *C*-protonation or *N*-alkylation of the corresponding enamines. This behavior has been illustrated in the chemistry of 1,2,3,4-tetrahydropyridines and the synthesis or biosynthesis of alkaloids. Alkylation or acylation of imines is another valuable strategy for the preparation of iminium species. For the pyridine series, the formation of acylpyridiniums by acylation provides a powerful tool for natural product synthesis.[12]

Amine *N*-oxides can lead to iminiums by an α-deprotonation−elimination sequence.[13] The Polonovski−Potier reaction with different promoters is generally used.[14] The regioselectivity of this type of reaction is usually substrate-dependent.

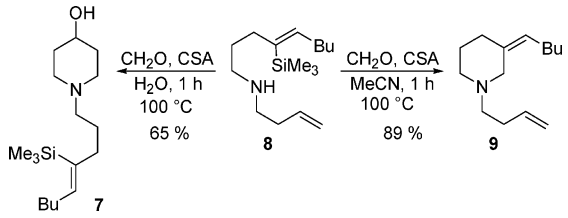
Numerous oxidative methods have been devised for the preparation of alkyl- and acyliminiums, including the use of chemical oxidizing reagents,[15] photochemical methods,[16] free radical processes,[17] and electrochemical oxidations.[18] The resulting iminium ions are generally trapped in situ either in an intramolecular way or by the solvent. Recent studies have shown that "free iminium species" can be electrogenerated at low temperature, and the accumulated cations in solution can then be reacted with various nucleophiles.[19]

α-Fragmentation is probably the most frequently used method for the generation of iminium species.[20] The equilibrium between the fragmented species and its precursor depends on the electronic properties of the nitrogen substituents, the nature of the leaving group, and the method of activation (Lewis acid, acylation,[21] or silylation,[22] thermal, and so forth). Fragmentation of α-silylated[23a−c] or stannylated[23d] amines can be performed under oxidative conditions, via the formation of a transient nitrogen-centered radical cation. Iminiums can also be generated by decarbonylative processes,[24] cascade reactions,[25] or the Schmidt rearrangement.[26]

## 2.3. General Aspects of Iminium Cyclization

The regio- and stereochemical outcome of cyclization reactions of iminium ions is governed by many

**Scheme 2**




factors. With $\pi$-nucleophiles, the ring closure results in the development of a carbocation, which can then evolve by elimination, rearrangement, inter- or intramolecular trapping, or fragmentation back[27] to the starting iminium. With aromatic nucleophiles, rearomatization follows cyclization (Pictet−Spengler reaction). The reaction is more complex with alkenes (Scheme 2). [28]

In a poorly nucleophilic solvent such as acetonitrile, compound **9** that comes from the most stabilized cationic intermediate was obtained as a single cyclization product. Identical treatment in water resulted in the formation of piperidine **7**, showing that even weak nucleophiles can participate in iminium ion cyclization in polar, nucleophilic solvents.

Baldwin's rules, based on the Bürgi−Dunitz trajectory of a nucleophile onto a neutral $\pi$-system,[29] have been proposed to account for cyclization processes.[30] However, the "unfavored" 5-*endo-trig* cyclizations do occur readily with iminiums as reactive species. For cationic cyclizations involving $\pi$-nucleophiles, a more appropriate description has been proposed by Ben-Ishai[31] by specifying the mode of cyclization for both termini (Figure 5).

Using this classification, it has been demonstrated that 5-*endo-endo-trig* cyclization is disfavored with ground-state intermediates while the corresponding 5-*exo-endo-trig* and 5-*exo-exo-trig* cyclizations are favored, and, to a lesser extent, the 5-*endo-exo-trig* ring closure.[32]

Cyclization reactions with organometallic nucleophiles are not reversible, and the stereochemical outcome of the ring process is the result of a kinetically controlled cyclization. Reversible reactions can be observed with $\pi$-nucleophiles, and even more frequently with non-carbon nucleophiles. This reversibility is generally dependent on the substitution pattern of the reactive iminium species and on the basicity of the nitrogen atom of the final heterocycle.

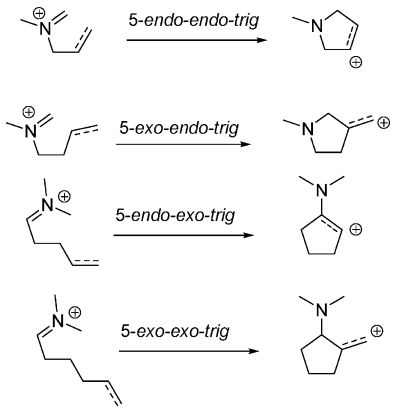



**Figure 5.**

Using the appropriate conditions, complementary stereoselectivities of the cyclization can be obtained under thermodynamic or kinetic conditions.

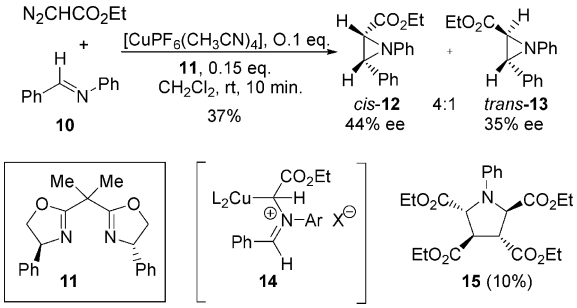
## 3. Cyclization Leading to Three-Membered Rings

This type of cyclization, as those involving the four-membered rings, constitutes a rather special case since most of the time the cyclization mechanism has to be carefully examined to attest whether an iminium ion is involved. It is only possible in some of these cases to make assumptions on a plausible mechanism involving an iminium ion cyclization.

### 3.1. *endo*-Mode Cyclization

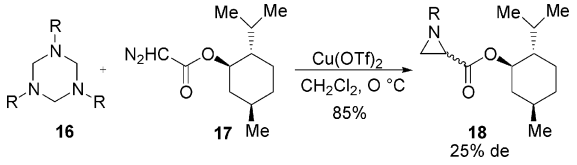
This cyclization mode results in the formation of an aziridine ring. To the best of our knowledge, the only report illustrating this cyclization is the transfer of a carbene to an imine. Two independent reports of asymmetric aziridine preparation through this process appeared in 1995. Treatment of **10** with ethyl diazoacetate in the presence of copper(I) hexafluorophosphate and chiral bis(hydrooxazole)copper **11** led to the formation of enantioenriched *cis*- and *trans*-aziridines **12** and **13** in low yields and ee's (up to 44%) (Scheme 3).[33]

**Scheme 3**




The authors proposed a mechanism involving the formation of a transient bis(dihydrooxazo)copper carbene complex which reacts with the imine nitrogen to form the iminium ion **14**. An azomethine ylide is formed from this iminium and cyclizes to the aziridine. Obtention of a minor amount of racemic pyrrolidine **15** suggests that a fraction of dissociated azomethine ylide can react with the in situ generated fumarate. A similar reaction has been reported from *N*-methylideneaniline trimer **16** (R = Ph) and *O*-menthyl diazoacetate **17** with $Cu(OTf)_2$ as a catalyst, showing an excellent 85% yield and a modest 25% de (Scheme 4).[34]

**Scheme 4**



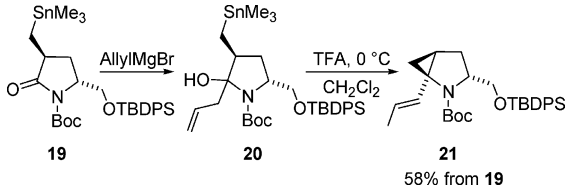

It should be noticed that synthesis of chiral aziridines via the condensation of alkyl diazoacetates and chiral derivatives of hexahydrotriazines **16** catalyzed

by Lewis acid ($SnCl_4$, $TiCl_4$) does not involve an iminium ion as intermediate.[35]

### 3.2. *exo*-Mode Cyclization

It has been recently reported that a trimethylstannyl species cyclizes on an acyliminium ion to form a fused cyclopropane ring.[36] Interesting 4,5-methanopyrrolidines were obtained with a stereochemistry controlled by the configuration of the trimethylstannyl side chain. The acyliminium ion, generated after acidic treatment of *anti*-α-hydroxycarbamate **20** obtained by addition of a Grignard reagent on a γ-lactam, led to the expected 4,5-*trans*-methano-D-proline analogue **21** (Scheme 5).

**Scheme 5**

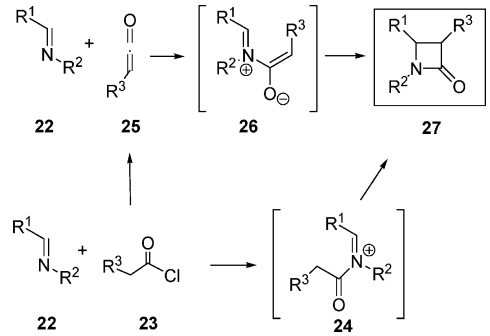



## 4. Cyclization Leading to Four-Membered Rings

As in the previous section, the formation of azetidines can occur via an intermediate iminium ion. Such a cyclization mode has been illustrated by the formation of β-lactams via the Staudinger reaction, which consists of a formal cycloaddition of an imine with a ketene. This reaction is well documented, and its asymmetric version has been reviewed.[37] The generally accepted mechanism (Scheme 6) involves two steps, with first an addition of imine **22** to ketene **25** that leads to the iminium dipolar intermediate **26**, and the formation of β-lactam **27** through a conrotatory cyclization. The ketene can be generated in situ from acyl chloride **23** using a tertiary amine as base. In this last case, it has also been proposed by some authors that acyliminium **24** is first formed by condensation of the acyl chloride to the imine.[38] In both cases, the reaction involves a zwitterionic species.

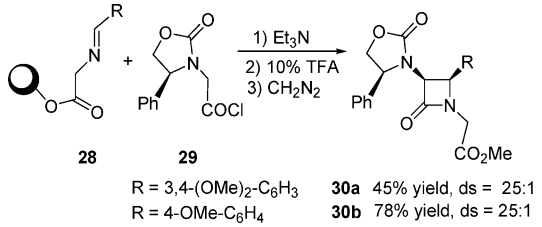
A relative *cis* configuration is commonly obtained from the usually more stable (*E*)-imine. However, the nature of the substituents or the experimental conditions (including the order of introduction of the reagents) can exert a strong influence on the stereochemical course of this reaction.[37] Some efforts have been made to favor the formation of the *trans* isomers. A two-step sequence from *N*-silylated imines has been proposed,[38] leading to the preferential formation of the *trans*-lactams.

**Scheme 6**



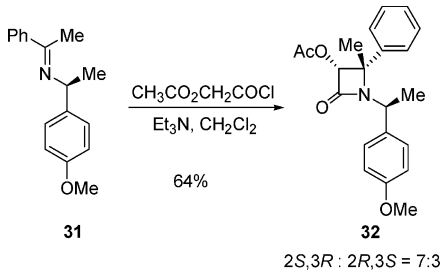

The synthesis of enantiopur β-lactams via the Staudinger reaction can be acheived by attaching a suitable chiral auxiliary to the imine (at the carbon or the nitrogen end) or to the carbene (or acyl chloride precursor). Recent examples found in the literature with different chiral auxiliaries[39] show that excellent stereoselectivities can be obtained using acyl chorides bound to a chiral oxazolidinone derived from phenylglycinol.[40] Asymmetric solid-phase synthesis of β-lactams using this oxazolidinone as a chiral auxiliary has also been reported:[39a] the resin-bound imines **28** can react with chiral acyl chloride **29** in the presence of triethylamine to give the optically active β-lactams **30a,b** after cleavage (Scheme 7).

**Scheme 7**



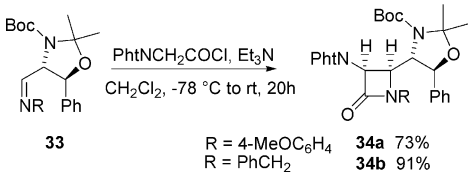

Imine **31** has been used in an efficient asymmetric synthesis of β-lactam **32** (Scheme 8), on the way to the docetaxel side chain synthesis.[39e]

**Scheme 8**



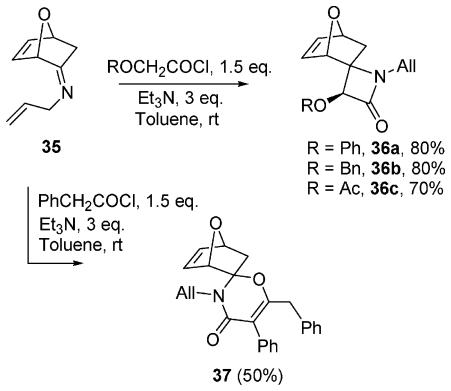

Cycloaddition with imines bearing a stereogenic center at the carbon end, as for **33** (Scheme 9), has also been investigated, leading to β-lactams **34a,b** in a diastereoselective manner.[41]

**Scheme 9**




An interesting study on the Staudinger reaction with imines derived from 7-oxanorbornenone has been recently described (Scheme 10).[39d] Although only racemic compounds are involved in this work, several features deserve to be examined. Whereas **35** reacts with aryl- or alkyloxyacetic acid chlorides to form β-lactams **36a**−**c** in good yields, when imine **35** reacts with arylacetic acid choride in the presence of $Et_3N$, oxazinone **37** is formed instead of β-lactams. The formation of these oxazinones is consistent with a

**Scheme 10**




mechanism involving the initial formation of an acyliminium which, in the case of arylacetic acyl chloride, reacts with an excess of acyl chloride to give oxazinones **37**.

A catalytic version of the asymmetric Staudinger reaction has recently been reported.[42] However, as the reaction is slowed by the use of an electron-deficient *N*-tosylimine, the mechanism is different and does not involve a cyclization on iminium species.

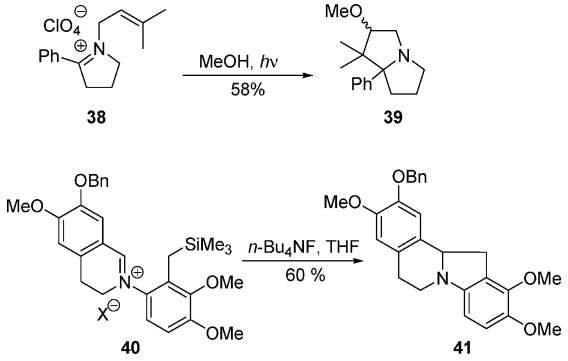
## *5. Cyclization Leading to Five-Membered Rings*

### 5.1. Cyclization Leading to Five-Membered Rings by Formation of a C–C Bond

#### *5.1.1. endo-Mode Cyclization*

**5.1.1.1. 5-*endo-endo* Cyclization.** According to the modified Baldwin rules, 5-*endo-endo* cyclization with $\pi$-nucleophiles is a disfavored process with ground-state reactive species. However, cyclization in an *endo* mode can occur under photochemical conditions, with a diradical species as a reactive intermediate.[43] A similar mode of cyclization has been reported with compound **40** (Scheme 11).

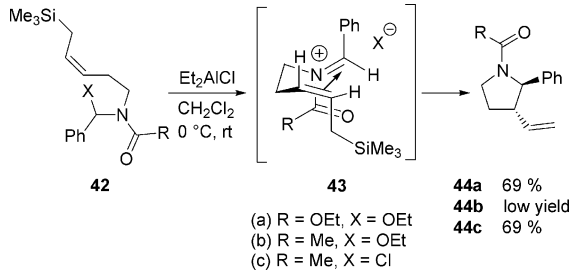
**Scheme 11**




This *endo-endo* selectivity can be formulated as a six-electron electrocyclization. Despite synthetic utility, this mode of cyclization has not been exploited for the preparation of enantiomerically pure compounds.

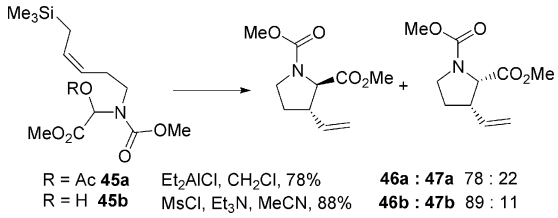
**5.1.1.2. 5-*exo-endo* Cyclizations.** *5.1.1.2.1. From Acyclic Precursors.* The diastereoselective synthesis of pyrrolidines from racemic linear precursors using a 5-*exo-endo-trig* cyclization has been reported (Scheme 12).[44]

**Scheme 12**




The exclusive formation of *trans* stereoisomers **44** was explained by the formation of a transient $\pi$-complex having the most stable *E* form of acyliminium in a planar *s-cis* conformation, with the six atoms participating in the ring formation arranged in a chair-type conformation. The reactivity proved to be dependent on the carbonyl functional group carried by nitrogen and the nature of the leaving group. A slightly different stereochemical outcome of this kind of cyclization was observed in the transformation of **45a** or **45b** to give **46** and **47** (Scheme 13).[45]

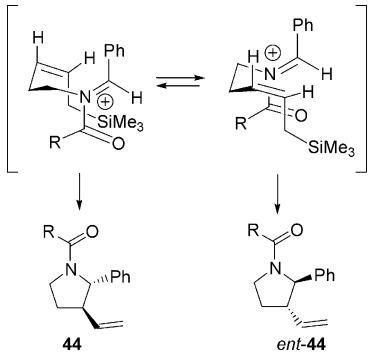
**Scheme 13**




Although unexplained, this example shows that substrate and reaction conditions can be tuned to get a highly stereoselective cyclization.

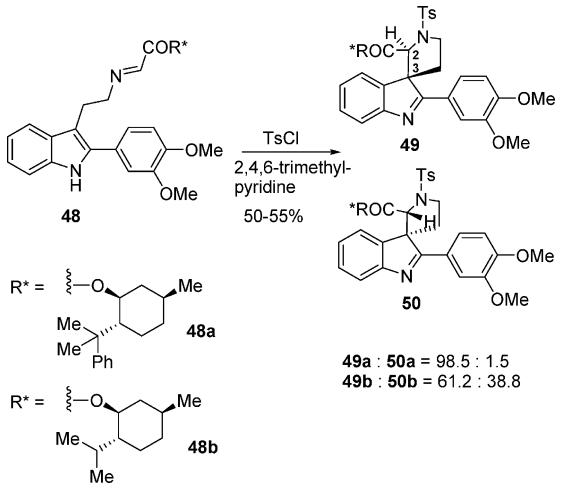
If a good *trans* relative configuration can be obtained in such a cyclization, the elaboration of enantiopure pyrrolidine requires the control of bond rotation to favor the annulation from only one face of the iminium (Scheme 14).

**Scheme 14**



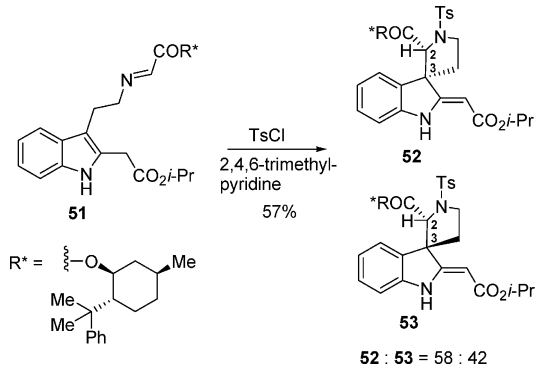

This approach was used in the enantioselective synthesis of spirocyclic indole derivatives **49** and **50**.[46] The relative 2,3-configuration, already established by Woodward and co-workers on similar structures,[47] can be explained by a kinetically controlled cyclization on a (*Z*)-tolsyliminium ion, arising from the tosylation of the (*E*)-imine with retention of configuration (Scheme 15).

**Scheme 15**



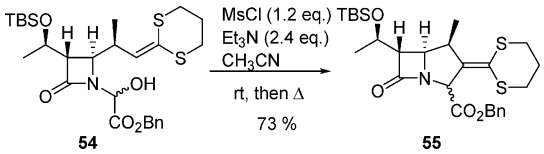

The use of a suitable chiral auxiliary enables the control of the absolute configuration of the spirocyclic center. The more rigid camphorsulfonamide-based auxiliary leads to similar results, however with a much slower cyclization rate.[48] A surprisingly low control of relative 2,3-configuration was obtained starting from imine **51**. This was explained by the isomerization of the transient iminium by a non-stereoselective, reversible, intramolecular Mannich-type side reaction (Scheme 16).

**Scheme 16**



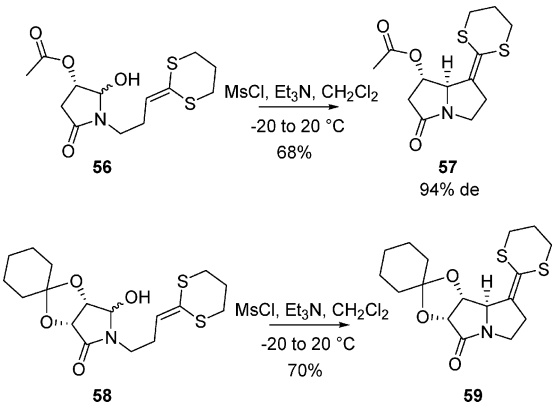

The formation of a mixture of stereoisomeric acyliminiums is also probably responsible for the lack of stereocontrol in the preparation of bicyclic compound **55**, an intermediate in the synthesis of carbapenem derivatives (Scheme 17).[49]

**Scheme 17**




*5.1.1.2.2. From Cyclic Precursors.* The easiest way to overcome the isomerization problem of iminium species is to include them in cyclic structures. This strategy has been widely used, especially for the synthesis of various polycyclic alkaloids.

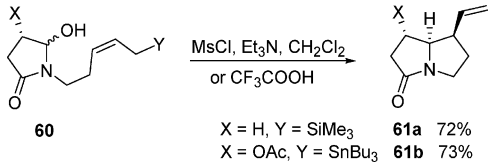
**Scheme 18**




A general entry into the pyrrolizidine general framework has been devised from a directed acyliminium−ketene dithioacetal cyclization (Scheme 18).[50]

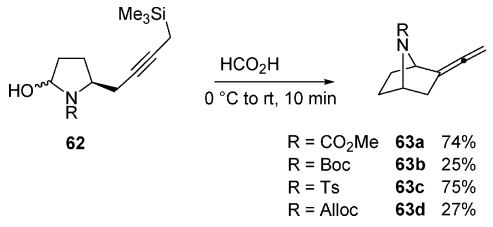
The high stereoselectivity of the cyclization does not arise from a neighboring group participation of the acetate, since similar results could be obtained from hydroxylactam **58**. A similar strategy, with different $\pi$-nucleophiles, has been used for the elaboration of the 5,5-pyrrolizidine framework (Scheme 19).[51]

**Scheme 19**




The synthesis of the 7-azabicyclo[2.2.1]heptane skeleton has also been performed by intramolecular cyclization onto a cyclic acyliminium species (Scheme 20).[52a]

**Scheme 20**



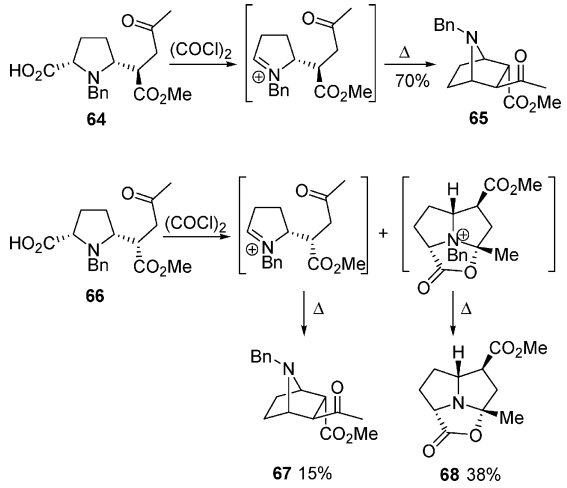

The choice of the nitrogen protective group proved to be crucial for an efficient cyclization.

The use of intramolecular Mannich cyclization has been described for the preparation of the azabicyclo-[2,2,1]heptane framework (Scheme 21).[52b]

Different reactivity patterns have been observed starting from **64** or its diastereomer **66**. *trans* bicyclic compound **65** was obtained in 70% yield, whereas **66** led to a mixture of bicycle **67** coming from a decarbonylation process and pyrrolizidine **68**. This competitive reaction explains the low yield of bicycle **67** in comparison with that found for bicycle **65**.

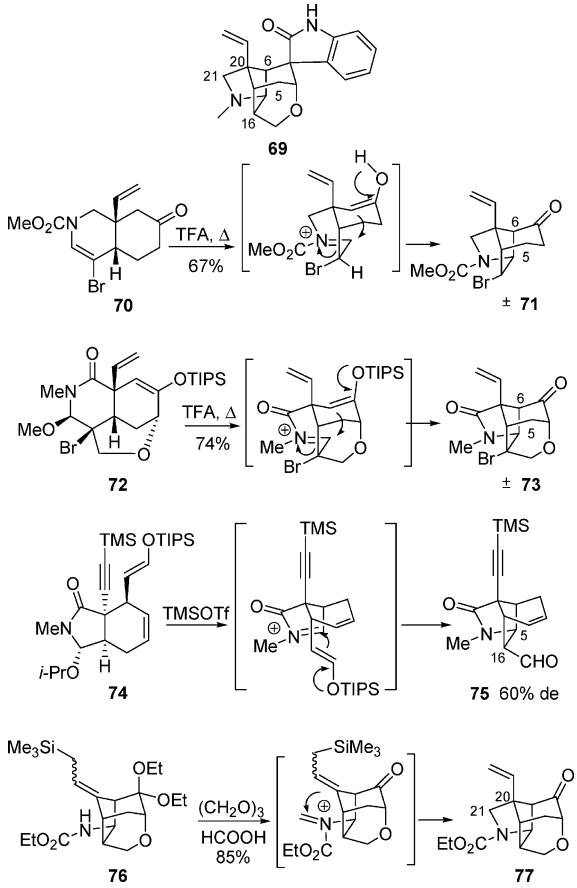
Several complex polycyclic natural products have been synthesized using a 5-*exo*-*endo*-*trig* cyclization as a key step. The different synthetic approaches of

**Scheme 21**




gelsemine (**69**) illustrate the general usefulness of this reaction (Scheme 22).[53]

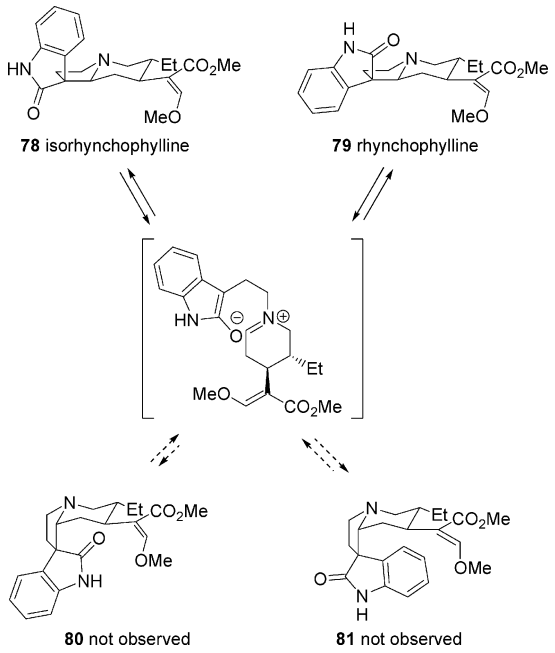
**Scheme 22**




Thus, the tricyclic skeleton has been constructed by the formation of the C5−C6,[54] the C5−C16,[55]or the C20−C21 bond.[56]

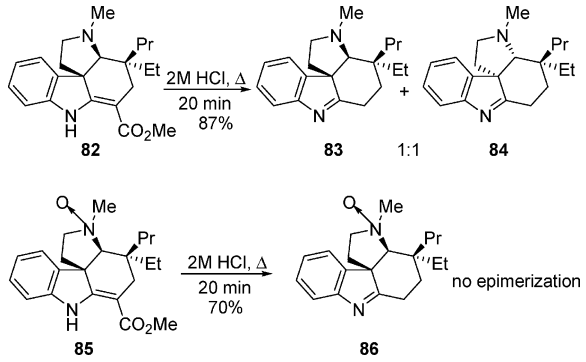
Most of the *5-exo-endo-trig* cyclizations reported above are kinetically controlled, and the stereoselectivity has been explained by transition-state analysis (except for Scheme 21). In some cases, however, the cyclization's issue might be the result of thermodynamic control. This behavior is typical in the indole alkaloid biogenesis and synthesis.[57] The isolation, from several natural sources, of isorhynchophylline (**78**) and rhynchophylline (**79**), and the absence of their pseudo-oxoindole isomers **80** and **81** is a good example of such a stereocontrol (Scheme 23).

**Scheme 23**




This equilibration, which has been noticed several times, is favored by the presence of a strained structure and/or a tertiary basic nitrogen atom, which leads to Grob-type fragmentations under acidic conditions. The role of the nitrogen atom basicity has been illustrated in degradation studies of (−)-tabersonine tetracycle **82** (Scheme 24).[58]

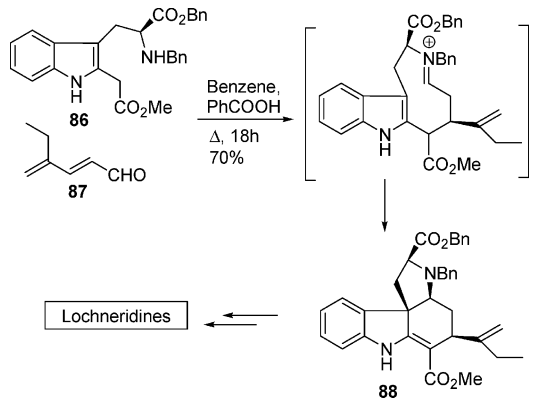
**Scheme 24**




Compound **82** led to an equimolar mixture of two isomeric indolenines (**83** and **84**) whereas its *N*-oxide **85** led only to a decarboxylated species, without any Grob-type fragmentation.

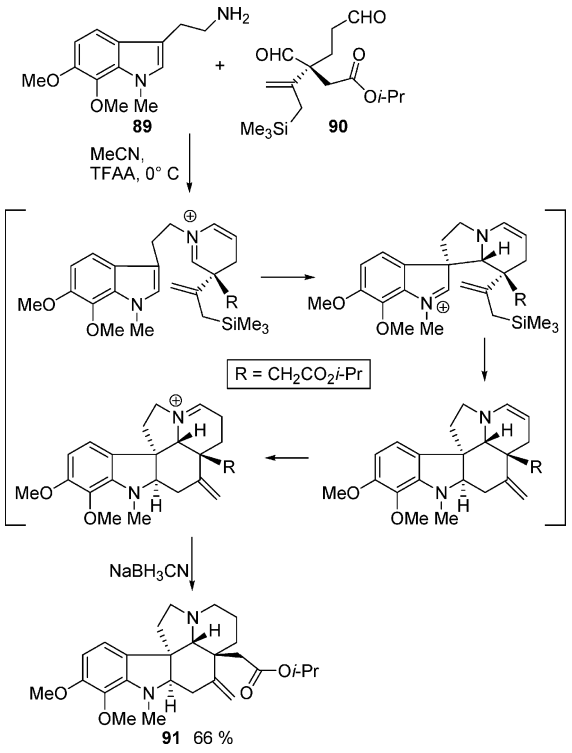
Since this isomerization process is believed to occur in several alkaloid biosyntheses, all the synthetic planning involving a biomimetic transannular cyclization should deliver advanced intermediates possessing the natural relative configuration as major stereomers. In the enantioselective synthesis of lochneridines, the general skeleton **88** of this strychnan-type alkaloid has been constructed by such a reaction (Scheme 25).[59]

**Scheme 25**




Aspidophytine has also been obtained by two successive cyclizations onto iminiums (Scheme 26).[3]

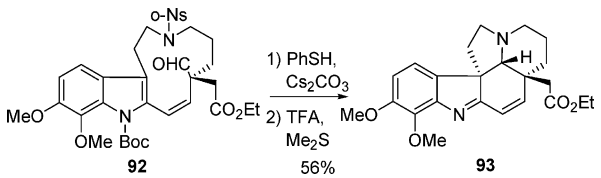
**Scheme 26**




In this approach, compound **91** was obtained as a single isomer in 66% yield after reduction and chromatographic purification. The reasons for this selectivity were not discussed.

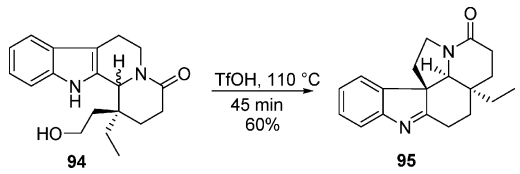
In another approach, the aspidophytine skeleton has been constructed via a diastereoselective intramolecular Mannich reaction starting from **92** (Scheme 27).[60]

**Scheme 27**



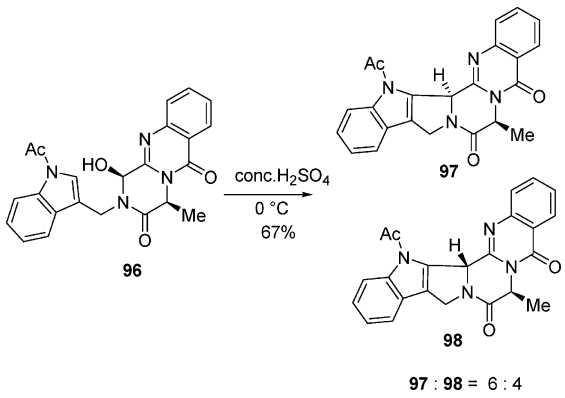

A fragmentation−cyclization sequence can occur with acyliminium species, albeit under harsher reaction conditions. The construction of the aspidospermine skeleton has been described through this ring contraction, by treatment of **94** in triflic acid at 100 °C (Scheme 28).[61]

**Scheme 28**



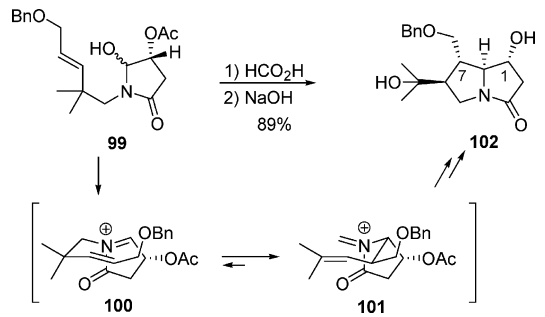

Similarly, the 6/4 diastereomeric ratio of compounds **97** and **98** has been explained by the result of a cyclization under thermodynamic control (Scheme 29).[62]

**Scheme 29**




*5.1.1.2.3. From an Aza-Cope Mannich Tandem Reaction.* In the *5-exo-endo-trig* cyclizations (and also for the *6-endo-endo* ring closure) with $\pi$−nucleophiles, a charged 1,5-diolefinic species is generated as a reactive intermediate. It can therefore rapidly reorganize under mild conditions via a cationic Cope rearrangement.[63] Cyclization via rearrangement can be favored by suitable substitutions. Introduction of a *gem*-dimethyl group enables the formation of pyrrolizidinone **102**, with the nucleophilic capture of the transient tertiary carbocation (Scheme 30). The generation of the electronically more attractive olefin **101** during the rearrangement is sufficient to drive the reaction in one direction.[64]

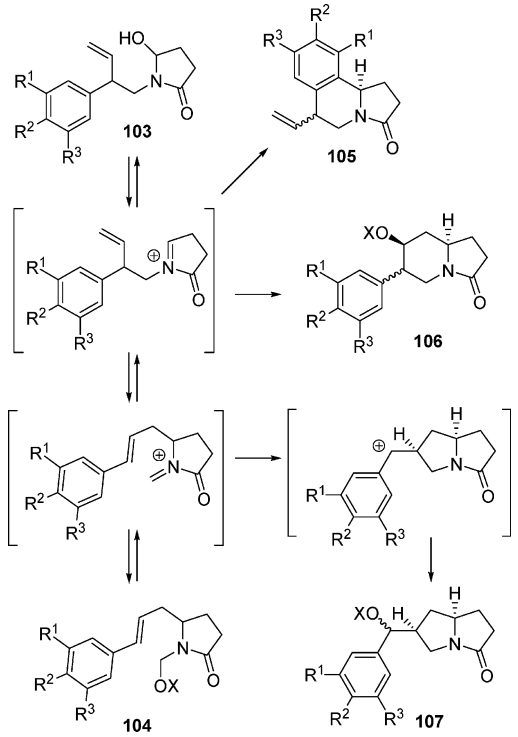
**Scheme 30**




It is worth noting that the relative configuration of the C1 and C7 centers, coming from a six-membered chair transition state, is opposite that obtained by a direct cyclization using allylsilane nucleophiles (see Scheme 19).

Although this example showed that the sigmatropic rearrangement can be directed to the formation of a single cyclization product, this is usually not the case. In a general study, Speckamp and co-workers described the different product distributions resulting from aza-Cope rearrangements trapped by external nucleophiles starting from various substituted aromatic cyclic *N*-acyliminium precursors (Scheme 31).[65]

**Scheme 31**

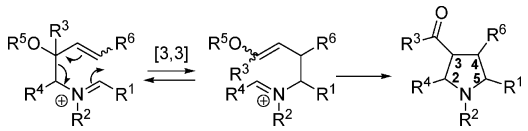



Product distribution proved to be dependent on the reaction medium, substitution pattern, and reaction time. In most of the cases, a mixture of at least two compounds (**106** and **107**) arising from the initial and the rearranged iminium was obtained.

The reversibility of this rearrangement is generally unproductive (and can lead to racemization, vide supra) unless the equilibrium is biased by thermodynamic factors or shifted by a subsequent highly exothermic reaction. In this case, an aza-Cope rearrangement followed by an irreversible reaction might lead to cyclic structures via thermodynamically unfavored iminiums.

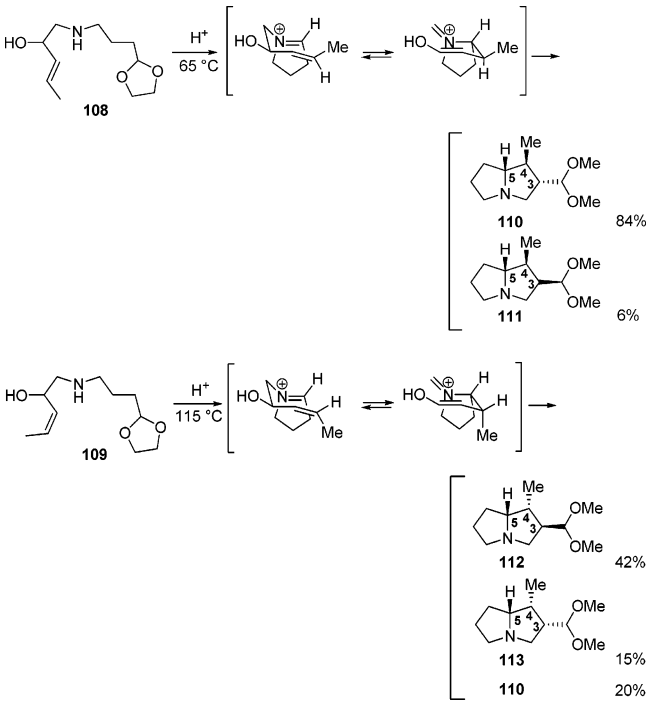
This concept has been employed in numerous syntheses, especially by the group of Overman, with the use of the Mannich reaction as an aza-Cope rearrangement terminator (Scheme 32).[10]

**Scheme 32**




In this process, several asymmetric centers are created. The prediction of the relative configuration of the final pyrrolidine can be performed by the analysis of the transition state of the Mannich

**Scheme 33**

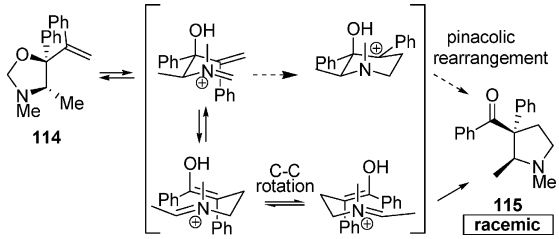



cyclization, with a geometry coming from the rearrangement for this exothermic reaction (Scheme 33).

In a comparative study, it was shown that (*E*)-alkenes rearranged to 4,5-*cis*-pyrrolizidines via a chair topography, while the corresponding *trans*-olefins required significantly higher temperature to furnish 4,5-*trans*-pyrrolizidines, albeit in lower stereoselectivity and with a small amount of compound **110**, probably via a boat topography.[66]

The formation of an acyclic iminium intermediate in such a reaction can lead to uncontrolled epimerization. Disubstituted pyrrolidine **115** could be diastereoselectively prepared in a 79% yield from enantiomerically pure oxazolidine via an aza-cope Mannich cyclization, but in racemic form (Scheme 34).

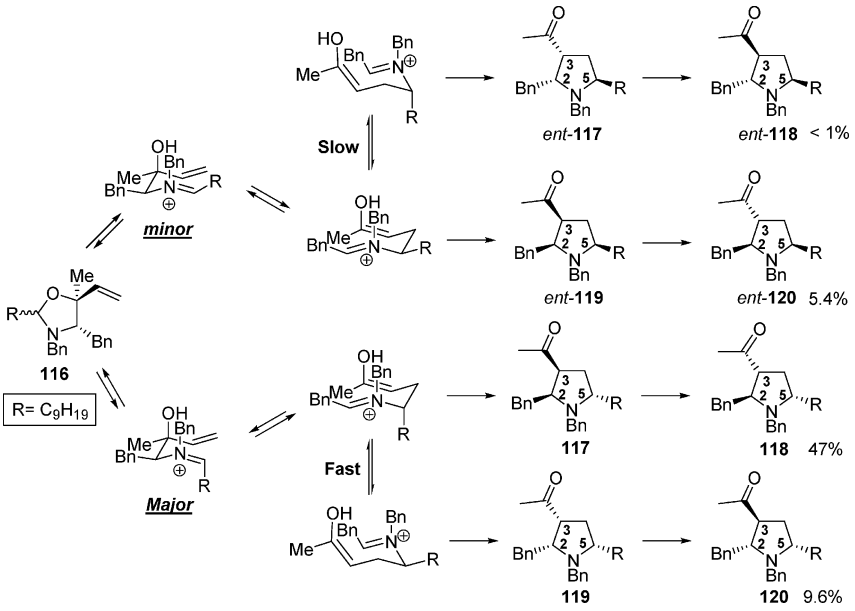
**Scheme 34**




Racemization was explained by the suppression of the stereogenic center during the rearrangement *and* fast C−C bond rotation that leads to cyclization on both faces of the transient iminium. Thus, racemic material is obtained if the rotation is faster than the cyclization. This racemization rules out the possible cyclization−pinacolic rearrangement for the overall transformation, since this route should deliver enantiopure material.

The racemization with acyclic intermediates is not unavoidable, and can be controlled by the iminium geometries and C−C bond rotation rate. Several

**Scheme 35**




strategies have been used to avoid the problem of C−C bond rotation.

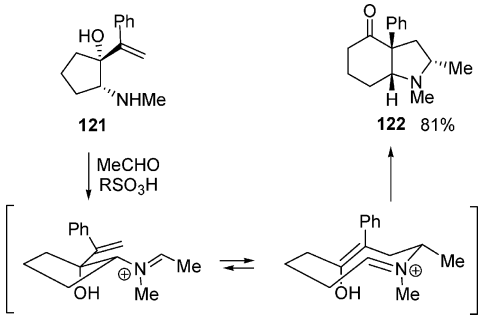
The enantioselective syntheses of all four stereoisomers of preussin have been described, using an aza-Cope Mannich rearrangement (Scheme 35).[67]

Thus, compound **118** could be isolated in 47% yield with 97% ee, with compound **120** (15%, 28% ee) as a side product. This result was rationalized by the preferential formation of (*Z*)-iminium as a major intermediate, leading to compound **117**, and in a lesser extent compound **119** after C−C bond rotation. The minor (*E*)-iminium is responsible for the formation of pyrrolidine *ent*-**119**, with almost no conformational equilibrium with intermediate *ent*-**117**.

All the 2,3-*cis* intermediates led to the corresponding more stable *trans*-pyrrolidines by a retro-Mannich, Mannich tandem process. The presence of a bulky substituent on the carbonated linker between the iminium and the enol group is probably responsible for a higher barrier of conformational equilibrium than in the case of unsubstituted iminiums (Scheme 34).

Conformational equilibrium can also be suppressed by the formation of a macrocyclic iminium, leading to bicyclic pyrrolidines after a transannular Mannich reaction (Scheme 36).[68]

**Scheme 36**




The stereochemistry of the final compound **122** has been explained by the formation of an (*E*)-iminium in a chair conformation.

The tandem aza-Cope−Mannich cyclization has been exploited in numerous alkaloid syntheses, mainly by the Overman group, as depicted in Figure 6.[69]

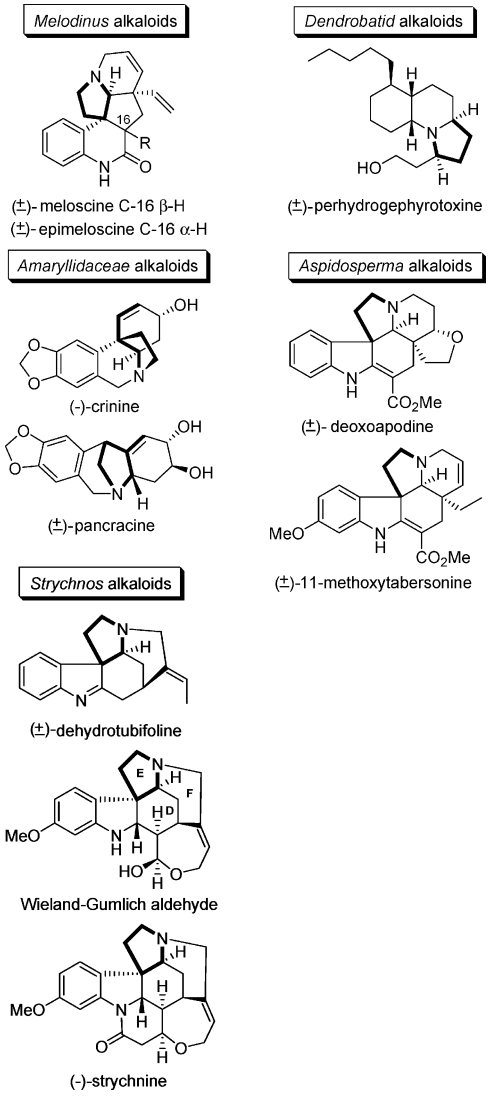
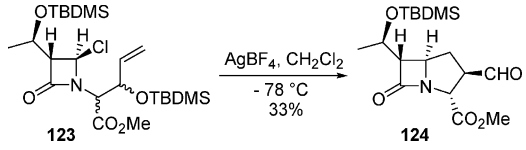



**Figure 6.**

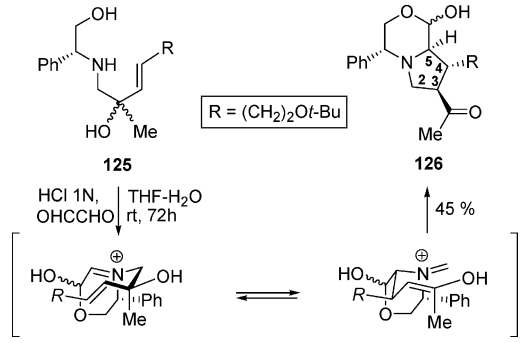
The stereochemistry of the final pyrrolidine can also be controlled by stereogenic centers not directly involved in the sigmatropic rearrangement. An enantioselective approach to the carbapenem skeleton has been proposed. The relative configuration of the final compound results from the influence of a stereocenter located in the $\beta$-lactam adjacent ring (Scheme 37).[70]

**Scheme 37**



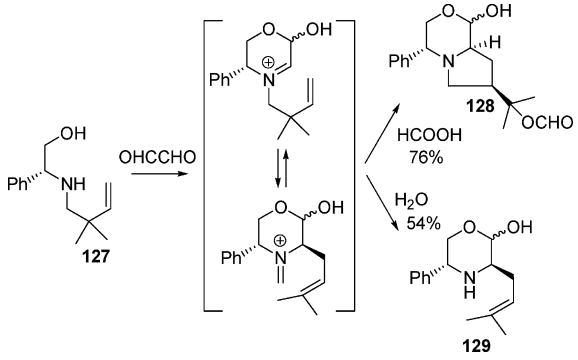

A general strategy, based on the use of chiral auxiliaries, was developed for the synthesis of polysubstitued prolines (Scheme 38).[71]

**Scheme 38**




In this process, the cyclization occurred on the less sterically hindered cyclic iminium face, leading to a good control of the C-5 configuration. The C-3 and C-4 configurations arose from a chairlike transition state with a synclinal attack of the enol. Interestingly, a similar tandem reaction could be performed using an ene−iminium cyclization as terminator (Scheme 39). If water was used instead of formic acid, hydrolysis product **129** was obtained.

**Scheme 39**




This example shows that even if the Mannich reaction has been intensively used to direct the cationic aza-Cope rearrangement, some other irreversible reactions can play the same role and be of interest in the stereoselective construction of pyrrolidine derivatives.

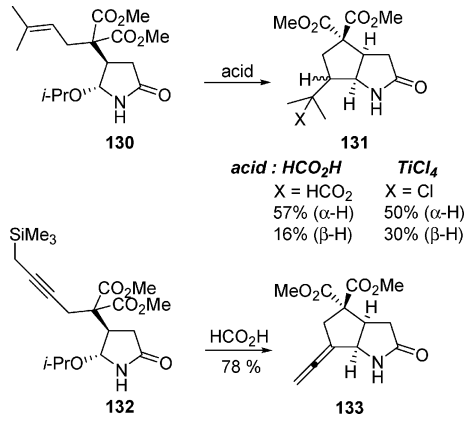
### 5.1.2. exo-Mode Cyclization

Only a limited number of examples of 5-*exo* cyclizations with formation of a C−C bond have been reported for the asymmetric synthesis of heterocycles. With cyclic iminiums, some of them can also be considered as 6 or more *endo* cyclizations.

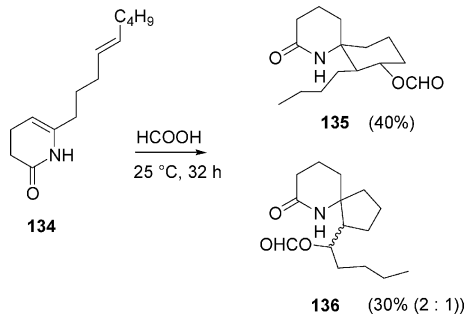
A general approach for the synthesis of enantiopure 1-azabicyles, as intermediates in the synthesis of roseophilin, has been reported.[72]

Starting from alkoxylactam **130**, a *cis* ring junction was obtained with an epimeric mixture of isomers resulting from the nonspecific capture of the transient carbocation (Scheme 40). Cyclization from propargylsilane **132** led to the corresponding bicyclic allene as a single diastereomer. The preference for a 5-*exo*-*exo* instead of a 6-*endo*-*exo* cyclization (via a secondary cation) was explained by the relative stability of the two carbocationic intermediates. In spirocyclizations involving cations with similar stability, as for iminium derived from **134**, it has been shown that a 6-*exo* mode is preferred over a 5-*exo* ring closure by a ratio of 4/3 (Scheme 41).[73]

**Scheme 40**



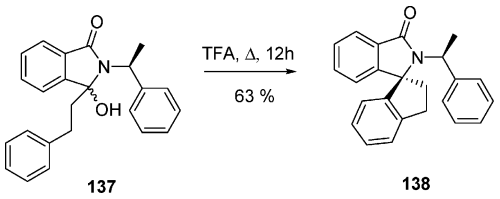

**Scheme 41**




5-*exo* cyclization is a powerful tool for controlling the diastereoselectivity of spirocyclizations. A single diastereomer could be obtained from a mixture of alkoxylactams **137** under relatively harsh acidic conditions (neat refluxing TFA).[74] The stereochemical outcome of the ring closure was explained by a Felkin−Ahn-like transition state (Scheme 42).

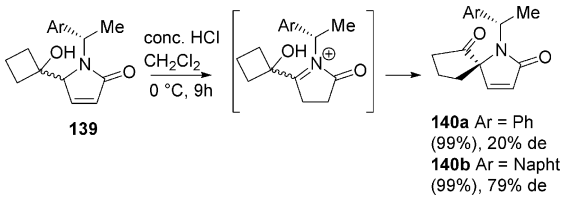
The 1-azaspiro[4,4]none skeleton of (−)-cephalotaxine has been constructed by a stereoselective semipinacolic rearrangement.[75] Final diastereomeric excess of the spirobicyclic lactam **140** proved to be dependent on the nature of the chiral auxiliary, with the best de observed when using α-methylnaphthylamine, but not related to the isomeric ratio of the

**Scheme 42**




starting unsaturated lactam, showing that an acyliminium was the reactive species in this process (Scheme 43).

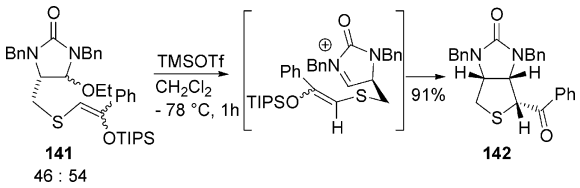
**Scheme 43**




A different racemic approach of the cephalotaxine skeleton based on a 5-*exo* cyclization on an acyliminium has been reported.[76]

The use of a thio-tethered nucleophile in a 5-*exo* cyclization has been described in the synthesis of D-(+)-biotin.[77] The bicyclic urea **142** could be obtained from a 46/54 mixture of silylenol ethers **141** in excellent yield (Scheme 44). The formation of a single isomer, regardless of the geometry of the double bond, was explained by a chairlike conformation of the reactive acyliminium.

**Scheme 44**

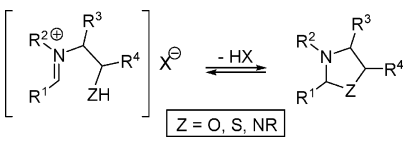



## 5.2. Cyclization Leading to Five-Membered Rings by Formation of a C–Heteroatom Bond

### *5.2.1. endo-Mode Cyclization*

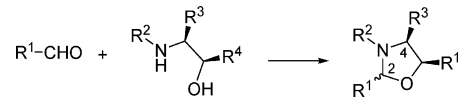
Heteroatoms such as O, S, or N act as nucleophiles in the intramolecular addition onto iminium ions, leading to oxazolidines, thiazolidines, or imidazolidines. These heterocycles not only are well-known and important compounds, especially in the field of medicinal chemistry, but also represent stable potential iminium equivalents since the addition of heteroatoms to iminium ions is a reversible process (Scheme 45).

**Scheme 45**




**5.2.1.1. Oxygen Nucleophile.** *5.2.1.1.1. From Acyclic Precursors. Single-Ring N-Alkyloxazolidines.* Numerous examples of this cyclization mode are available in the literature since chiral oxazolidines are useful intermediates for the resolution of racemic aldehydes, and more generally in asymmetric synthesis. The condensation of a carbonyl derivative with a chiral 1,2-amino alcohol is the most widely used method for the preparation of five-membered heterocycles in high yields and diastereoselectivities (Scheme 46). This reaction, analogous to the acetalization of

**Scheme 46**



keto groups with a 1,2-diol, is favored by removal of the water formed during the reaction. It generally needs acidic-catalysis conditions, but this is not always necessary since acetalization is easier with an amino alcohol than with a diol. Indeed, the nitrogen being more nucleophilic than oxygen, an iminium is readily formed and then trapped by the oxygen atom.

Several experimental conditions have been described to achieve the condensation, including the use of acid catalysts[78] and drying agents,[79] refluxing neat or in aromatic solvent,[80] or not introducing any solvent or additive.[81]

The reaction is generally highly diastereoselective with de's up to 100%. The configuration of the new chiral center formed at C2 was initially controversial. Indeed, due to the reversibility of the reaction, the stereoselectivity is thermodynamically controlled. Thus, quite different results can be obtained according to the experimental reaction conditions. It is now well established that the major diastereomer obtained through equilibrating conditions is the 2,4-*cis*-oxazolidine. As the *N*-alkylated oxazolidines are the sole stable products (NH-oxazolidines mainly exist as open imines),[82] one can say that a product with substituents at positions 2, 3, and 4 in a 2,3-*trans*, 3,4-*trans* relationship is the most stable isomer.[83]

The first X-ray analysis of a chiral oxazolidine published in 1971 introduced some confusion: the authors claimed that the condensation of ephedrine and 4-bromobenzaldehyde in refluxing benzene gave as the sole product 2,4-*trans*-oxazolidine.[80b] This configuration's assignment appeared to be false and was revised by G. Just in 1985, who, using the same conditions, proved the *cis* configuration after X-ray analysis.[84] A plausible explanation is that the first authors probably peaked a crystal of the minor diastereomer in a highly enriched mixture!

The relative 2,4-*cis* configuration, now commonly accepted, is usually observed under several experimental conditions for aromatic or aliphatic aldehydes condensed with ephedrine,[84] *N*-benzyl- or *N*-methylphenylglycinol,[80c] and *N*-methylvalinol[80d] (i.e., **143**, **144**, and **145** (Figure 7)).

Some exceptions to the 2,4-*cis* configuration have been reported. By reacting the methyl hemiacetal of ethyl glyoxylate with *N*-benzylphenylglycinol in refluxing $CH_2Cl_2$ and in the presence of molecular sieves, Pedrosa and co-workers observed the diaste-

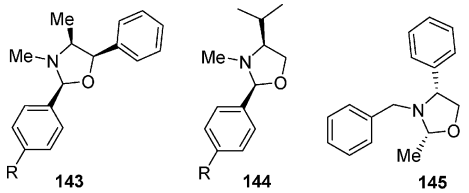



**Figure 7.**

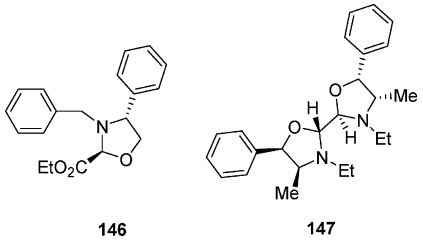



**Figure 8.**

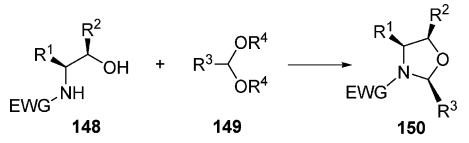
reoselective formation of the 2,4-*trans* isomer **146** (Figure 8)[79] (the opposite *cis* configuration was described by O'Brien[85] and Agami[86] for the condensation of glyoxylate with *N*-Boc-ephedrine under different conditions). A similar *trans* configuration was also claimed for compound **147** (Figure 8) resulting from the double condensation of ephedrine with glyoxal in $H_2O-THF$.[87]

These (apparent) exceptions may be explained by the particular structures and/or the experimental conditions. In a comprehensive study, Agami and Rizk showed that aromatic aldehydes with electron-withdrawing groups led to *trans*-oxazolidines as kinetic products, and that the rate of isomerization toward the more stable *cis* isomer was solvent-dependent.[88]

The use of imines produced by in situ reduction of nitriles[89] or fluorinated hemiacetals[78b] as valuable precursors for the oxazolidine synthesis has been reported.

*Single-Ring N-Acyl- and N-Arylsulfonyloxazolidines.* Cyclization onto *N*-acyl- and *N*-sulfonyliminiums has been broadly reported. In this case, the in situ generation of the iminium by condensation is much more difficult and the reaction requires an acid catalysis. The reaction of an *N*-arylsulfonylamino alcohol with aromatic aldehydes in methylene chloride with sulfuric acid as catalyst was reported to give an oxazolidine with 2,4-*cis* configuration as a single product.[90] However, in most cases, the use of an acetal instead of the aldehyde is more convenient (Scheme 47).[91]

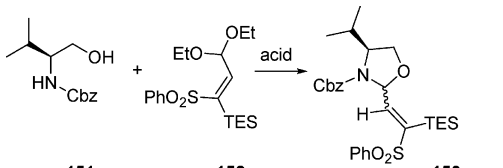
**Scheme 47**




EWG = Cbz, Ts, $CO_2Me$, $CO_2t$-Bu
$R^1$ = Me, $R_2$ = Ph; $R_1$ = *i*-Pr, $R^2$ = H
$R^3$ = alkyl, aryl
$R^4$ = Me, Et, $CH_2CH_2$
$R^4$, $R^4$ = $CH_2$-$CH_2$

Ring opening of *N*-acyloxazolidine is slowed by the presence of electron-withdrawing groups on nitrogen; thus, *N*-acyloxazolidines are more stable than their *N*-alkyl counterparts. Scolastico and co-workers thoroughly studied this reaction with ephedrine derivatives and showed that the *cis* configuration is the result of both kinetic and thermodynamic factors.[92] Once again, the reaction conditions are quite important for the stereochemical outcome of the reaction. Several Brønstedt (*p*-TsOH, CSA, ...) or Lewis ($BF_3$·$OEt_2$) acids have been used as catalysts. Isobe and co-workers showed that Cbz-L-valinol **151** (Scheme 48) condensed with heteroolefin dimethyl ketal **152**

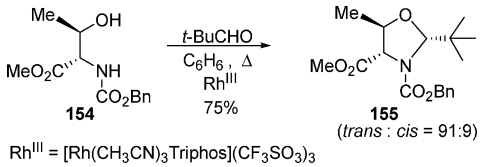
**Scheme 48**




to afford *trans*-oxazolidine **153** as the major compound (10/1) in the presence of CSA, whereas the use of $BF_3$·$OEt_2$ favored the formation of the corresponding *cis*-oxazolidine (1/3).[91h]

Conditions involving the use of Rh(III) salts as catalysts allowed the preparation of 2,4-*trans*-oxazolidines **155** (Scheme 49).[93]

**Scheme 49**



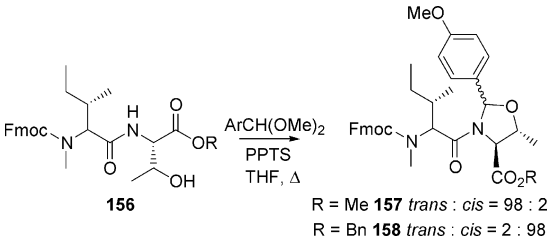

$Rh^{III}$ = $[Rh(CH_3CN)_3Triphos](CF_3SO_3)_3$

The condensation of L-serine methyl ester with pivalaldehyde has been reported to provide a 1/1 mixture of unstable NH-oxazolidines which were formylated ($HCOOH/Ac_2O$) to a highly *cis* enriched mixture (95:5).[94] This condensation/acylation sequence was found to be general, and was used by several authors with different heterocycles including thiazolidines and imidazolidines (vide infra). It has been suggested that this *cis*/*trans* equilibrium occurs via a faster acylation of the *cis* derivative.[86]

Some structural features strongly influencing the stereochemical outcome of the reaction have also been pointed out. The condensation of anisaldehyde dimethyl acetal with a protected Ile-Thr dipeptide under equilibrating conditions led to the 2,4-*cis*-oxazolidine **158** (*cis*/*trans* = 98/2) when terminal carboxylate was protected by a benzyl group, and to the *trans*-oxazolidine **157** (*cis*/*trans* = 2/98) when a methyl ester was used (Scheme 50). The authors suggested a favorable stacking interaction between the aromatic ring *p*-methoxyphenyl and the benzyl ester.[91f]

*5.2.1.1.2. From Cyclic Precursors. Fused-Ring N-Alkyloxazolidines.* Fused-ring oxazolidines can be formed by cyclization onto alkyliminiums. When the iminium is included in a ring, the latter can control the stereoselectivity of the reaction. Numerous examples of oxazolopiperidine syntheses through this

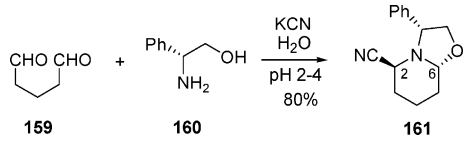
**Scheme 50**




cyclization mode can be found in the literature. These heterocycles are valuable intermediates in the synthesis of piperidine alkaloids.

Treatment of phenylglycinol with glutaraldehyde in the presence of KCN led to the formation of **161** in 80% yield (Scheme 51) as a single isomer after

**Scheme 51**

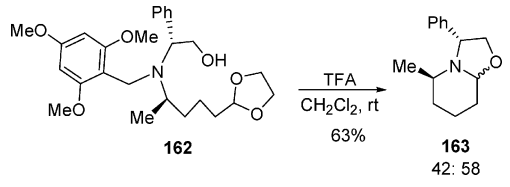



equilibration. This product is a starting material for the synthesis of various chiral heterocycles according to the CN(*R*,*S*) method.[95]

The same reaction was conducted with benzotriazole instead of KCN, to give a benzotriazole oxazolopiperidine for which the configuration was not given.[96]

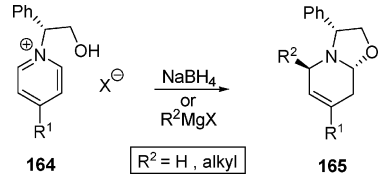
The relative configurations of **161** show an axial position of the cyano group as a result of a highly favorable anomeric effect and a *trans* arrangement of the 6 + 5 bicyclic system. The oxazolidine exhibits a 2,4-*cis* configuration. Interestingly, the intramolecular condensation of amino alcohol **162** (Scheme 52) led to a 42/58 mixture of diastereomeric oxazolopiperidines **163**.[97]

**Scheme 52**



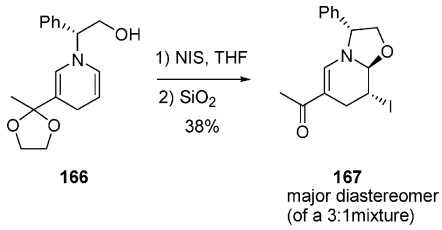

Marazano and co-workers developed an interesting methodology for the preparation of chiral *N*-(2-hydroxy-1-phenylethyl)pyridinium salts. Upon alkylation or reduction of such pyridinium salts, the so-formed dihydropyridinium can be trapped in an intramolecular way to give oxazolopiperidines **165** (Scheme 53).[98]

**Scheme 53**



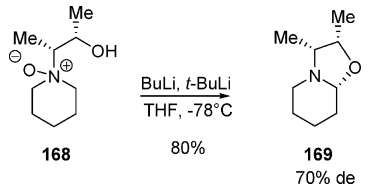

The cyclization was found to be highly diastereoselective, and the relative configuration of the oxazolidine was the same as for compound **161** (Scheme 51). In another example, the iodocyclization of 1,4-dihydropyridines **166** gave moderate diastereoselection in favor of *trans*-**167** (Scheme 54).[99]

**Scheme 54**



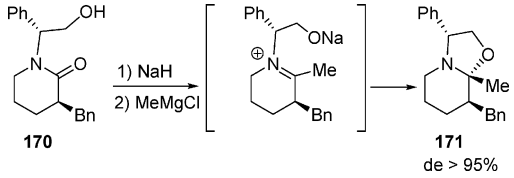

In the absence of any substituent on the piperidine ring, a highly diastereoselective 2,4-*cis* configuration (85/15) was observed for compound **169**.[100] In this case, the iminium was generated by treatment of *N*-oxide **168** with a strong base (Scheme 55).

**Scheme 55**




Partial reduction of a *δ*-lactam gave rise to a potential iminium ion which could be trapped intramolecularly to oxazolopiperidine.[101] Oxazolopiperidine **171** with a quaternary carbon at C2 was prepared by addition of Grignard reagents to piperidinone. A unique product exhibiting a *cis* configuration was observed (Scheme 56). This configuration corresponds to the kinetic product whose formation is governed by an $A^{1,2}$ allylic strain.[102]

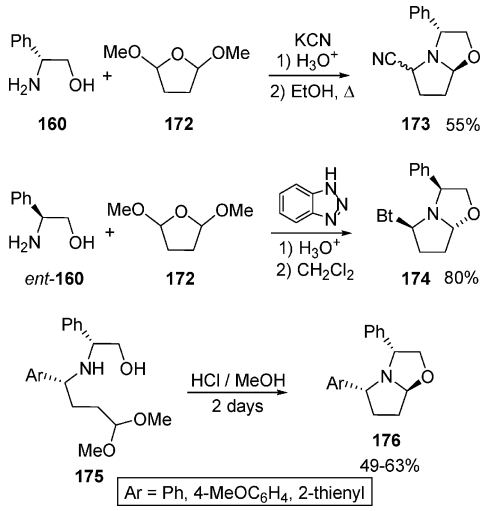
**Scheme 56**




Oxazolopyrrolidines can also be reached through the same pathways. The stereochemical course of the reaction seems to be quite different since an opposite configuration at C2 was observed. This is probably the result of a more important strain introduced by the fused 5 + 5 bicyclic system.

Although formed in low yield from a succinaldehyde equivalent, the cyanooxazolopyrrolidine derivative **173** analogue of **161** has been obtained in a mixture of two diastereomers at C5. The oxazolidine showed a *trans* configuration (Scheme 57).[103] Accordingly, the corresponding benzotriazole derivative **174** was described as a *trans* isomer.[104] The same *trans* configuration was evidenced in the intramolecular condensation of compound **176** (Scheme 57).[105]

**Scheme 57**

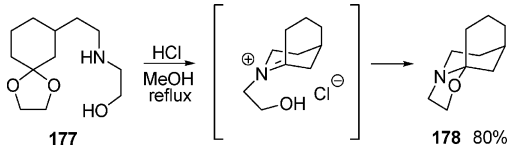



Oxazolopyrrolidine has been formed from easily available prolinol. The intermediate iminium is *exo* to the pyrrolidine ring and does not present the same stereochemical requirements as 3,4-dihydropyrrole. Consequently, a mixture of isomers was observed.[106]

Oxazolidines incorporated in other bicyclic or more complex structures were obtained through cyclization onto iminium ions produced with various methods involving aminonitrile displacement,[107] oxidation of the benzylic position,[108] azaelectrocyclization to dihydropyridine,[109] amine−aldehyde condensation,[110] and *N*-oxide deprotonation.[111] The configuration of the new chiral center proved to be highly structure-dependent.

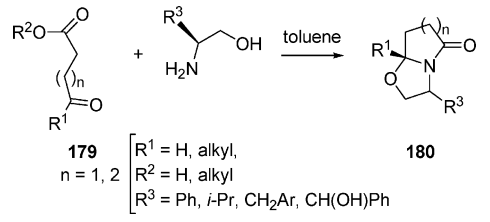
Although the synthesis of chiral oxazolidines derived from ketones has been scarcely described, one example has recently been reported for a bicyclic system. It concerns the formation of oxazolidine **178** involving an anti-Bredt iminium ion (Scheme 58).[112]

**Scheme 58**




*Fused-Ring N-Acyloxazolidines.* The most representative heterocycles arising from such a cyclization mode are oxazololactams obtained by the condensation of a chiral primary amino alcohol with γ- or δ-keto acid or ester according to the pioneering work of A. I. Meyers. This condensation shown in Scheme 59 is a high-yielding process, obtained without any additive in refluxing toluene.[113]

**Scheme 59**



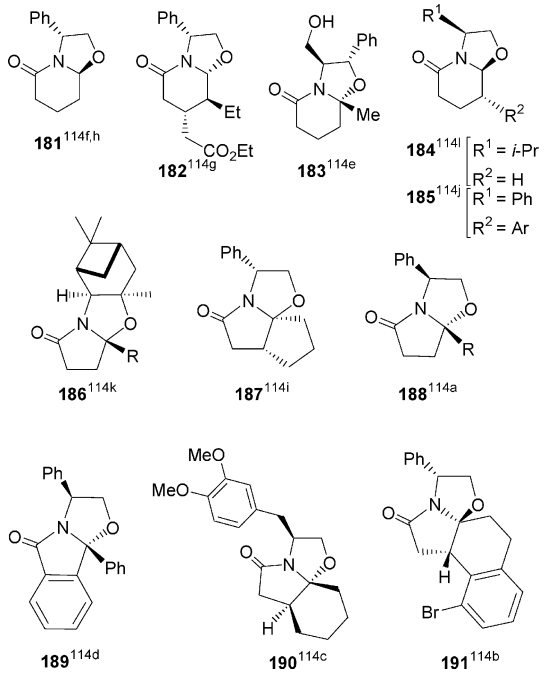
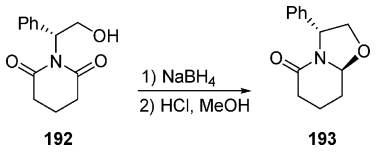




**Figure 9.**

This reaction has been used by several authors to prepare various bicyclic oxazololactams as shown in Figure 9.[114]

The configuration of the newly created carbon center formed depends on the experimental conditions. It was shown that the condensation of methyl 5-oxopentanoate with (*R*)-phenylglycinol in toluene gave the *cis* bicyclic lactam (85/15), which was isomerized to the *trans* isomer **181** (14/86) by acidic treatment. The partial reduction of cyclic imides offers a straightfoward alternative preparation of such bicyclic lactams. The partial $NaBH_4$ or DIBAL reduction of a cyclic imide is probably the best way to access acyliminium ions, which can be trapped intramolecularly by an oxygen atom to form an oxazolidine (Scheme 60).[115]

**Scheme 60**

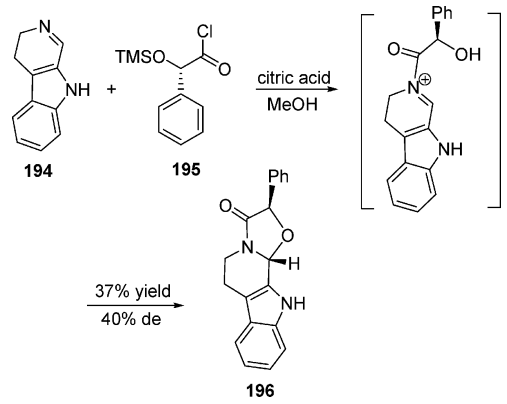



Few other methods have been developed to synthesize similar derivatives through iminium ion cyclization. Among them, the protonation of enamides,[116] the aromatic carbonylation with palladium(0) catalyst,[117] and the acylation of imines (Scheme 61)[118] were proven effective and proceed with various diastereoselectivities.

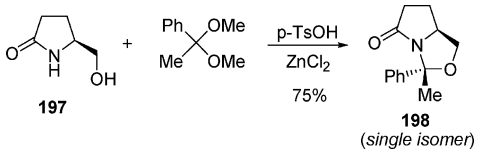
Chiral lactam alcohols, as pyroglutaminol (**197**), were reacted with aldehyde or ketone dimethyl acetals in refluxing toluene and in the presence of TsOH to give rise to oxazololactams **198** in high yield and as a single stereomer (Scheme 62).[119] The reaction was also applied to the piperidine series[120] and to the synthesis of dipeptide mimetics.[121]

Intramolecular condensation leads to bicyclic oxazolidines.[12] In some cases the amino alcohol moiety

**Scheme 61**

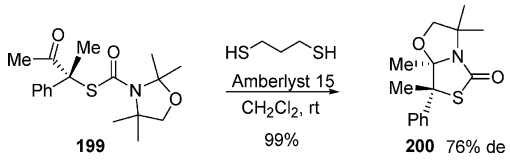



**Scheme 62**



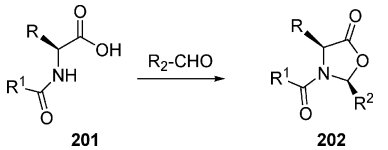

has been protected as an *N*,*O*-acetal. For example, transformation of oxazolidine **199** (Scheme 63) into bicyclic oxazolidine **200** was obtained in very high yield and good diastereoselectivity under acidic conditions.[122d]

**Scheme 63**



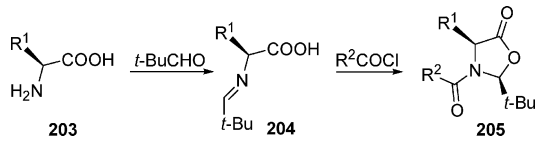

*5.2.1.1.3. 1,3-Oxazolidin-5-ones.* The carboxylate group can also act as a nucleophile in cyclization reactions. These so-formed 1,3-oxazolidin-5-ones are generally the result of the condensation of an aldehyde to an *N*-acyl α-amino acid. The presence of the *N*-acyl group (*N*-Boc, *N*-Bz, *N*-Alloc, *N*-Cbz, ...) is important to stabilize this hydrolysis-sensitive heterocycle. The oxazolidinone synthesis is the basis of the general asymmetric alkylation method developed by D. Seebach. The condensation of sterically hindered aldehyde (mainly pivalaldehyde) with several *N*-acyl proteinogenic amino acids leading to oxazolidinones was reported by this author and reviewed in 1996.[123] All oxazolidinones **202** derived from alanine, valine, isoleucine, methionine, phenylalanine, tryptophan, lysine, tyrosine, and ornitine exhibit a *cis* configuration (Scheme 64), as the result of a reaction under thermodynamic control.

**Scheme 64**




The most widely used method is the condensation of amino acid **203** (as its carboxylate salt) with the aldehyde to provide imine **204**, which is treated with

**Scheme 65**




an acyl chloride or a chloroformate to give *cis*-oxazolidinone **205** (Scheme 65).[124] This method was first described by Hiskey 40 years ago.[125]

Surprisingly, benzaldehyde dimethyl acetal in ether and in the presence of $BF_3{\cdot}OEt_2$ has been reported to condense with *N*-Cbz-L-alanine and *N*-methoxycarbonyl-4-benzyloxyphenylglycine to give *cis*-oxazolidinone **206**[126] and *trans*-oxazolidinone **207**,[127] respectively (Figure 10).

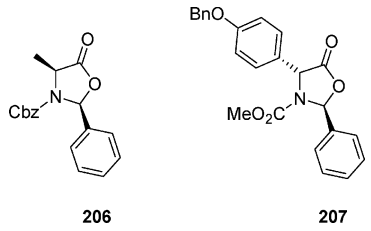
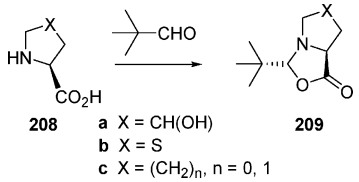



**Figure 10.**

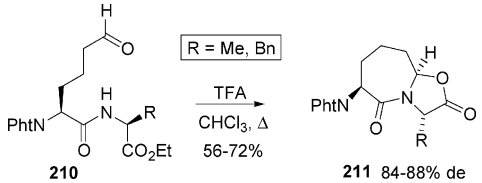
As mentioned above, the presence of an *N*-acyl group strongly stabilizes the oxazolidinone ring. *N*-Akyloxazolidinones **209** can be however obtained through the condensation of aldehyde with cyclic amino acids. Azetidinecarboxylic acid-, proline-, 4-hydroxyproline-, and cysteine-derived 4-thiazolines **208** were used as starting materials (Scheme 66).[128]

**Scheme 66**




Carboxylate intramolecular cyclization was also used for the preparation of **211**, a dipeptidomimetic (Scheme 67).[129]

**Scheme 67**




**5.2.1.2. Sulfur Nucleophile.** Although similar cyclization behavior could be expected with sulfur instead of oxygen in 5-*endo* cylizations, only a few syntheses of chiral thiazolidines reported in the literature are based on this cylization mode. One of the main reasons is that chiral aminothiols are not so easily available compared to chiral amino alcohols (the propensity of thiols to oxidize to disulfides is also a difficulty). The most easily available chiral aminothiol is cysteine. This primary aminothiol forms stable NH-thiazolidines through imine cyclization.

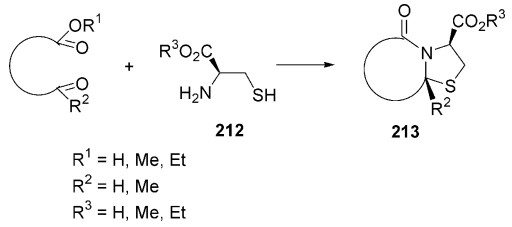
This stability strongly contrasts with the stability of NH-oxazolidines that mainly exist in solution in equilibrium with the opened imine form (vide supra).[82]

Cysteine readily reacted with an aldehyde to give a thiazolidine as a 1/1 mixture of isomers,[130] which was cleanly converted into a single 2,4-*cis* product upon *N*-acylation.[131]

Only very few examples of condensation of secondary aminothiol have been reported. The reaction of phenylglyoxal with *N*-methylphenylglycinethiol afforded a 7/3 mixture of epimeric thiazolidines.[132] Thio analogues of ephedrine and pseudoephedrine have been condensed with acetaldehyde to give, respectively, a mixture of 80/20 and 70/30 *cis*/*trans* stereomers. The authors suggested an equilibrium between both isomers.[83]

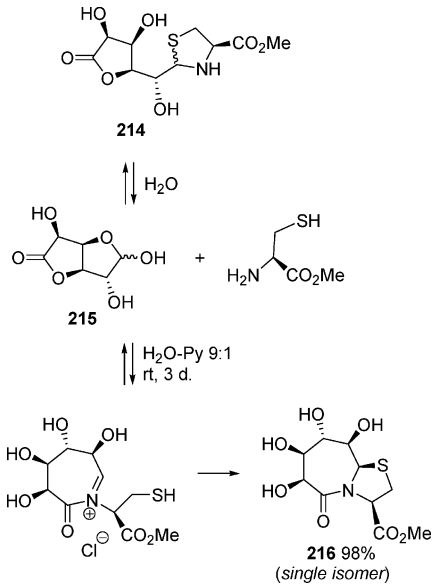
While single thiazolidine syntheses are scarce, numerous fused lactam thiazolidines **213** have been described. Thio analogues of Meyers' bicyclic lactams (vide supra) have been prepared (Scheme 68).

**Scheme 68**




Even though the cyclization of the lactam may follow the initial formation of the thiazolidine, an acyliminium is involved during the equilibration process.[133] In an attempt to prepare compound **216** (Scheme 69),[133d] it was found that D-glucorono-3,6-

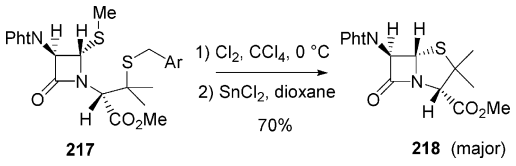
**Scheme 69**




lactone **215** rapidly condensed with cysteine methyl ester in water or pyridine to give isomeric NH-thiazolidine **214**, which was unable to form the lactam linkage. On the other hand, the same products reacted in a pyridine−water mixture to give **216**, probably via an acyliminium.

An iminium ion cyclization was also used in the synthesis of the penicillin skeleton. $\beta$-Lactams such as **217** with chloro or thioether substitution α to the nitrogen (Scheme 70) were the acyliminium precur-

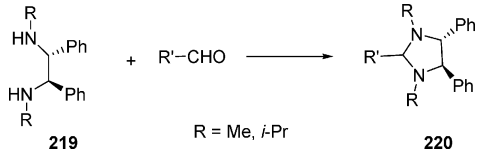
**Scheme 70**




sors in most cases.[134] A formal inversion or retention of the configuration at the α-position of the nitrogen atom was observed, leading in every case to a *trans* configuration of the substituents on the azetidine ring, indicating that an acyliminium ion was an intermediate.

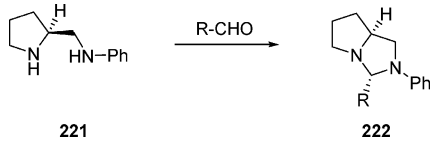
**5.2.1.3. Nitrogen Nucleophile.** Imidazolidines are characterized by their greater stability compared to oxazolidine and thiazolidines. Single imidazolidines **220** were easily prepared from chiral *N*,*N*-disubstituted 1,2-diamines **219** possessing a C-2 symmetry axis (Scheme 71).[135] Following the work

**Scheme 71**




of Mukaiyama,[136] numerous bicyclic compounds **222** were obtained from 1,2-diamine **221** derived from proline (Scheme 72). High diastereoselectivity was

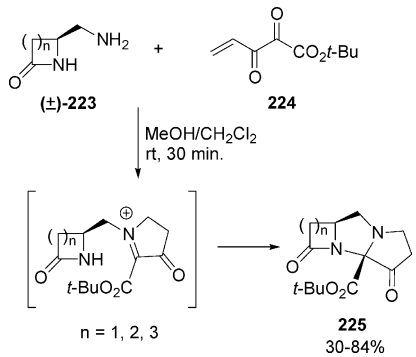
**Scheme 72**




observed, and the configuration was the same as for oxazolidines in the bicyclic 5 + 5 series (vide supra).

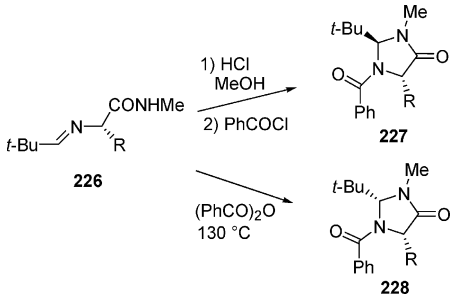
Tricyclic derivatives **225** were prepared by Wasserman and co-workers.[137] The primary amine function of aminomethyl-$\beta$-, -$\gamma$-, or -$\delta$-lactams **223** was condensed with the tricarbonyl derivative **224** to give the reactive acyliminium (Scheme 73).

**Scheme 73**



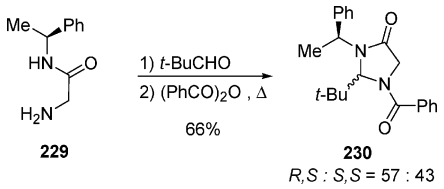
Imidazolidin-5-ones have also been synthesized and used as interesting intermediates in the asymmetric synthesis of amino acids, peptides, and peptidomimetics.[138] An efficient preparation of *cis* or *trans* heterocycles was devised. *N*-Methylamides of amino acids were condensed with pivalaldehyde to give imines **226** which could be cyclized to stable *trans*-NH-imidazolidine and then smoothly acylated to *trans*-imidazolidinone **227**. In an other example, *cis*-*N*-acylimidazolidine **228** could be directly obtained upon treatment of imine **226** in boiling benzoic anhydride (Scheme 74).[139]

**Scheme 74**




This stereodivergent preparation allows access to the *R* or *S* series of substituted amino acids. An attempt to prepare enantiomerically pure imidazolidinone, by the use of an *N*-chiral auxiliary, was reported.[140] Unfortunately, the condensation of chiral amide **229** with pivalaldehyde was shown to be poorly diastereoselective (Scheme 75).

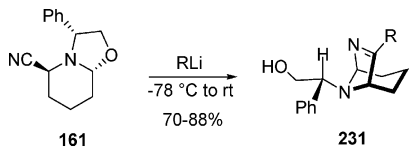
**Scheme 75**




The double condensation of a bisaldehyde was first used by Husson and co-workers[95] with an amino alcohol and then by Katritzky[96] (vide supra). It was later been extended by these two authors to the formation of imidazolidines[141] and imidazolidinones.[142]

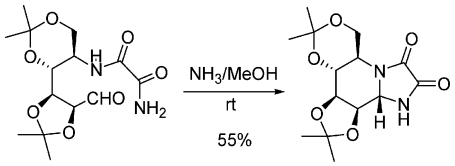
When treated with phenyllithium, the cyano group of oxazolopiperidine **161** was mono (or bis) alkylated, and the so-formed imino (or amino) group cyclized onto the iminium ion resulting from the opening of the oxazolidine, leading to bicyclic compound **231** (Scheme 76).[143]

**Scheme 76**




The greater stability of imidazolidine is again clearly shown in these examples. A highly diastereoselective condensation to imidazolidine was reported in the synthesis of kifunensine. Cyclization of unstable aldehyde **232**, in $NH_3$/MeOH, afforded **233** in 55% yield as a unique stereomer (Scheme 77).[144]

**Scheme 77**



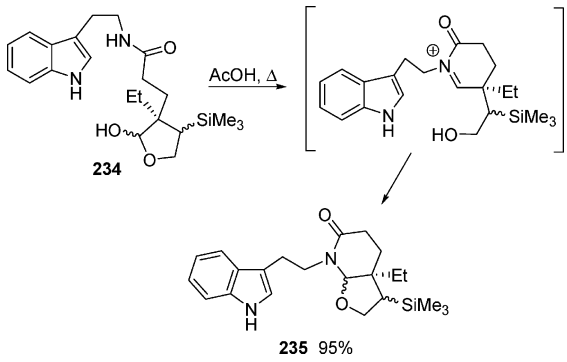

### 5.2.2. exo-Mode Cyclization

Heteroatom cyclization reactions involving iminiums *exo* with regard to the ring being formed (Scheme 78) are considered in this part.

**Scheme 78**

Despite the reversibility of this cyclization mode, several described products (in particular in bi- or polycyclic series) are stable compounds, and can be formed in a highly stereoselective manner. The formation of a tetrahydrofuryl ring has been observed after acidic treatment of the indole derivative **234**.[145] An acyliminium was involved, and it was expected that **235** would generate it back to give the Pictet−Spengler cyclization. However, this last reaction failed, and **235** was the only product obtained (Scheme 79).

**Scheme 79**

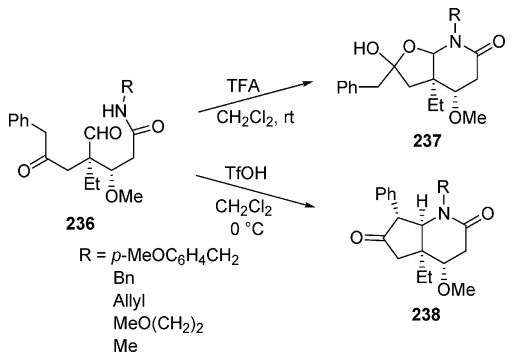



Similar difficulties were encountered in the total synthesis of (+)-meloscine.[146] Under standard acidic conditions, compound **236** did not cyclize to the expected Mannich product **238**, but gave the acetal derivative **237** as a mixture of stereomers arising from the trapping of the acyliminium ion by the ketone. Nevertheless, the use of a stronger acid (TfOH instead of TFA) allowed the formation of the most stable Mannich product **238** (Scheme 80).

5-*exo* cyclization by an oxygen atom has also been used for the diastereoselective preparation of nucleoside analogues.[147] Spiro compounds were obtained by iodolactonization of enamines.[148]

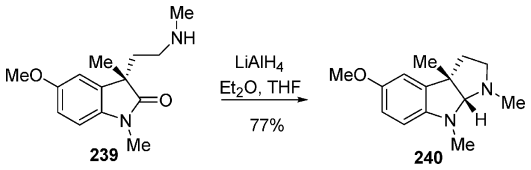
The synthesis of the skeleton of physostigmine and congener alkaloids is a nice example of nitrogen-triggered 5-*exo* cyclization. This reaction was used by several authors,[149] mostly with iminium ions

**Scheme 80**



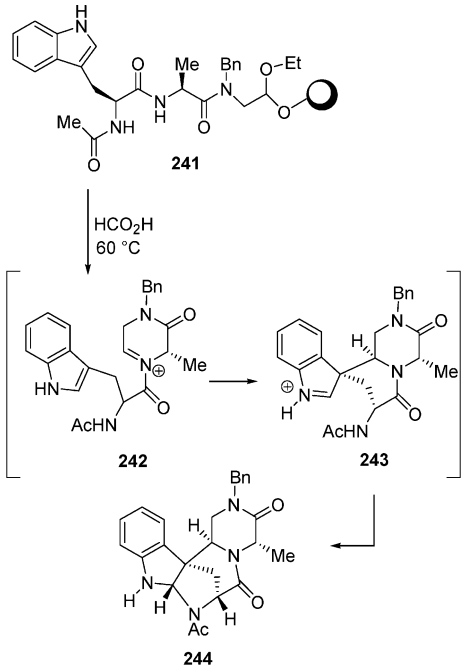

generated by partial reduction of lactam **239** that lead to **240** (Scheme 81). A thia analogue has also been prepared by a similar strategy.[150]

**Scheme 81**




Treatment of **241** with formic acid (Scheme 82) led to a nice tandem 6-*endo*/5-*exo* cyclization. The transient iminium **242** underwent a Pictet−Spengler reaction followed by a 5-*exo* cyclization, and gave **244** in high purity and good yield (not given).[151]

**Scheme 82**




## 6. Cyclization Leading to Six-Membered Rings

The formation of six-membered rings by iminium ion cyclization is an easy process for which numerous examples have been reported in the literature. It usually occurs through highly ordered transition states and can therefore deliver diversely substituted heterocyclic compounds in a stereocontrolled manner.

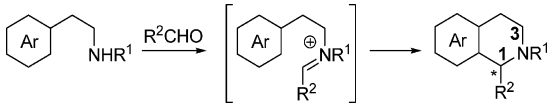
### 6.1. Cyclization Leading to Six-Membered Rings by Formation of a C–C Bond

#### *6.1.1. endo-Mode Cyclization*

Addition of a carbon nucleophile to an iminium following an *endo* cyclization affords piperidine derivatives that are highly common structures in the field of both natural and synthetic products. Aromatic and nonaromatic nucleophiles, leading to Pictet−Spengler- or Mannich-type reactions, will be discussed separately in the following sections.

**6.1.1.1. Aromatic Nucleophile.** 6-*endo* cyclizations of aromatic or heteroaromatic nucleophiles onto iminiums is a classical entry to the skeleton of various natural products or bioactive compounds. The Pictet−Spengler reaction, first described in 1911,[2] involves the condensation of an $\omega$-aromatic amine and an aldehyde or a ketone, leading to polycyclic structures of great interest (Scheme 83).

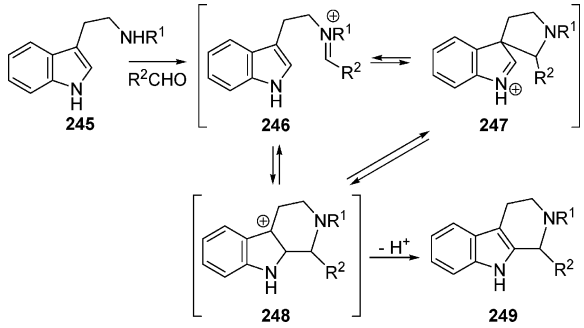
**Scheme 83**




Although this condensation can be conducted with primary amines, leading to imines as reactive intermediates, only iminium-based cyclization will be described here. Furthermore, the Pictet−Spengler reaction has been recently reviewed, especially in the context of indole alkaloid synthesis.[152] This part will therefore emphasize the stereochemical outcome of this mode of cyclization and recent results.

Two likely pathways have been reported to take place in the reaction (Scheme 84). Most of the studies

**Scheme 84**




have been performed with protonated imines as intermediates. The formation of a transient spiroindolenine has been detected by isotopic labeling in the synthesis of 3-azatetrahydro-$\beta$-carbolines. The formation of a similar intermediate is believed to occur, but in a fast and reversible manner. For protonated imines ($R^1 = H$), the rearrangement from intermediate **247** to **248** has been calculated to be energetically unfavorable.[153] The direct attack from the indole 2-position is therefore believed to be the key step in the Pictet−Spengler reaction.

The diastereoselective condensation between an aldehyde and *N*-alkyltryptophan methyl ester is a general entry to the 1,3-disubstituted 1,2,3,4-tetrahydro-$\beta$-carboline framework. It is now well established

that the use of a bulky group on the nitrogen (benzyl group) in conjunction with large aldehydes leads preferentially to 1,3-*trans* isomers.[154] In a comparative study, Cook and co-workers have investigated the role of each substituent in the stereoselectivity of the condensation, under both nonacidic and acidic conditions (Scheme 85 and Table 1).[155]

**Scheme 85**

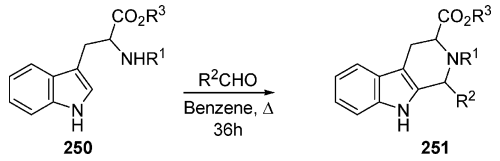



**Table 1**

| compd | $R^1$ | $R^2$ | $R^3$ | *trans*/*cis* (nonacidic) | *trans*/*cis* (acidic) |
|---|---|---|---|---|---|
| **251a** | Bn | Me | Me | 74/26 | 88/12 |
| **251b** | Bn | Pr | Me | 77/23 | 89/11 |
| **251c** | Bn | chex | Me | 100/0 | 100/0 |
| **251d** | $CH(Ph)_2$ | Me | Me | 90/10 | 100/0 |
| **251e** | $CH(Ph)_2$ | Me | *i*Pr | 100/0 | 100/0 |
| **251f** | Bn | Me | *i*Pr | 77/23 | 87/13 |

This study showed that the size of the aldehyde has little influence on the diastereoselectivity, although an increase of the steric bulk to cyclohexyl excluded the formation of the *cis* isomer. The change of methyl for isopropyl ester did not lead to significant improvement, whereas the use of a bulky *N*-protective group enabled the stereoselective formation of 1,3-*trans*-carboline, even with acetaldehyde.[156] The formation of the *trans* isomer is kinetically and thermodynamically favored, and can be explained by a Felkin−Ahn-like attack of the (*E*)-iminium from the face opposite the ester group (Figure 11).

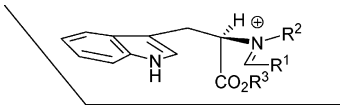
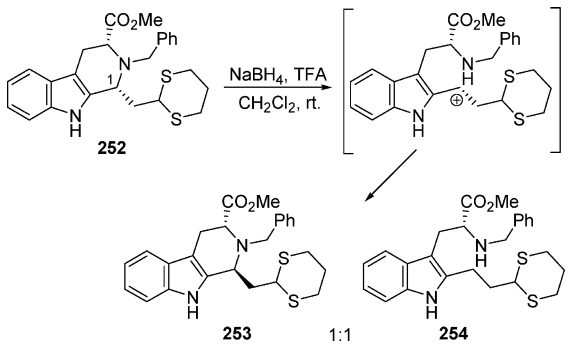


**Figure 11.**

Furthermore, equilibration experiments in TFA showed that the *trans*-*N*-substituted diastereomers are thermodynamically more stable than their *cis* congeners. This isomerization has been explained by a C−N bond cleavage, isomerization of the carbocation, and recyclization as shown in Scheme 86. Indirect evidence for the formation of this stabilized cation is the recovery of reduction compound **254** in the presence of sodium borohydride.

**Scheme 86**

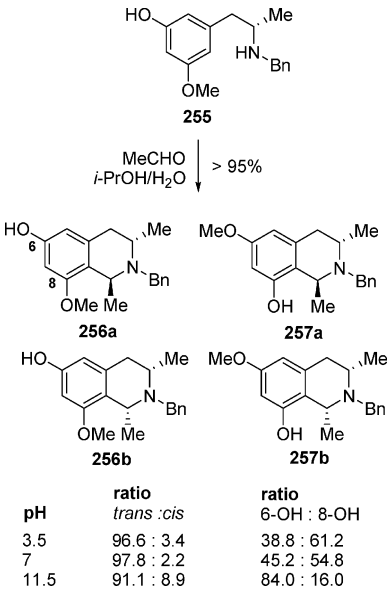



Under the same conditions, no reaction was observed with the *trans* isomer. Other mechanisms, involving a retro-Pictet−Spengler reaction[157] or initial protonation of the indole nitrogen followed by a reversible iminium−enamine equilibrium, have also been evocated.[158]

The use of a bulky *N*-protective group in the condensation is essential to get a *trans* selectivity not only under kinetic control, but also under acidic, thermodynamic conditions. Lower selectivity was for instance observed with the corresponding *N*-methyl derivatives,[159] while replacement of the phenyl ring by a 2-pyridyl, furyl, or thienyl group did not change the exclusive formation of *trans*-*β*-carboline.[160]

A similar stereochemical outcome can be obtained in the synthesis of tetrahydroisoquinolines (Scheme 87). The condensation of secondary amine **255** with acetaldehyde led to four different products.[161]

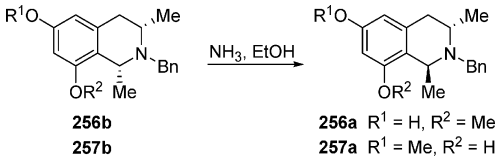
**Scheme 87**




| pH | ratio *trans* :*cis* | ratio 6-OH : 8-OH |
|---|---|---|
| 3.5 | 96.6 : 3.4 | 38.8 : 61.2 |
| 7 | 97.8 : 2.2 | 45.2 : 54.8 |
| 11.5 | 91.1 : 8.9 | 84.0 : 16.0 |

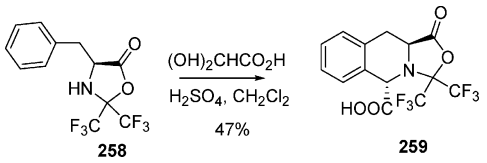
Interestingly, the regioselectivity of the cyclization proved to be pH-dependent. Moreover, the reaction under basic conditions was faster (15 min) but less stereoselective than in acidic medium (72 h). The thermodynamically less stable *cis*-configurated byproducts **256b** and **257b** could be transformed into the corresponding *trans*-configurated tetrahydroisoquinolines by base-catalyzed isomerization (Scheme 88).

**Scheme 88**



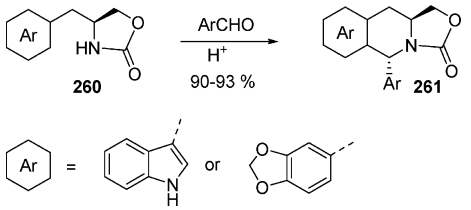

Tetrahydroisoquinolinecarboxylic acid derivatives **259** have been obtained from oxazolidinone **258** (Scheme 89). The condensation with glyoxylic acid hydrate under acidic conditions led to a single diastereomer.[162]

**Scheme 89**



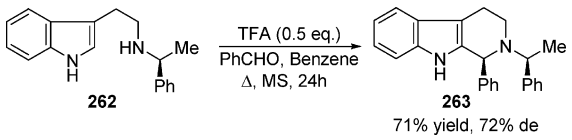

The use of protected amino alcohols instead of amino ester derivatives has been described in diastereoselective condensations (Scheme 90). Chiral nonracemic oxazolidinones **260** were readily prepared from tryptophan or DOPA.[163]

**Scheme 90**



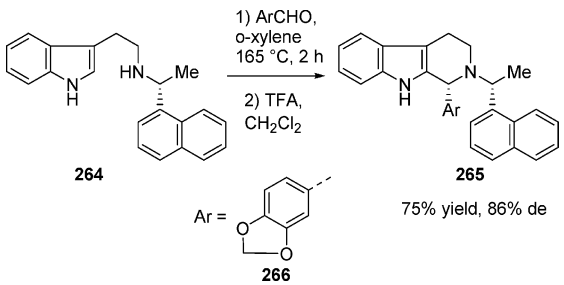

Although tryptophan-based Pictet−Spengler adducts can be decarboxylated to furnish enantiopure *β*-carbolines, several stereoselective strategies using a removable chiral auxiliary have been developed to get similar compounds. The use of a chiral amine for stereoselective transformations of iminiums has found extensive applications in the asymmetric synthesis of amino derivatives.[164] The use of α-methylbenzylamine as a chiral auxiliary group has been reported in Pictet−Spengler reactions (Scheme 91).[165]

**Scheme 91**



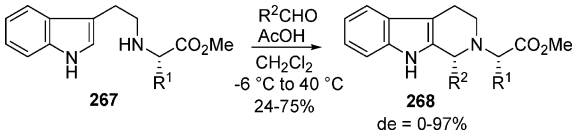

The best diastereoselectivity was obtained with benzaldehyde in refluxing benzene, in the presence of trifluoroacetic acid. The diastereomeric ratio was the result of thermodynamic control, since it was obtained when either the minor or the major isomer was treated with TFA (0.5 equiv) for 6 h. The use of bulkier α-methylnaphthylamine led to a better diastereoselectivity with aldehyde **266**, after acidic equilibration. In this case, however, the cyclization only occurred at high temperature (165 °C) (Scheme 92).

**Scheme 92**




Waldmann's group has been involved in the design of suitable chiral auxiliaries for the Pictet−Spengler cyclization. In a first approach, the use of amino acids for this purpose has been investigated (Scheme 93).[166]

**Scheme 93**




A good to excellent isomer ratio could be obtained, except with aliphatic aldehydes. The diastereoselectivity increased when the temperature was decreased, and was better with aromatic aldehydes bearing electron-donating substituents. It has been proposed that the formation of **268** occurred under kinetic control, although the major isomer formed was also the thermodynamically most stable one. The stereochemical outcome of the reaction was explained by analogy to the model proposed by Cook, with a Felkin−Anh-type attack on a transient (*E*)- iminium (Figure 12).

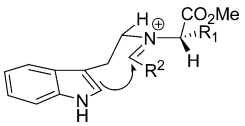
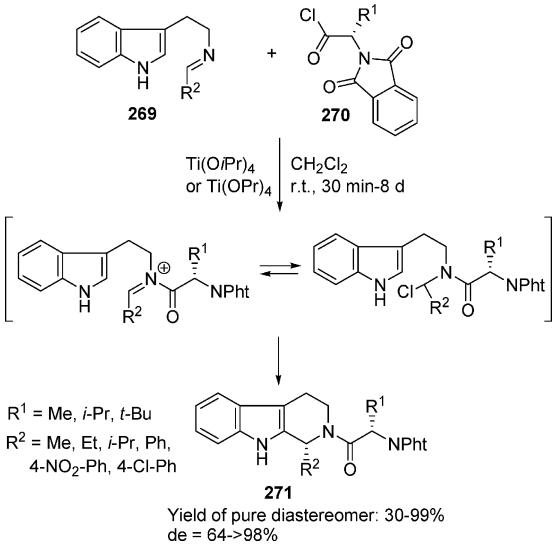


**Figure 12.**

Since only aromatic aldehydes gave preparatively useful results with alkyliminium intermediates, a second approach was proposed by the same group, based on more electrophilic acyliminium reactive species.[167] The best results were obtained with *N*,*N*-phthaloylamino acids as chiral auxiliary groups, as depicted in Scheme 94.

**Scheme 94**




The reactions involving aliphatic imines **269** were complete within several minutes, whereas 8−9 days was required for aromatic Schiff bases. An increase of diastereoselectivity was observed with the size of the amino acid side chain. The role of titanium alkoxide, which had a remarkable effect on the selectivity, was explained by a coordinated interme-

diate, with a preferred attack on a (*Z*)- acyliminium (Figure 13).

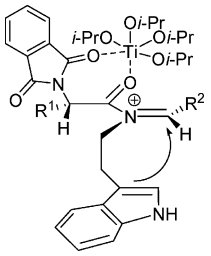
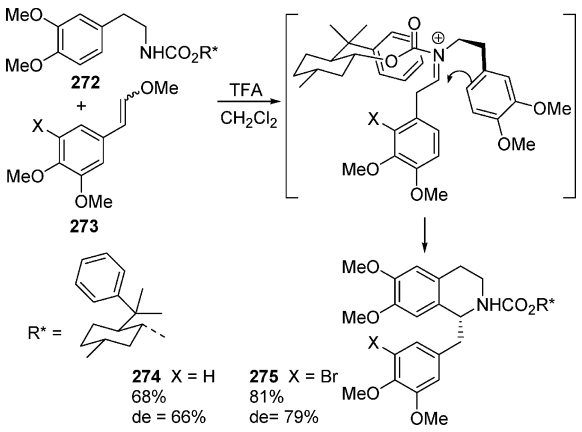


**Figure 13.**

A similar strategy has been devised for the preparation of enantiomerically pure tetrahydroisoquinolines.[168]

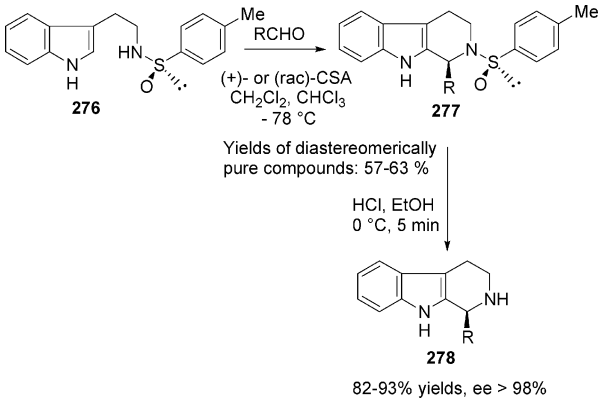
The use of (−)-8-phenylmenthyl chloroformate can direct the Pictet−Spengler condensation to afford compounds **274** and **275** in 68−81% yield (Scheme 95). The vinyl ether proved to have a better stability to storage and reaction conditions than the corresponding aldehyde.

**Scheme 95**



The influence of *N*-sulfinyl chiral auxiliaries on the stereochemistry of the Pictet−Spengler reaction has also been investigated (Scheme 96).[169]

**Scheme 96**

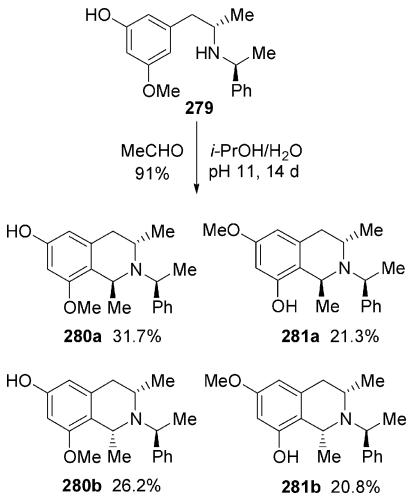


Even though the diastereoselectivity of the condensation with aliphatic aldehydes ranges from 46% to 76%, the major diastereomer can be obtained after a single crystallization. The main advantage of this strategy is the ease of the auxiliary cleavage, leading to enantiopure material in good chemical yield. No change in the diastereomeric ratio was observed using (+)-CSA instead of the racemic acidic catalyst.

The use of chiral nonracemic aldehydes could lead to stereoselective condensations with *N*-protected amines. Some examples have been reported, with limited success for intermolecular reactions.[170]

In some cases, double induction can be expected with the combination of a chiral auxiliary and a stereogenic center coming from the amine skeleton or the aldehyde.[171] However, the absence of a cooperative effect has been observed in the tetrahydroisoquinoline series starting from amine **279** bearing two stereogenic centers instead of only one (Schemes 87 and 97).[161]

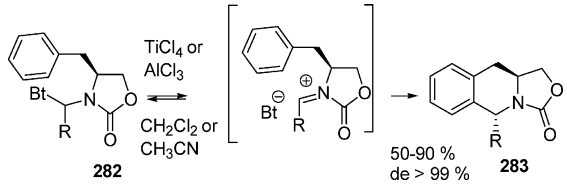
**Scheme 97**



In several cases, Pictet−Spengler reaction involving aliphatic alkyliminiums proved to be less efficient than with the use of aromatic aldehydes. Competitive side reactions, such as aldol condensation, can occur under acidic conditions, and an excess of aldehyde is generally required for a good chemical conversion. This problem can be solved by the use of masked carbonyl reagents, such as oxazolidines, perhydrooxazines,[172] ketals, or enol ethers.

Although the classical Pictet−Spengler reaction involves a bimolecular process, numerous 6-*endo* cyclizations have been described with only intramolecular steps. Thus, acyliminium intermediates have been generated via **282** using the aminobenzotriazole methodology and were trapped in a completely *trans* manner (Scheme 98).[173]

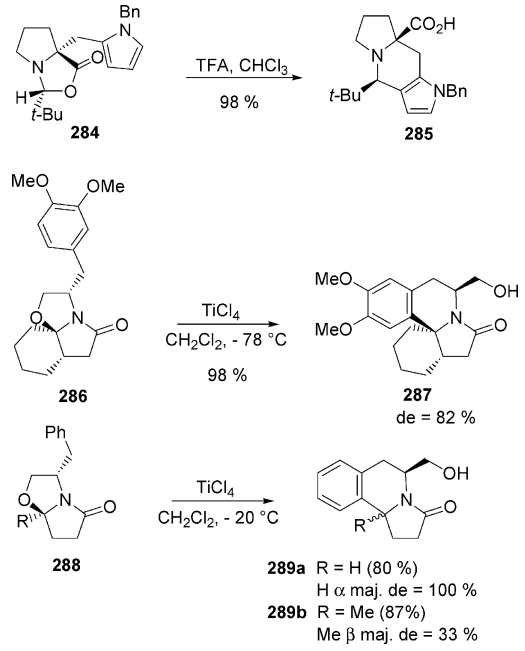
**Scheme 98**



This reaction provided a single isomer, whereas the direct condensation was reported to occur in slightly lower selectivities.[174] The preparation of tricyclic lactams via the intramolecular trapping of an acyliminium has been reported with different precursors. The use of five- or six-membered alkoxylactams

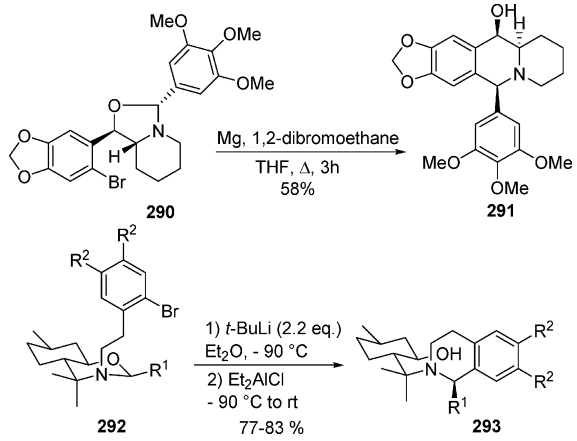
has been recently reviewed.[20] Oxazolidinones and oxazolidines are also valuable precursors in such an approach, as depicted by the stereoselective rearrangement of compound **284** into hexahydropyrroloindolizine **285** (Scheme 99)[175] or the general approach developed by Allin and co-workers, leading to pyrroloisoquinoline **287** or **289**.[176]

**Scheme 99**



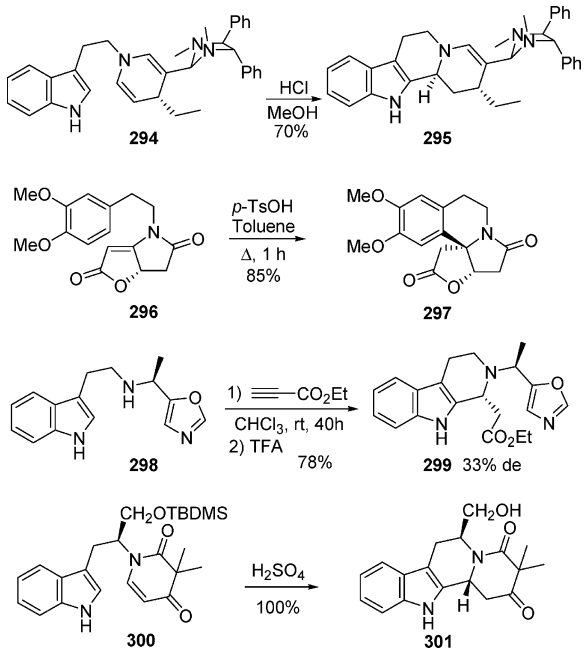

Not only $\pi$-nucleophiles but also in situ generated organometallics can react with iminium precursors, leading to the diastereoselective formation of tetrahydroisoquinolines **291** or benzoquinolizidines **293** (Scheme 100).[177]

**Scheme 100**




Acid treatment of enamines can lead to reactive iminium ions, which can be trapped by nucleophiles (Scheme 101). Thus, the treatment of dihydropyridine **294** with a saturated solution of methanolic hydrochloric acid furnished the indoloquinolizine **295** as a single isomer.[178] The formation of the *trans* compound was explained by a kinetic intramolecular cyclization to the iminium from the less hindered $\beta$-side. The presence of the aminal increased the ring closure selectivity.

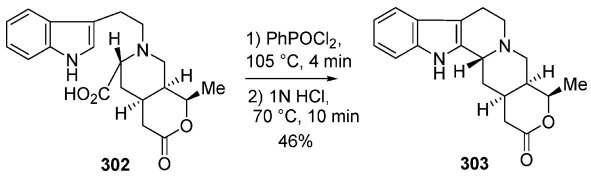
**Scheme 101**




The stereoselective formation of the *erythrina* alkaloid skeleton has also been explained by cyclization to the less hindered face, giving the less strained *cis*-fused tetracyclic compound **297**.[179] Application of the modified Pictet−Spengler cyclization[180] led to carboline **299** after acidic izomerization and cyclization, however in modest diastereoselectivity.[181] On the contrary, a completely stereoselective transformation was observed in the related cyclization from tryptophan-based compound **300**.[182]

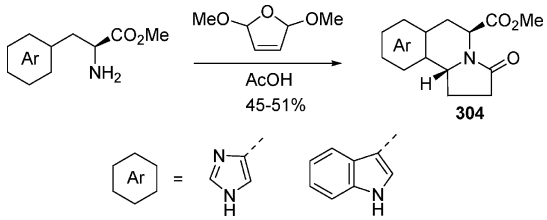
Amino acids can serve as iminium precursors in the Pictet−Spengler cyclization. The enantioselective synthesis of (+)-3-isorauniticine has been achieved via a stereoselective Rapoport cyclization from **302** (Scheme 102).[183]

**Scheme 102**




Intramolecular condensation of aldehydes or ketones with *N*-substituted amines is an expedient way to generate a transient iminium species which can then be trapped by an aromatic nucleus. A general entry to arylindolizidinones **304** has been reported from easily available starting material (Scheme 103).[184]

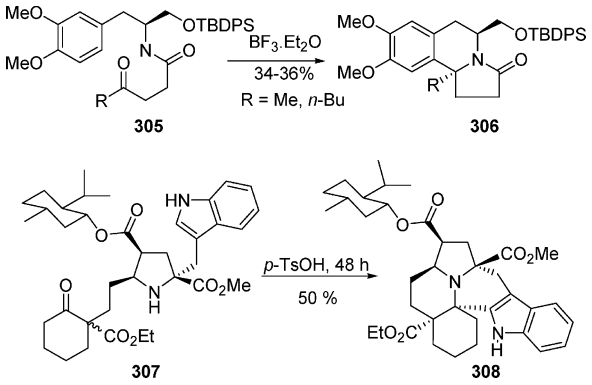
**Scheme 103**



As expected, only the 1,3-*trans* adduct was obtained. A similar strategy, using the trapping of an acyliminium intermediate by benzotriazole, followed by a Lewis-acid-induced cyclization, has been recently described.[185]

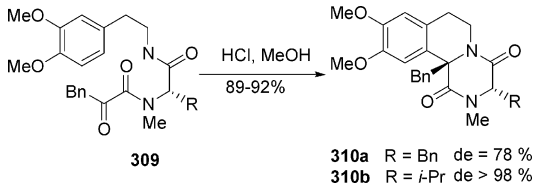
A particularly attractive solid-phase synthesis of various heterocycles has been reported. This traceless strategy, already mentioned for 5-*exo* processes (vide supra), enables the preparation of complex polycyclic compounds in a diastereoselective manner (Scheme 82).[151] A total diastereoselectivity has also been reported for cyclization of ketoamides, leading to pyrroloisoquinolones[186] **306** or complex polycyclic spirocycles **308** (Scheme 104).[187] Chemical yields for these transformations are lower than with aldehydic precursors.

**Scheme 104**



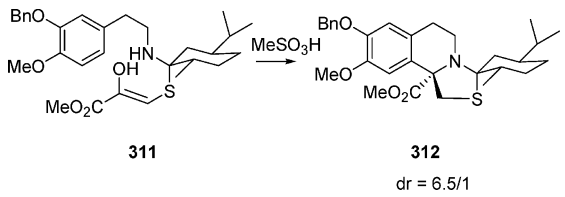

An easy cyclization has been however reported from ketoamides **309**, leading in almost quantitative yields to benzyltetrahydroisoquinolines **310**. The diastereoselectivity increased with the bulkiness of the side chain[188] (Scheme 105).

**Scheme 105**



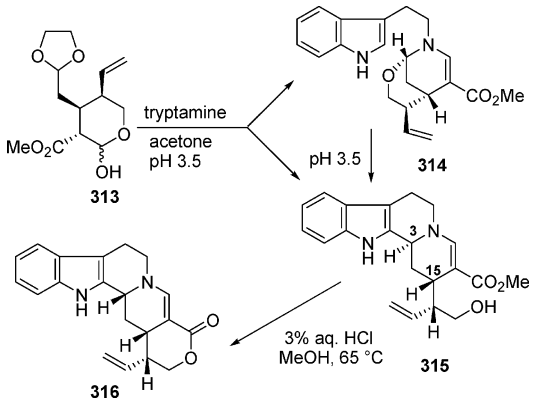

The use of ketoesters can also lead to reactive iminium species, as described for the synthesis of spirotetrahydroisoquinoline **312** (Scheme 106).[189]

**Scheme 106**



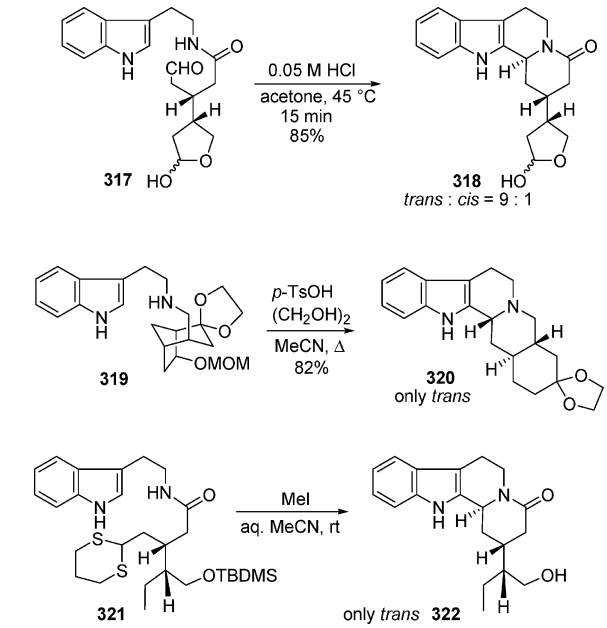

Intramolecular cyclization of aldehydes or their precursors is a general entry to the monoterpenoid indole alkaloid family. A biomimetic condensation between the lactol **313** and tryptamine led to the kinetic adduct **314** with an H3−H15 *trans* configuration (Scheme 107).[190]

**Scheme 107**



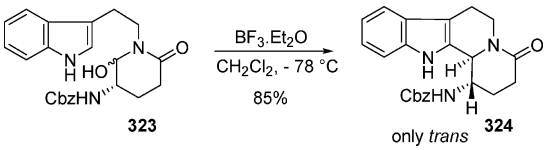

The thermodynamically more stable lactone **316** was obtained after acidic equilibration. Numerous examples involving a similar mode of cyclization have been reported, always with the H3−H15 *trans* relationship as the kinetic product (Scheme 108).[158,170,191]

**Scheme 108**



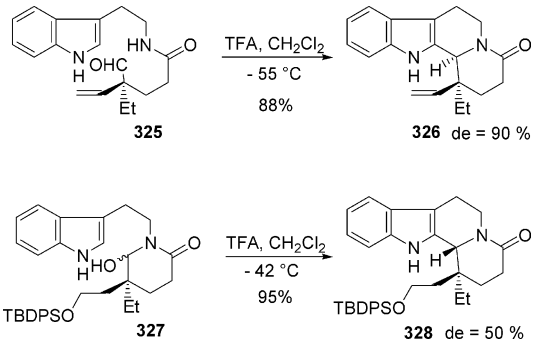

The azaeburnane skeleton has been constructed using a similar strategy. In the synthesis of *trans*-1-aminoindoloquinolizidine **324**, the use of $BF_3 \cdot Et_2O$[192] instead of TFA[193] for the iminium generation avoids the racemization via an iminium−enamine equilibrium (Scheme 109).

**Scheme 109**




In the course of the asymmetric synthesis of the eburnamonine skeleton, the cyclization of amido aldehydes bearing a quaternary stereogenic center proved to be highly substrate sensitive. A very good diastereoselectivity could be obtained starting from compound **325**,[145] whereas, under similar conditions,

**Scheme 110**




the $\beta$-H diastereomer **328** was only obtained in a 3/1 selectivity (Scheme 110).[194,195] A $\pi-\pi$ interaction between the transient iminium and the vinylic side chain has been proposed to explain the excellent selectivity observed in the first cyclization.

The power of 6-*endo* cyclization of aromatic nucleophiles onto iminiums is particularly well highlighted in the total synthesis of ecteinascidin-743 (Scheme 111). This complex polycyclic alkaloid has been constructed via two intramolecular Pictet–Spengler cyclizations, leading to key intermediates **330** and **332**, and an intermolecular one (involving an imine instead of an iminium). All these cyclizations proved to be completely stereoselective, and were achieved in the presence of sensitive functional groups in good yields.[196]

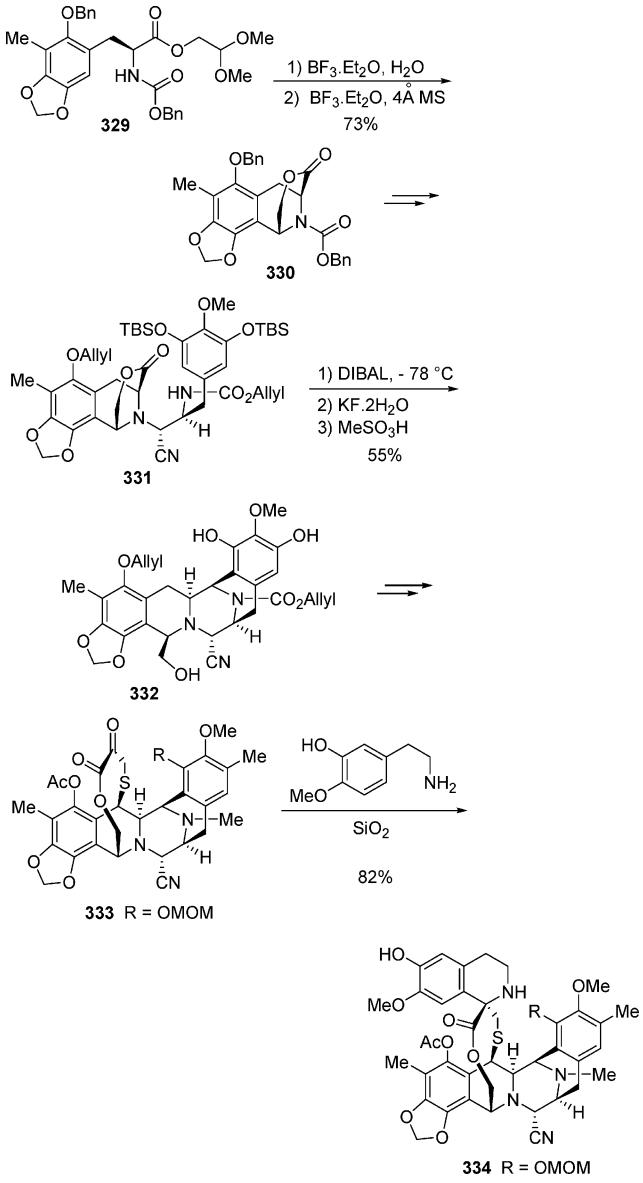
**6.1.1.2. Nonaromatic $\pi$-Nucleophile.** As far as nonaromatic $\pi$-nucleophiles are involved, all these cyclizations are generally referred to the so-called "Mannich reaction". The nature of the nucleophile (an enol for the Mannich reaction, a simple double bond, an allylsilane, ...) displays however a quite important role in the cyclization process and more importantly in the stabilization of the cyclized moiety, and will therefore influence the stereochemical outcome of the reaction. The structure of the iminium must also be taken into account in such a cyclization as well (vide supra).

The formation of a single piperidine ring and fused and bridged bicyclic rings will be presented separately.

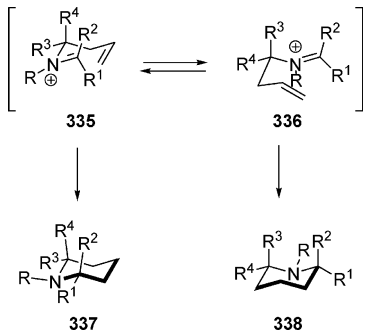
*6.1.1.2.1. From Acyclic Precursors.* Simple *endo* cyclizations on iminiums leading to the formation of single piperidine rings has only been scarcely reported. With an enol group, an enol ether, or a ketal as the nucleophile, the reaction has been reported so far only with protonated imines as reactive intermediates, and was shown to be highly diastereoselective in the preparation of 2,6-dialkylpiperidine derivatives.[197]

The diastereoselective synthesis of single piperidine rings via a double bond, a vinyl, and an allylsilane cyclization onto iminium ions has attracted much more attention. The stereochemical outcome of the cyclization can be rationalized via the chairlike iminium intermediates **335** and **336** (Scheme 112). Analysis of steric (or stereoelectronic) effects of substituents in each particular structure will then enable the prediction or explanation of the observed stereoselectivity of the cyclization.

**Scheme 111**




**Scheme 112**

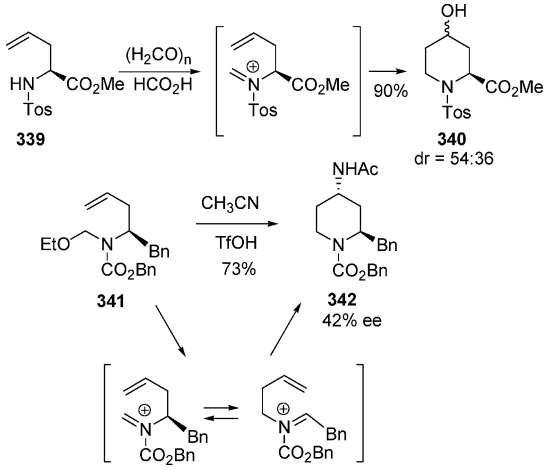



High asymmetric induction, mainly governed by allylic 1,3-interactions, is usually observed with the formation of *trans*-2,6-dialkylpiperidines[198] (in contrast to the imine series, which mainly gives *cis* compounds[197]).

With enantiopure starting material, the possibility of a competitive aza-Cope reaction must be carefully examined since partial or total racemization may be observed. The structure of the starting material is

essential. It has been recently pointed out that the *N*-tosylallylglycine **339** leads to the pipecolic acid derivative **340** without racemization[199] whereas the cyclization of 2-alkylbutenamine **341** occurs with important racemization (Scheme 113).[200]

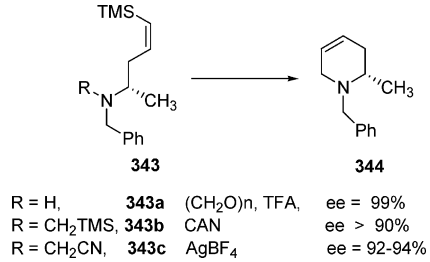
**Scheme 113**




This difference could be explained by the difficulty, in the first example, to form an iminium α to the ester group through a 3,3-sigmatropic rearrangement.[199]

Extensive work from Overman,[201] and more recently by Mariano,[202] allows some rationale in the occurrence of the aza-Cope reaction and its detrimental effect on the stereochemical integrity in the reaction of enantiomerically pure compounds. In the case of an allyl- or vinylsilane−iminium ion cyclization, the stabilization of the carbocation would allow a more rapid reaction to avoid the undesired 3,3-sigmatropic rearrangement. Indeed, careful examination of the electrophilic cyclization of enantiomerically pure (*Z*)-vinylsilane **343** did not reveal any racemization by reaction with iminium ions generated through various methods (Scheme 114).[198b]

**Scheme 114**

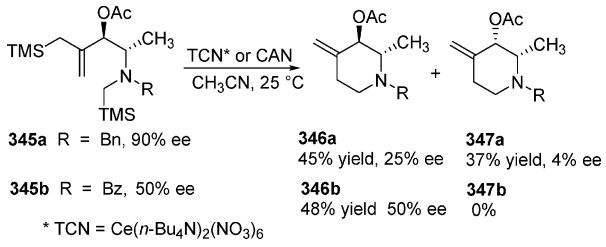



However, some racemization (ca. 30%) has been reported for cyclization of **343a** using paraformaldehyde in the presence of *p*-TsOH−$H_2O$.

Allylsilane cyclization of iminium ions generated by oxidative elimination of TMS group were found to occur with partial or total epimerization (Scheme 115).[202] This side reaction could be suppressed when the reaction was conducted from the corresponding *N*-benzoyl **345b** derivative, involving the cyclization of an acyliminium ion.

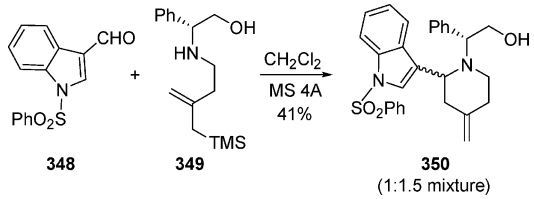
This undesired racemization through the aza-Cope reaction only exists if the chiral center is part of the

**Scheme 115**



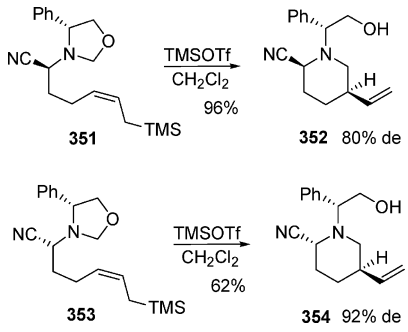

ring which is formed, as in the previous examples. The use of a chiral auxiliary external to the piperidine ring has been examined. A moderate chiral induction was obtained in the cyclization of the in situ generated iminium ion from aldehyde **348** and amine **349** (Scheme 116).[203]

**Scheme 116**




On the contrary, a stereoselective cyclization could be acheived upon (TMSOTf) treatment of oxazolidines **351** and **353** (Scheme 117).[204] In this case, the

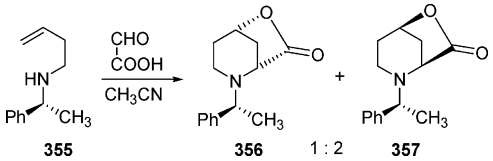
**Scheme 117**




stereoselectivity of the cyclization was mainly controlled by the external stereogenic center since **351** gave the piperidine **352** with 80% de, while **353** gave **354** with excellent 92% de.

The chiral center was also external in the example depicted in Scheme 118, but a moderate selectivity

**Scheme 118**

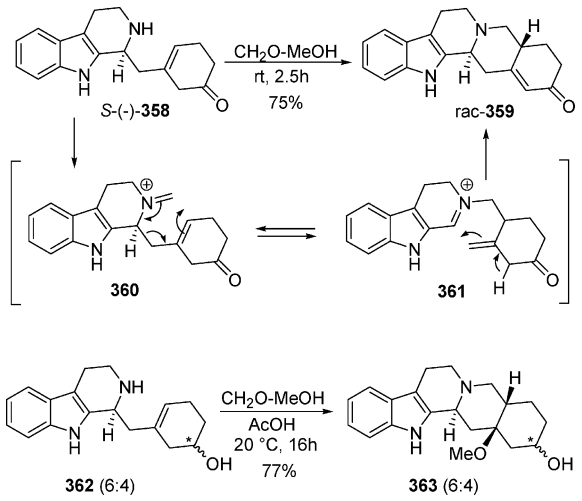



was then observed. The internal trapping of the carbonium intermediate allowed the sole isolation of the *cis*-4-hydroxypipecolic acid derivatives **356** and **357** (Scheme 118).[205]

*6.1.1.2.2. From Cyclic Precursors.* Numerous reports can illustrate this cyclization. As in the case of five-membered ring cyclization, the occurrence of the aza-Cope side reaction associated with racemization

processes will be strongly dependent on the relative stability of the starting and final iminium ions, as depicted in Scheme 119. It was reported, in an

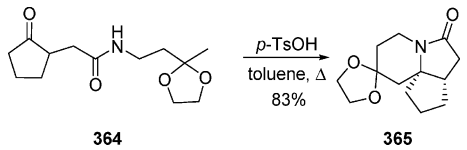
**Scheme 119**




elegant asymmetric synthesis of yohimbone, that when optically pure $\beta,\gamma$-enone **358** was treated with methanolic formaldehyde, **359** was obtained with 75% yield but with complete racemization (Scheme 119). Conformational change and ene-type reaction of rearranged iminium **361** could occur to give non-diastereoselective cyclization. On the contrary, when alcohol **362** (6/4 mixture of epimers) was treated under the same conditions, a 6/4 mixture of diastereomers **363**, only differing by their configuration at the *C*-hydroxyl center, was obtained.[206]

The preparation of the tricyclic lactam **365** (Scheme 120) in the synthesis of daphniphyllum alkaloids by

**Scheme 120**

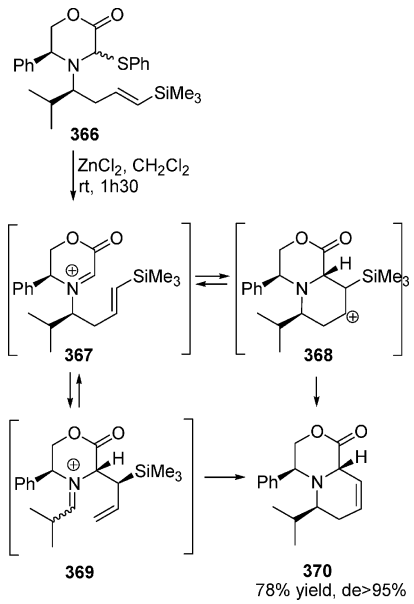



Heathcok and co-workers is an excellent example (in racemic series) of the power of such methodology in the synthesis of complex alkaloids. Two new rings were formed in a total diastereomeric fashion by the acidic treatment of keto amide **364**.[207]

In a recent report on the enantioselective synthesis of *trans*-6-substituted pipecolic acids, the reactivity of $\beta$-amino alcohols having a vinyl- or allylsilane terminator toward glyoxal was examined. The vinylsilane cyclization of morpholinone **366** occurred to give the bicyclic lactone **370** without racemization (Scheme 121).[208] This could be the result of a direct cyclization or of a tandem aza-Cope/allylsilane addition, since the aza-Cope rearrangement could generate a new chiral center ($\alpha$ to silicon in **369**) which could induce a rapid diastereoselective allylsilane cyclization.

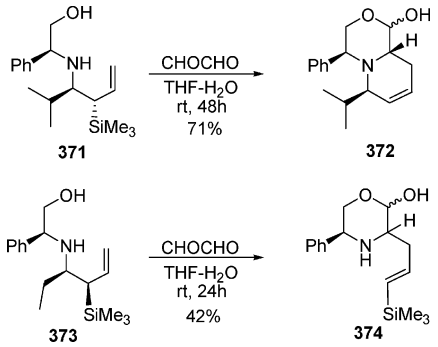
The corresponding allylsilane cyclization of **371** in the presence of glyoxal gave **372** in good yield without noticeable loss of optical purity (Scheme 122). Compound **373** could not cyclize and furnished **374**, which

**Scheme 121**



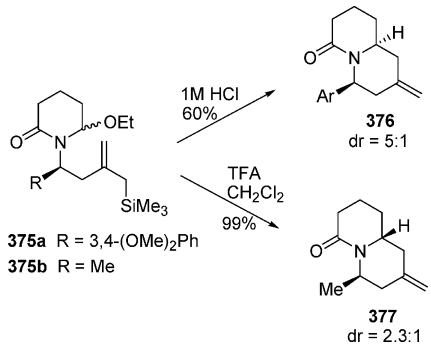

was supposed to be the result of the hydrolysis of the aza-Cope-rearranged iminium ion.

**Scheme 122**




The asymmetric synthesis of several bicyclic alkaloids was obtained through stereoselective allylsilane iminium ion cyclization.[209−211] The presence of a first chiral center on the starting material allowed a good 2,6-induction as in the cyclization of **375a** to **376** (Scheme 123) on the way to the preparation of (−)-

**Scheme 123**



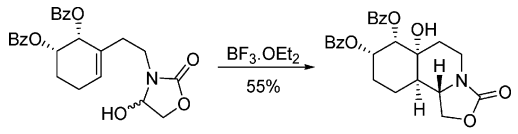

lasubine.[210] It is worth noting that the same authors[211] reported the cyclization of **375b** to **377** as the major product.

Cyclization with vinylsilane has been extensively studied.[212] Overman and co-workers developed ste-

reoselective strategies devoted to the preparation of several dendrobatid alkaloids of the pumiliotoxin class,[212a−c] which are interesting bioactive substances. Electrophilic cyclization with triple bonds as terminator functions was also used[212,213] to reach a control of the *E*/*Z* geometry of the *exo* double bond.

Chiral induction could also be observed with a stereogenic center external to the formed six-membered ring. The formation of bicyclic compounds was generally accomplished with a good diastereoselectivity. In a work devoted to the asymmetric access to morphinanes, Hudlicky and co-workers described the $BF_3{\cdot}OEt_2$-catalyzed cyclization of **378** to give the perhydroisoquinoline derivative **379** as a single isomer (Scheme 124).[214]

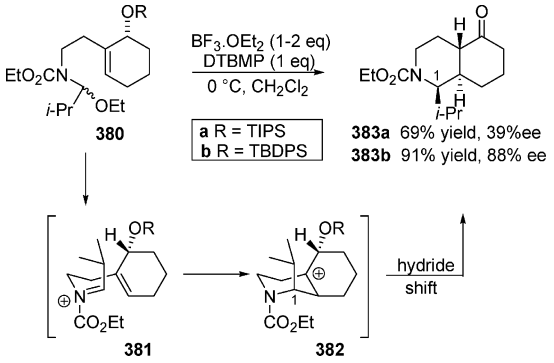
**Scheme 124**




**378** **379**

Chiral perhydroisoquinolines were also formed from chiral allylsilane[215] and *O*-silylated allylic alcohol. In this last case, a Prins-pinacolic-type reaction allowed the termination of the cationic cyclization (Scheme 125). The use of enantioenriched cyclohexenols **380** furnished the *trans*-decahydroquinolines **383** with excellent diatereoselectivity (20/1).[216]

**Scheme 125**




**380**

**383a** 69% yield, 39%ee
**383b** 91% yield, 88% ee

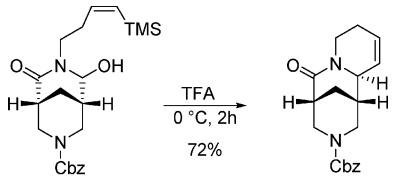
**381** **382**

Stereoselection was explained by a preferential cyclization of the (*E*)-*N*-acyliminium **381** in which $A^{1,3}$ interactions were minimized and approach was from the cyclohexene face opposite the bulky silyl group. Both the yield and enantioselection were improved by use of the more acid stable and bulky TBDPS group.

An enantioselective approach to quinolizidine alkaloids has been described by *N*-acyliminium ion cyclization. When (*Z*)-vinylsilane **384** was treated with TFA at 0 °C for 2 h, the condensation proceeded smoothly to provide the quinolizidine **385** in 72% yield as the only isolated product (Scheme 126).[217] A similar iminium ion−acetylene cyclization gave the corresponding ketone by treatment with formic acid, and the same *trans* relative configuration was obtained for the unique compound formed.[217]

The tricyclic core of the nonchiral ladybug alkaloid precoccinelline (**387**) (Scheme 127) has been formed

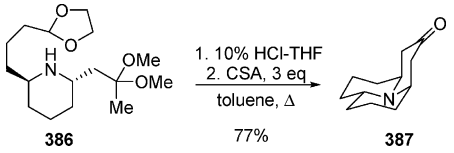
**Scheme 126**




**384** **385**

by a Mannich reaction of *trans*-2,6-dialkylated piperidine **386**.[218] The high diastereoselectivity observed with this cyclization was brought about by the tricyclic system.

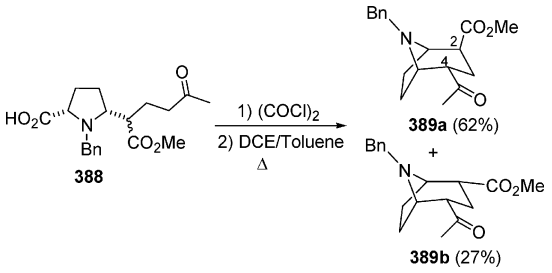
**Scheme 127**




**386** **387**

*6.1.1.2.3. Formation of Polycyclic Bridged Compounds.* The formation of bridged compounds through an iminium cyclization is a very attractive process. Starting from an optically pure compound bearing an adequately substituted side chain α to a nitrogen atom and a potential iminium ion, a bridged compound would be expected with complete stereoselectivity. In such a cyclization, the need for an axial position of the arm bearing the nucleophilic function avoids stereoselectivity problems or racemization processes via an aza-Cope reaction.[219] This strategy has been used by Rapoport in an asymmetric synthesis of epibatidine. Pyrrolidine **388** (Scheme 128)

**Scheme 128**




**388**

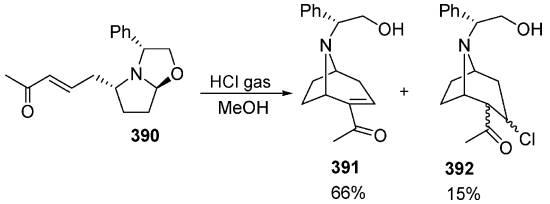
**389a** (62%)

**389b** (27%)

was treated by $(COCl)_2$ to give, upon heating, a decarbonylation which led to the iminium ion, which was cyclized to the 2,4-disubstituted tropanes **389a** and **389b**.[220,52b]

The cyclization of an enone on *N*-acyliminium, first reported by the group of Speckamp, has been applied to the chiral alkyliminium ion derived from **390** in the asymmetric synthesis of ferruginine (Scheme 129).[221] The cyclization proceeded smoothly to give

**Scheme 129**




**390**

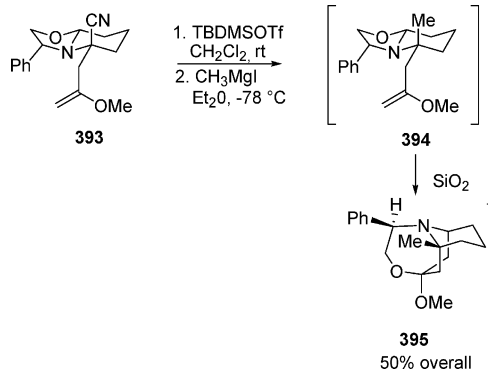
**391** 66%

**392** 15%

the bridged enone **391** in good yield accompanied with some amount of the chloro derivative **392**.

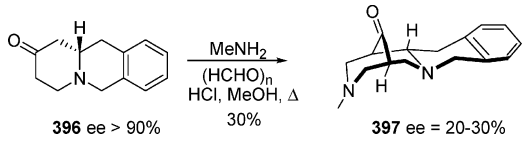
A very similar reaction was reported with acyliminium[222] or alkyliminium ions.[219,221,223] In the synthesis of (−)-euphococcinine, the bridged bicyclic skeleton was obtained by addition of a Grignard reagent on aminonitrile **393** (Scheme 130). The resulting methylated oxazolidine **394** was the precursor of the iminium ion onto which the enol ether was cyclized.[224]

**Scheme 130**



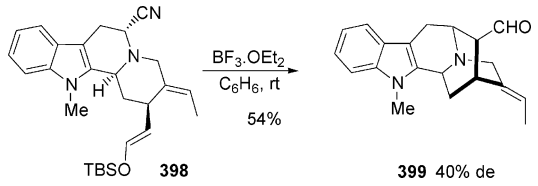

A double Mannich reaction (using three components) was recently reported among chiral cyclic ketone **396**, methylamine, and formaldehyde, to give the bridged spartein-like compound **397** (Scheme 131).[225] Unfortunately, a severe racemization was observed during this process, most likely through a retro-Michael reaction.

**Scheme 131**



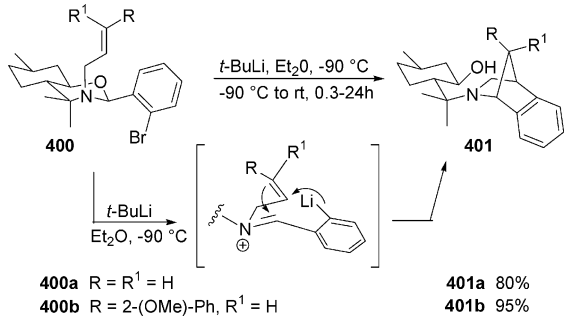

6-*endo* cyclizations have been frequently used in indole alkaloid synthesis.[226] Martin and co-workers recently reexamined the existence of a biogenetic pathway directed to the sarpagan indole alkaloid family through the very nice cyclization shown in Scheme 132.[226b]

**Scheme 132**




Another interesting reaction has recently been described by Pedrosa and co-workers.[227] The stereoselective synthesis of [2.2.1]azabicycloheptane **401** was realized from a linear iminium intermediate (Scheme 133). In this reaction, an olefine cyclized onto an iminium ion, and the termination of the reaction was the trapping of the carbonium ion by an organometallic species.

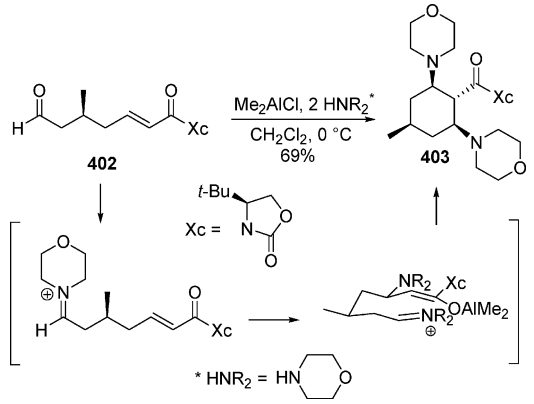
**Scheme 133**




### 6.1.2. exo-Mode Cyclization

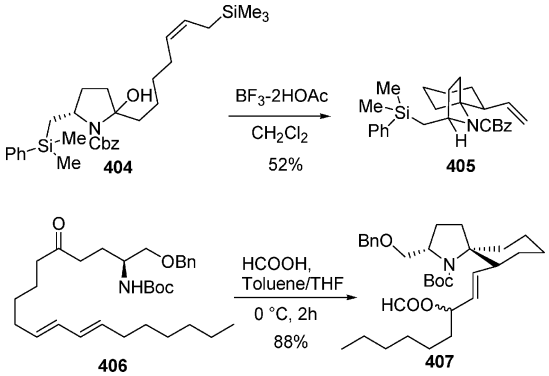
As with the 5-*exo* cyclizations, 6-*exo* cyclizations have been less described than their 6-*endo* counterparts. They can however proceed in an efficient manner, even with acyclic iminiums, as reported by Schneider and Reese (Scheme 134).[228]

**Scheme 134**



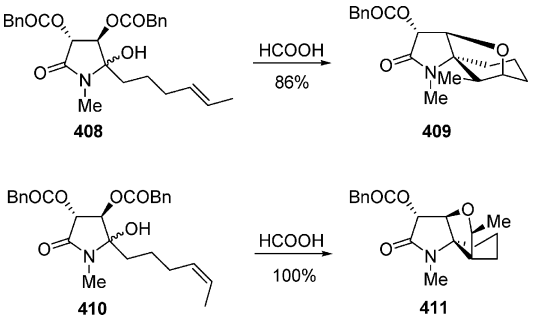

The cyclization described for the formation of 6,6- or 6,5-spirolactams has been adapted to the case of the 5,6-skeleton of the marine alkaloid lepadiformine.[229] Under acidic conditions, carbinolamide **404** cyclized to furnish a single diastereomer in 52% yield (Scheme 135). The stereoselectivity was explained by the attack of the allylsilane on the less hindered face of the acyliminium intermediate. Spirocyclization can also occur efficiently using a linear dienic precursor.[230]

**Scheme 135**




An intramolecular trapping of the transient carbocation has been described on a similar spirocyclization (Scheme 136).[231] Interestingly, the *E* isomer

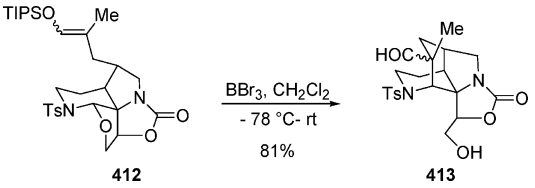
**Scheme 136**




hydroxylactam **408** led to 5,6-spirocyclic compound **409** as a single isomer, whereas the corresponding *Z* isomer **410** led to 5,5-spirolactam **411** in quantitative yield.

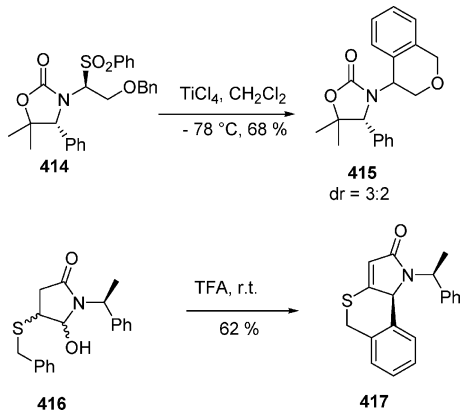
Intramolecular Mannich reaction has been reported from *N*,*O*-acetal **412**. Only $BBr_3$ promoted the ring closure, whereas $SnCl_4$, $BF_3{\cdot}Et_2O$, or $Me_3Al$ typically returned to the aldehyde precursor of **412** (Scheme 137).[232]

**Scheme 137**




6-*exo* cyclizations involving aromatic nucleophiles have been reported. The stereoselectivity of the ring closure leading to **415** was moderate with acyclic iminium reactive species,[233] whereas a single diastereomer (**417**) was obtained from cyclic intermediates (Scheme 138).[234]

**Scheme 138**

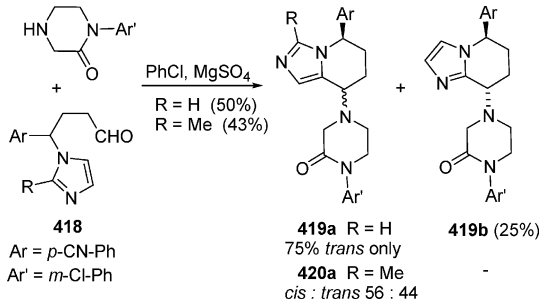



The stereochemical outcome of the cyclization of imidazole derivatives proved to be quite sensitive to the substitution pattern of the heterocyclic ring, as depicted in Scheme 139.[235]

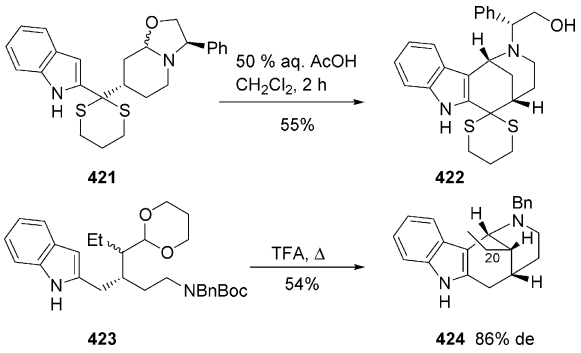
The use of indole derivatives as nucleophiles in 6-*exo* cyclizations has also been reported. For example, a stereoselective access to the general skeleton of dasycarpidone-type indole alkaloids is based on such a ring closure (Scheme 140).[236]

Interestingly, starting from a diastereomeric mixture of compounds **423**, the enamine−iminium equilibrium during the cyclization process enables the control of the configuration of the C-20 center.

**Scheme 139**




**Scheme 140**



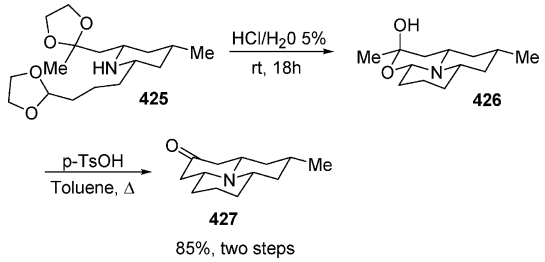

## 6.2. Cyclization Leading to Six-Membered Rings by Formation of a C–Heteroatom Bond

### *6.2.1. endo-Mode Cyclization*

The 6-*endo* iminium ion cyclization with nucleophilic heteroatoms such as O, S, or N leads, respectively, to 1,3-oxazine, 1,3-thiazine, or hexahydropyrimidine. These heterocycles are stable equivalent forms of the corresponding iminium ions. As for the five-membered heterocycles (oxazolidines, thiazolidines, and imidazolines), the addition of the heteroatom to the iminium ion is a reversible process and the heterocycle is generally obtained as a thermodynamic product. The rules which govern the configuration of the newly created centers are based on the relative stability of each possible diastereomer and rely on the classical steric interactions in the six-membered ring and the stereoelectronic effects.[237]

**6.2.1.1. Oxygen Nucleophile.** The formation of such heterocycles is a very easy process. In some attempts to perform a Mannich reaction, oxazine **426** was obtained through the O-cyclization of the keto group as in the preparation of myrrhine shown on Scheme 141.[238] The Mannich product could usually

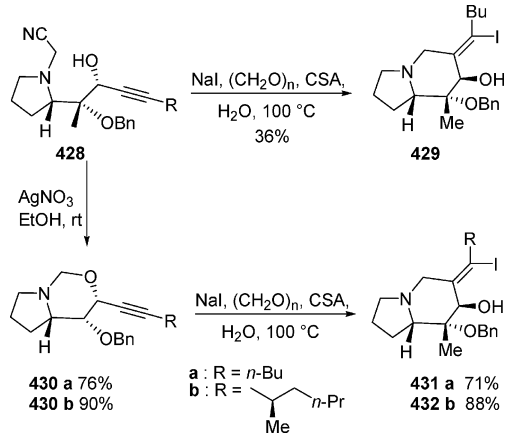
**Scheme 141**



be attained through *C*-alkylation by a more acidic treatment of the transient oxazine.

In a novel approach to the allopumiliotoxin A alkaloids, Overman and co-workers reported the access to oxazines **430** (Scheme 142) by displacement

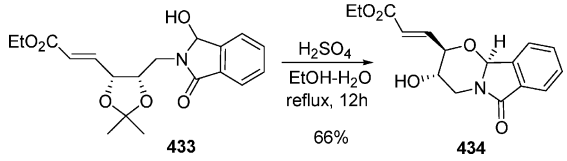
**Scheme 142**




of the CN group of the aminonitrile function. The oxazines **430a,b** were used as iminium ion equivalents in iodide-promoted iminium ion−alkyne cyclization, improving thus the preparation of this type of alkylidene−indolizidine skeleton.[239]

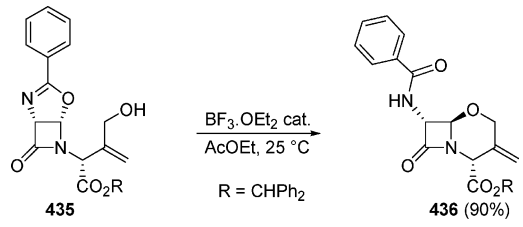
Isomeric pyrrolooxazine **434** was also reported by cyclization of an allylic hydroxyl group onto the acyliminium ion derived from phthalimide **433**.[240] In this case, the configuration at the chiral center which was formed in **434** was not assigned but is likely to be *S* (α-H) as depicted in Scheme 143.

**Scheme 143**



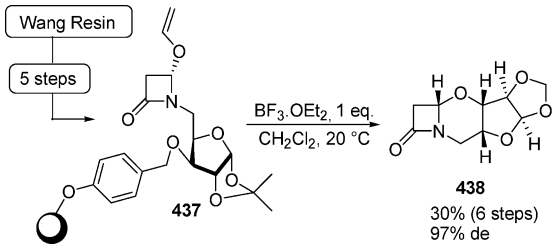

The oxazine ring is particularly stable when fused with a four-membered *β*-lactam ring. Lewis acid treatment of compound **435** (Scheme 144) gave an easy access to oxacepham precursor **436**.[241]

**Scheme 144**



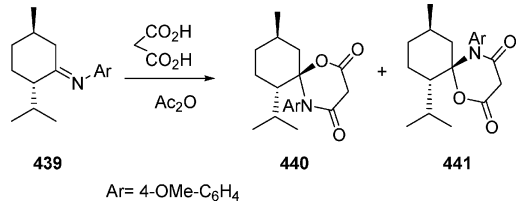

The reaction was highly diastereoselective and used with various alkoxyazetidinones, offering a straightforward entry to oxacepham derivatives.[242] An extensive study of this reaction showed the possible cyclization from ether derivatives. A particularly high yielding reaction was pointed out for ethers of enhanced nucleophilicity such as *p*-methoxybenzyl ether.[242b] Application of this reaction to solid-phase synthesis allowed the diastereoselective preparation of 1-oxacepham **438** (Scheme 145) using a very efficient cyclization/cleavage approach.[242c]

**Scheme 145**




An interesting cyclization was observed when imine **439** derived from menthone was reacted with malonic acid in acetic anhydride (Scheme 146). Two

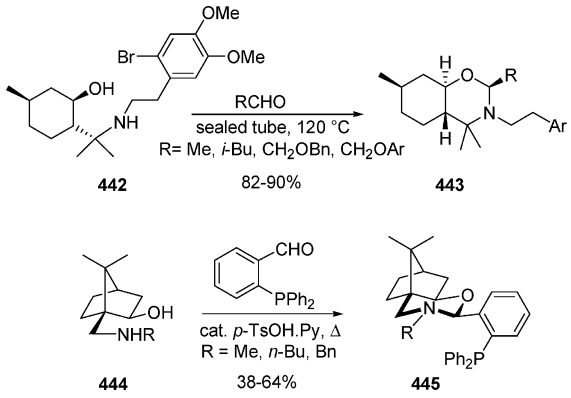
**Scheme 146**




stereomeric oxazinediones (**440** and **441)** were reported to be formed without indication about the diastereoselectivity, but most likely through an acyliminium intermediate.[243]

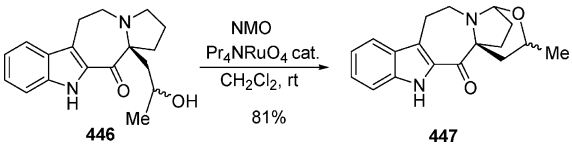
As for the oxazolidines, the oxazines can be prepared by condensation of an amino alcohol and an aldehyde. Several chiral 1,3-amino alcohols such as **442** or **444** (Scheme 147) were condensed using various experimental conditions, in very high diastereoselectivities.[244]

**Scheme 147**




Oxazines were also obtained by amine oxidation of a suitable amino alcohol.[245] Hydroxyacylindole **446** (Scheme 148) was found to be prone to oxidation at the position α to the nitrogen of the pyrrolidine ring,

**Scheme 148**

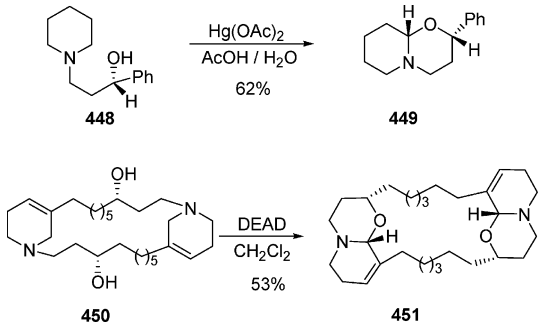


enabling an easy transformation of **446** to oxazine **447** in 81% yield.[245a]

As already mentioned, anodic oxidations of amides or carbamates are suitable methods for generating iminium ions. If several nitrogen atoms are present in the substrate, the regioselectivity of oxidation emerges as a crucial problem. It was found that the use of a silyl group could solve this chemoselectivity problem.[245e]

Amine oxidation of amino alcohols has also been realized using mercury(II) acetate or diethyl azodicarboxylate (Scheme 149). Thus, (*S*)-3-piperidyl-1-

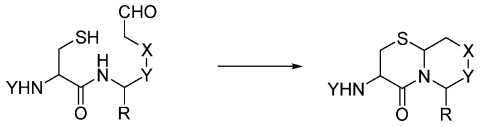
**Scheme 149**




phenylpropanol (**448**) was diastereoselectively converted to oxazine **449** in 62% yield.[245c] In another example of amine oxidation, diethyl azodicarboxylate oxidative dehydrogenation of the tetrahydropyridine dimer **450** gave dehydrobisoxaquinolizidine **451** (Scheme 149) in 53% yield, in an elegant biomimetic synthesis of (−)-xestospongin A.[245b]

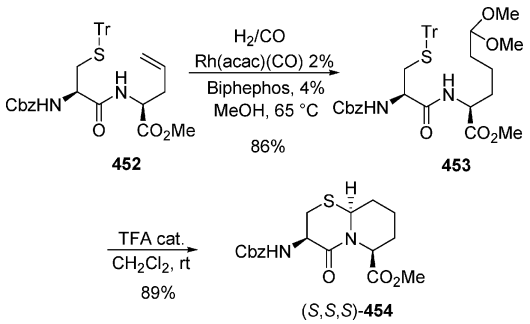
**6.2.1.2. Sulfur Nucleophile.** Bicyclic derivatives of 1,3-thiazine have been recently found of interest as peptidomimetics, and different strategies to attain aldehydic precursors involved in the cyclization depicted in Scheme 150 have been designed.[246]

**Scheme 150**



Among them, the hydroformylation of allylglycine derivative **452** appears a very attractive method, leading to high yield and complete diastereoselective transformations.[246b] The preparation of 1,3-thiazine **454** (Scheme 151) was achieved in an efficient two-step sequence. Similarly, the method was applied to

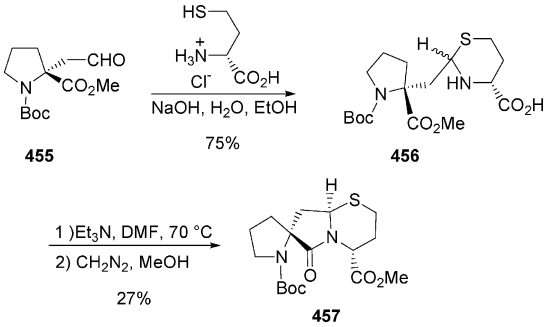
**Scheme 151**




the preparation of 1,3-oxazines, or hexahydropyrimidines for which a one-pot procedure was feasible.

Chiral thiazines can be obtained by the condensation of aldehydes and aminothiols. Homocysteine, the most commonly available 1,3-aminothiol, has been condensed with chiral aldehyde **455** to give NH-thiazine **456** via imine cyclization as a mixture of diastereomers (Scheme 152). Under thermal reaction

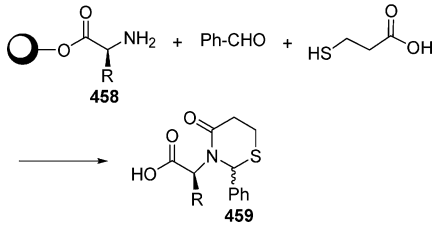
**Scheme 152**




conditions, only the spirobicyclic lactam diastereomer **457** was obtained through a ring opening and recyclization onto the transient *N*-acyliminium.[247]

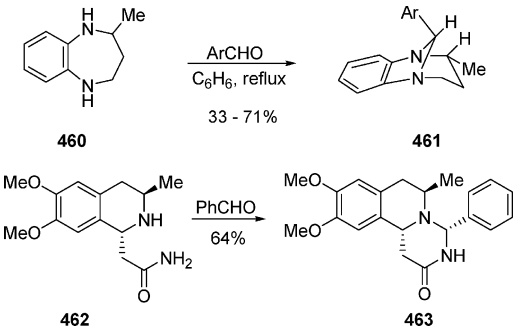
Stereoselective condensation was achieved starting from chiral amines. Preparation of thiazidinones **459** was proposed through a solid-phase synthesis although in low yield and without stereoselectivity (Scheme 153).[248]

**Scheme 153**




**6.2.1.3. Nitrogen Nucleophile.** The condensation of 1,3-diamines or 1,3-aminoamides with an aldehyde can provide the hexahydropyrimidine skeleton: benzodiazepine **460** gave rise stereoselectively to the bridged compound **461**,[249] while amide **462** gave the pyrimidoisoquinoline **463** as a single product (Scheme 154).[250]

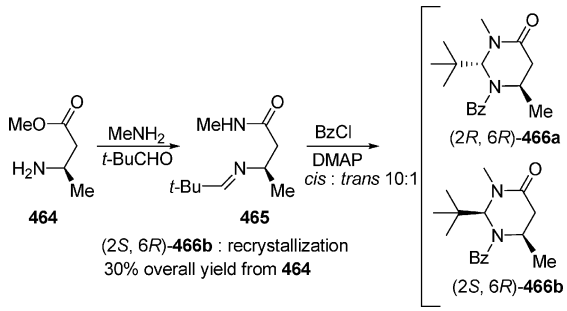
**Scheme 154**




Efforts were made to access chiral hexadropyrimidines as starting material for the asymmetric synthesis of $\beta$-amino acids. $\beta$-Amino acid derivative **465**

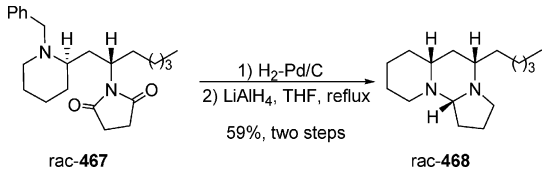
was condensed with pivalaldehyde to give predominantly the *cis* diastereomer **466b**, a valuable precursor in the enantioselective synthesis of other $\beta$-amino acids (Scheme 155).[251]

**Scheme 155**



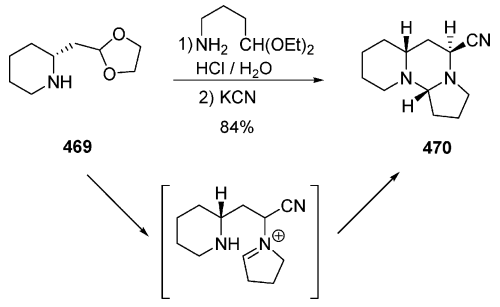

Tetraponerines are defensive ant alkaloids possessing an interesting and rare tricyclic pattern including a hexahydropyrimidine ring. Several efficient strategies based on iminium ion cyclization have been proposed for the synthesis of these compounds. The cylization on the acyliminium generated from the corresponding imide **467** offered an easy entry to tetraponerine **468** (Scheme 156).[252]

**Scheme 156**




An efficient method was developed which allowed the asymmetric preparation of all eight natural products.[253] In this synthesis, a cross condensation between two different amino aldehydes was used to construct, in a one-pot procedure, the skeleton of the alkaloids. Enantiopure protected aldehyde **469** and commercially available protected aminobutanal (Scheme 157) were condensed in acidic medium to

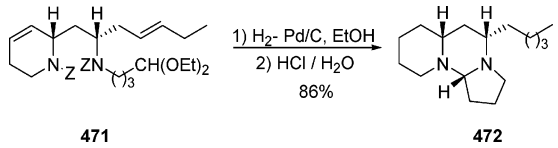
**Scheme 157**




give successively two iminium ions which were trapped intramolecularly by an amine and intermolecularly by a cyanide ion to give **470** in high yield. The reaction was totally diastereoselective. Once again, the stereoselectivity was the result of a series of equilibria leading to the most stable compound.

Recently, an elegant asymmetric accesss to protected diamine **471** has been described (Scheme 158). This diamine was conveniently cyclized through the formation of an iminium to give tetraponerine **472**

**Scheme 158**



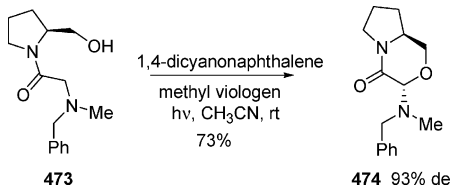

in high yield and as a single diastereomer. The preparation of all the alkaloids of the series was also decribed in this paper.[246a]

### 6.2.2. exo-Mode Cyclization

Although this cyclization is a favored process, quite a few examples in the asymmetric series have been reported.

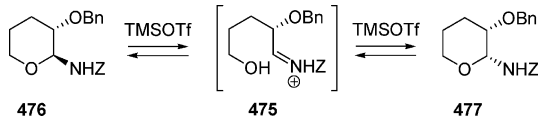
**6.2.2.1. Oxygen Nucleophile.** In general, oxidation $\alpha$ to the nitrogen of a 1,5-amino alcohol is able to promote the cyclization to a tetrahydropyran ring. This was proven to be possible (Scheme 159) by the oxidation of amino alcohol **473** to morpholine derivative **474** using a photoinduced electron transfer.[254]

**Scheme 159**




A single tetrahydropyran ring was found to be formed through oxygen cyclization onto the protonated imine **475**, giving a 40/60 *cis*/*trans* mixture of isomers **476** and **477** (Scheme 160). Each isomer could be isolated but gave back the same mixture in the presence of (TMSOTf).[255]

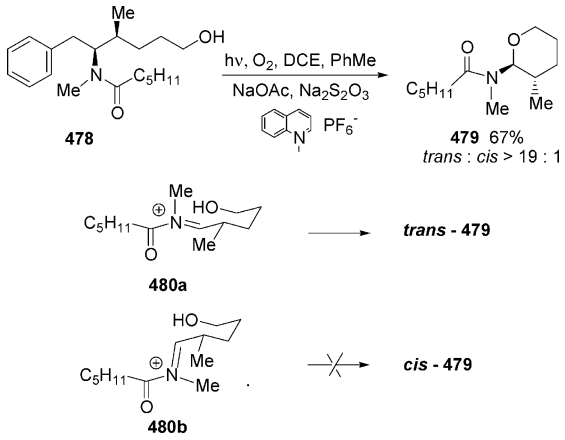
**Scheme 160**



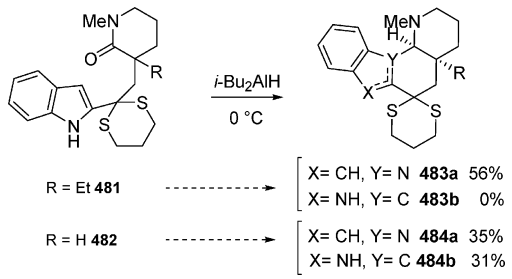

The stereochemical control of the cyclization was different in the reaction involving an iminium ion (and governed by allylic interactions) and not a protonated imine as in the precedent case. Photochemical oxidation of amide **478** was followed by a homolytic benzylic cleavage and led to the acyliminium ion, which cyclized to give **479** in 67% yield and excellent diastereoselectivity (*trans*/*cis* = 19/1). The same result was obtained starting from a 1/1 epimeric mixture of lactams (Scheme 161).[256] This highly stereoselective process was attributed to the enhanced allylic strain in conformer **480b** relative to **480a**.

**6.2.2.2. Nitrogen Nucleophile.** In the synthesis of *rac*-aspidospermidine, it was shown that the partial reduction of $\delta$-lactam **481** allowed the formation of an iminium ion which cyclized to naphthyridoindole **483** (Scheme 162). In this case, the nitrogen of indole acted as a nucleophile without competition with the C-3 nucleophilic carbon of the indole ring.[257] This result contrasted with the behavior of desethyl compound **482**, which gave a mixture of compounds **484a** and **484b** resulting from *N*- and *C*-cyclization. As expected, the pyridocarbazole derivative **484b** was

**Scheme 161**




**Scheme 162**




the most stable compound, and C−C cyclization was obtained by aqueous AcOH treatment of **482**.

Similar examples (also in the racemic series) showing the facile cyclization of the indolic NH have been reported.[258]

## 7. Cyclization Leading to Seven-Membered Rings

Cyclization leading to seven-membered rings is a facile process in the *endo* or *exo* mode. However, only a few examples corresponding to this cyclization are available due to much less occurrence of azepines compared to piperidines or pyrrolidines as natural product substructures.

### 7.1. Cyclization Leading to Seven-Membered Rings by Formation of a C–C Bond

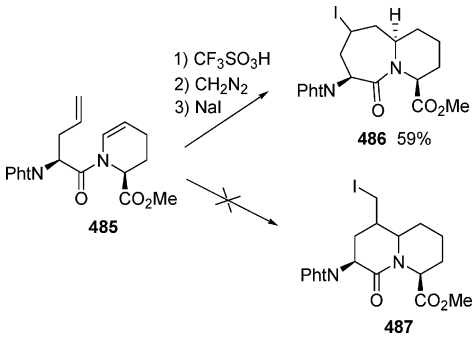
#### 7.1.1. endo-Mode Cyclization

Successful 7-*endo* cyclizations of simple olefins on *N*-acyliminium ions can be found in the literature. They show the preference of 7-*endo*-*endo* vs 6-*exo*-*endo*, which was not observed (without any stabilization by a silyl group for instance).[259] Thus, enamide **485** was cyclized by acid treatment followed by re-esterification and NaI termination to give the 6 + 7 bicyclic compound **486** as one stereoisomer (in addition to a small amount of elimination product), while no trace of quinolizidine **487** could be isolated (Scheme 163).[259a]

Cyclization of triple bonds has also been reported to form simple azepines from acyclic precursors[260] or piperidinoazepine from piperidine precursors.[261]

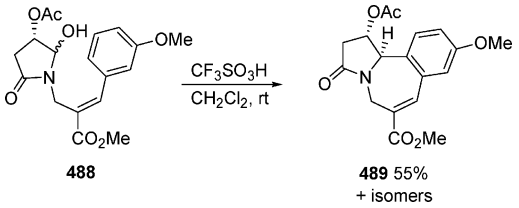
Interestingly, the intramolecular addition of aromatic species on *N*-acyliminiums to form the benzoazepine ring, which could be referred to as a

**Scheme 163**




Pictet−Spengler reaction, has been quite frequently described. For example, the 5 + 7 + 6 tricyclic system of compound **489** was the result of the acid treatment of potential *N*-acyliminium ion **488**. Good regioselectivity (7/1) and diastereoselectivity (4/1) was observed for this cyclization (Scheme 164).[262]

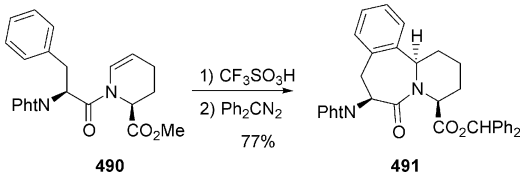
**Scheme 164**




The reaction starting from the corresponding indole derivative and leading to indoloazepine has also been reported.[263]

This cyclization mode was chosen as a very efficient method to construct dipeptide mimetics[264] or original heterocycles.[265] Thus, acidic treatment of **490** (Scheme 165) followed by re-esterification gave the optically

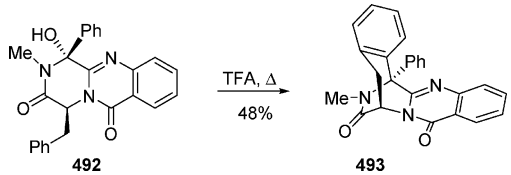
**Scheme 165**




pure benzhydryl ester **491** in 77% yield. The excellent stereoselectivity may be a result of a preferred equatorial conformation of the phthalimide moiety in the acyliminium intermediate.

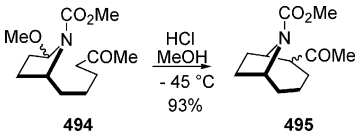
A similar Pictet−Spengler-type reation was reported for the construction of a bridged compound. The potential iminium ion **492**, obtained by phenylmagnesium bromide treatment of the corresponding imide, cyclized after acidic treatment to give the bridged compound **493** in 48% yield (Scheme 166).[266]

**Scheme 166**



Finally, this type of cyclization was used for the construction of bridged compounds in the synthesis of natural compounds such as anatoxine[267] and pinnamine.[268] In these syntheses, the nucleophilic part may be an acetonyl group as with **494** (Scheme 167),[267c−e] a keto ester,[268] an olefin,[267f] or an α,β-unsaturated ketone,[267a,b] which allowed the direct introduction of this function present in anatoxine.

**Scheme 167**

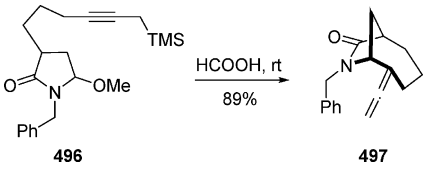



494 495

### 7.1.2. exo-Mode Cyclization

This mode is illustrated by the cyclization of 2-propynylsilanes **496** reported by Speckamp and Hiemstra some years ago (Scheme 168).[269]

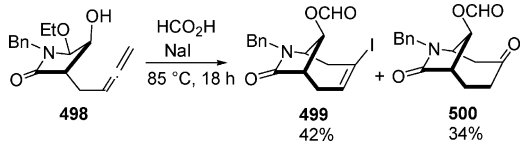
**Scheme 168**




496 497

The reaction was found to be successful with allene derivative **498**,[270] and the method was applied to the synthesis of (+)-gelsedine.[271] In this synthesis the required iodo product **499** was the result of cyclization promoted by formic acid in the presence of a large excess of sodium iodide (Scheme 169).

**Scheme 169**



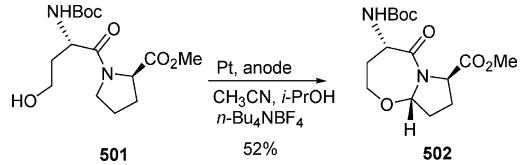

498 499 42% 500 34%

## 7.2. Cyclization Leading to Seven-Membered Rings by Formation of a C–Heteroatom Bond

### 7.2.1. endo-Mode Cyclization

As for the five- or six-membered rings, heteroatom 7-*endo* cyclization is an easy process. As an example, dipeptide **501** was regioselectively oxidized by anodic oxidation, to give bicyclic compound **502** in 52% yield.[272] The cyclization was highly diastereoselective since only one isomer was isolated (Scheme 170).

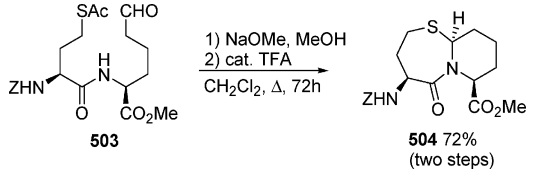
**Scheme 170**




501 502

The resulting product of condensation of a carbonyl with an amine could be trapped in a 7-*endo*-mode cyclization by an oxygen atom[273] or a sulfur atom, as shown in the intramolecular condensation of thiol **503** in acidic medium to form peptidomimetics **504** (Scheme 171).[274]

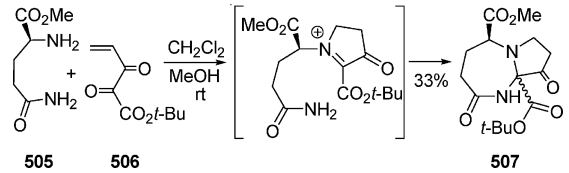
**Scheme 171**




503 504 72% (two steps)

Reactions of diamino compounds with tricarbonyl reagents leading to the formation of 5,5-, 5,6-, and 5,7-bicycles have been mentioned (see section 5.2.1.3). Addition of glutamine to the vinyl tricarbonyl reagent **506** (Scheme 172) gave a "one-pot" access to the

**Scheme 172**



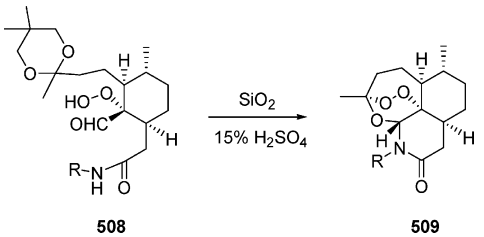

505 506 507

bicyclic compound **507**. Nevertheless, this reaction was not so efficient in this seven-membered ring series: 33% yield and no stereoselectivity (compared to six-membered rings, which gave only one isomer in 81% yield).[275]

### 7.2.2. exo-Mode Cyclization

A very interesting synthesis of an aza analogue of artemisin is based on such a cyclization mode. Transient aldehyde **508** resulting from the ozonolysis of a vinylsilane was condensed to give the oxepane ring **509** of the target product (Scheme 173).[276]

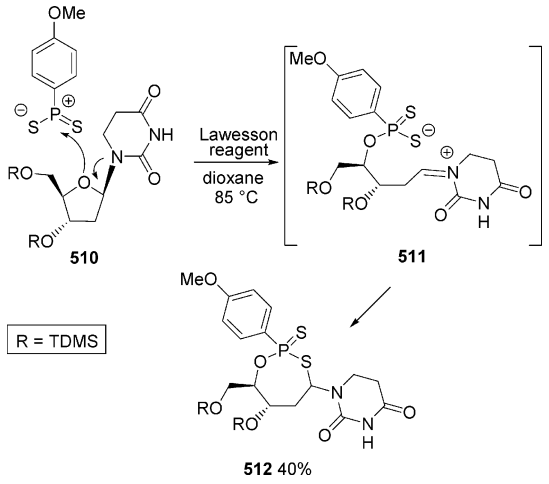
**Scheme 173**




508 509

Another example of *exo*-mode cyclization was the unexpected incorporation of Lawesson's reagent into the deoxyribose moiety of a nucleoside analogue. It was suggested by the authors that an addition of the reactive species of the reagent on substrate **510** promoted the sugar ring opening with formation of iminium ion **511**, which underwent nucleophilic cyclization by the sulfur atom to give **512** (Scheme 174).[277]

**Scheme 174**

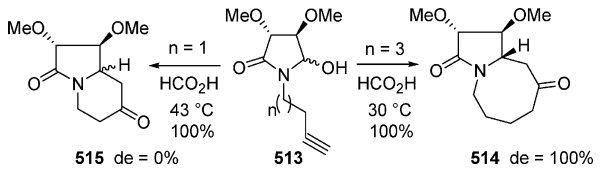



## 8. Cyclization to Eight and More Membered Rings

Cyclization to eight and more membered rings can work in principle, since a lot of reactions involving iminium as an electrophile can proceed easily in an intermolecular manner. However, very few examples of the stereoselective version of such ring closures have been reported in the literature. Furthermore, the creation of large rings is generally concomitant with the formation of smaller ones, and has already been treated in other parts (see, for example, Scheme 137, where a formal 8-*endo* cyclization has been presented as a 6-*exo* closure).

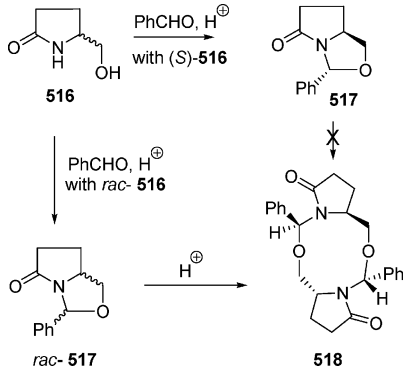
8-*endo* cyclization has been reported from compound **513**, leading to bicyclic lactam **514** as a single isomer (Scheme 175). Interestingly, a similar 6-*endo* cyclization led to a 1/1 mixture of diastereomers **515**.[278]

**Scheme 175**




The formation of 10-membered heterocycles has been described as a side reaction of 5-*endo* ring closure.[279] An interesting *meso*-specific condensation has been reported from a racemic mixture of amido alcohols **516** (Scheme 176). Racemic solutions of reactants **516** underwent an acid-catalyzed dimerization, leading to a *meso* ten-membered ring (**518**), while optically pure solutions were inert under the same conditions, leading to the expected oxazolidinone **517**.

**Scheme 176**




## 9. Conclusion

As described in this review, iminium ion cyclizations have been employed as key strategic steps in the stereoselective synthesis of numerous heterocycles. Several factors contribute to the popularity of such a process. This transformation enables the creation of a large variety of structures, from three- to more than eight-membered rings, with both *endo*- and *exo*-mode cyclizations, and in most of the cases with a good control of regio- and stereoselectivity. Another reason for this success derives from the possibility of using a large range of nucleophiles ($\sigma$, $\pi$, aromatic, heteroaromatic) in ring closures, leading to a huge variety of compounds. Not only chemical, but also stereochemical, diversity can be achieved using iminium ring closures, since in some cases the stereochemical outcome of the cyclizations can be tuned with few reaction condition variations (kinetic or thermodynamic control). Like many reactions involving cationic intermediates, iminium cyclizations can lead in a single operation to the formation of complex polycyclic structures in a predictable stereocontrolled manner, through sigmatropic rearrangements and/or cascade processes. Last but not least, all the chemical arsenal developed for the generation of iminiums from easily available precursors enables these transformations to occur on functional substrates, in reproducible and scalable manner.

Although most of the reactions presented in this review have been involved in natural product syntheses (especially in the field of alkaloids) or in the preparation of bioactive derivatives, it is clear that iminium cyclization could also play a growing role in the future in the field of diversity-oriented synthesis, especially if one includes stereochemical aspects.

## 10. Acknowledgment

We are grateful to Professor H.-P. Husson for helpful discussions and to Dr. A. Perez-Luna for careful reading of the manuscript and suggestions. We also thank F. Cossart and A. Decristoforo for technical assistance.

## 11. References

(1) Keinman, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 893.
(2) Pictet, A.; Spengler, T. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030.
(3) He, F.; Bo, Y.; Altom, J. D.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 6771.
(4) For a review, see: Paukstelis, J. V.; Cook, A. G. In *Enamines*, 2nd ed.; Cook, A. G., Ed.; Marcel Dekker: New York, 1988; p 275.
(5) Mayr, H.; Ofial, A. R. *Tetrahedron Lett.* **1997**, *38*, 3503.
(6) Mayer, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66.
(7) Yamamoto, Y.; Nakada, T.; Nemoto, H. *J. Am. Chem. Soc.* **1992**, *114*, 121.

(8) Lamatsch, B.; Seebach, D.; Ha, T.-K. *Helv. Chim. Acta* **1992**, *75*, 1095.
(9) D'Oca, M. G. M.; Moraes, L. A. B.; Pilli, R. A.; Eberlin, M. N. *J. Org. Chem*. **2001**, *66*, 3854.
(10) For an authoritative review, see: Overman, L. E.; Ricca, D. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 1007.
(11) For a review, see: Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed*. **1998**, *37*, 1044.
(12) Lavilla, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1141.
(13) (a) Roussi, G. *Trends Org. Chem*. **1993**, *4*, 101. (b) Carbonnelle, A.-C.; Gott, V.; Roussi, G. *Heterocycles* **1993**, *36*, 1763.
(14) (a) Polonovski, M.; Polonovski, M. *Bull. Soc. Chim. Fr*. **1927**, *41*, 1190. (b) Ahond, A.; Cavé, A.; Kan-Fan C.; Potier, P. *Bull. Soc. Chim. Fr*. **1970**, 2707. (c) Grierson, D. *Org. React. (N.Y.)* **1990**, *39*, 85. (d) Edward, J. T.; Whiting, J. *Can. J. Chem*. **1971**, *49*, 3502. (e) Ferris, J. P.; Gerwe, R. D.; Grapski, G. R. *J. Am. Chem. Soc.* **1967**, *89*, 5270. (f) Suau, R.; Najera, F.; Rico, R. *Tetrahedron* **2000**, *56*, 9713. (g) Hwang, D.-R.; Uang, B.-J. *Org. Lett.* **2002**, *4*, 463.
(15) For a review, see: Dayagi, S.; Degani, Y. In *The Chemistry of the Carbon−Nitrogen Double Bond*; Pataï, S., Ed.; John Wiley: New York, 1970; p 117.
(16) For reviews, see: (a) Padwa, A. *Chem. Rev*. **1977**, *77*, 37. (b) Mariano, P. S. In *Organic Photochemistry*; Padwa, A., Ed.; Marcel Dekker: New York, 1987; Vol. 9, p 1.
(17) Chao, W.; Weinreb, S. M. *Tetrahedron Lett*. **2000**, *41*, 9199.
(18) (a) Shono, T.; Matsumura, Y.; Tsubata, K. *J. Am. Chem. Soc.* **1981**, *103*, 1172. (b) Bidan, G.; Genies, M. *Tetrahedron* **1981**, *37*, 2297.
(19) Yoshida, J.-I.; Suga, S.; Suzuki, S.; Kinomura, N.; Yamamoto, A.; Fujiwara, K. *J. Am. Chem. Soc.* **1999**, *121*, 9546.
(20) Recent review: Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817 and references herein.
(21) Kinast, G.; Tietze, L. F. *Angew. Chem., Int. Ed. Engl*. **1976**, *15*, 239.
(22) Heaney, H.; Papageorgiou, G.; Wilkins, R. F. *Tetrahedron* **1997**, *53*, 2941.
(23) (a) Zhang, X.; Jung, Y. S.; Mariano, P. S.; Fox, M. A.; Martin, P. S.; Merkert, J. *Tetrahedron Lett*. **1993**, *34*, 5239. (b) Le Gall, E.; Hurvois, J.-P.; Sinbandhit, S. *Eur. J. Org. Chem*. **1999**, 2645. (c) Suga, S.; Nagaki, A.; Tsutsui, Y.; Yoshida, J.-I. *Org. Lett.* **2003**, 945. (d) Narasaka, K.; Kohno, Y. *Bull. Chem. Soc. Jpn*. **1993**, *66*, 3456.
(24) (a) Dean, R. T.; Padgett, H. C.; Rapoport, H. *J. Am. Chem. Soc.* **1976**, *98*, 7448. (b) Rigo, B.; Fasseur, D.; Cherepy, N.; Couturier, D. *Tetrahedron Lett*. **1989**, *30*, 7057. (c) Yasuda, S.; Yamamoto, Y.; Yoshida, S.; Hanaoka, M. *Chem. Pharm. Bull*. **1988**, *36*, 4229. (d) Adesogan, E. K.; Alo, B. I. *J. Chem. Soc., Chem. Commun*. **1979**, 673. (e) Alo, B. I.; Adegoke, E. A.; Ligali-Ali, M.; Adesogan, E. K. *J. Chem. Soc., Perkin Trans. 1* **1986**, 805.
(25) Padwa, A. *Chem. Commun*. **1998**, 1417.
(26) Pearson, W. H.; Fang, W.-K. *J. Org. Chem*. **2000**, *65*, 7158.
(27) Grob, C. A. *Angew. Chem., Int. Ed. Engl*. **1969**, *8*, 535.
(28) McCann, S. F.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 6107.
(29) Bürgi, H. B.; Dunitz, J. D. *Acc. Chem. Res*. **1983**, *16*, 153.
(30) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun*. **1976**, 734. (b) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun*. **1976**, 736.
(31) Ben-Ishai, D. *J. Chem. Soc., Chem. Commun*. **1980**, 687.
(32) Lochead, A. W.; Proctor, G. R.; Caton, M. P. L. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2477.
(33) Hansen, K. B.; Finney, N. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 676.
(34) Rasmussen, K. G.; Jørgensen, K. A. *J. Chem. Soc., Chem. Commun*. **1995**, 1401.
(35) Ha, H.-J.; Kang, K.-H.; Suh, J.-M.; Ahn, Y.-G. *Tetrahedron Lett.* **1996**, *37*, 7069.
(36) Hanessian, S.; Buckle, R.; Bayrakdarian, M. *J. Org. Chem*. **2002**, *67*, 3387.
(37) (a) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem*. **1999**, 3223. (b) Arrieta, A.; Lecea, B.; Cossío, F. P. *J. Org. Chem*. **1998**, *63*, 5869.
(38) Bongini, A.; Panunzio, M.; Piersanti, G.; Bandini, E.; Martelli, G.; Spunta, G.; Venturini, A. *Eur. J. Org. Chem*. **2000**, 2379.
(39) (a) Delpiccolo, C. M. L.; Mata, E. G. *Tetrahedron: Asymmetry* **2002**, *13*, 905. (b) Alcaide, B.; Almendros, P.; Salgado, N. R. *Tetrahedron Lett*. **2001**, *42*, 1503. (c) Abbiati, G.; Rossi, E. *Tetrahedron* **2001**, *57*, 7205. (d) Arjona, O.; Csáky, A. G.; Murcia, M. C.; Plumet, J. *Tetrahedron Lett*. **2002**, *43*, 6405. (e) Lucatelli, C.; Viton, F.; Gimbert, Y.; Greene, A. E. *J. Org. Chem*. **2002**, *67*, 9468.
(40) (a) Evans, D. A.; Sjögren, E. B. *Tetrahedron Lett*. **1985**, *26*, 3783. (b) Evans, D. A.; Sjögren, E. B. *Tetrahedron Lett*. **1985**, *26*, 3787.
(41) Jayaraman, M.; Deshmukh, A. R.; Bhawal, B. M. *Tetrahedron* **1996**, *52*, 8989.
(42) (a) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831. (b) Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 1578.
(43) Mariano, P. S. *Acc. Chem. Res*. **1983**, *16*, 130.
(44) (a) Hiemstra, H.; Fortgens, H. P.; Stegenga, S.; Speckamp, W. N. *Tetrahedron Lett*. **1985**, *26*, 3151. (b) Hiemstra, H.; Fortgens, H. P.; Speckamp, W. N. *Tetrahedron Lett*. **1985**, *26*, 3155.
(45) Hiemstra, H.; Speckamp, W. N In *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 1047.
(46) Freund, R.; Mahboobi, S.; Noack, K.; Schönholzer, P.; Bernauer, K. *Helv. Chim. Acta* **1990**, *73*, 439.
(47) Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *Tetrahedron* **1963**, *19*, 247.
(48) Freund, R.; Allagiannis, C.; Schönholzer, P.; Bernauer, K. *Helv. Chim. Acta* **1994**, *77*, 615.
(49) Sakurai, O.; Horikawa, H. *Tetrahedron Lett*. **1996**, *37*, 7811.
(50) (a) Chamberlin, A. R.; Chung, J. Y. L. *J. Org. Chem*. **1985**, *50*, 4425. (b) Chamberlin, A. R.; Nguyen, H. D.; Chung, J. Y. L. *J. Org. Chem*. **1984**, *49*, 1682. (c) Chamberlin, A. R.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1983**, *105*, 3653.
(51) (a) Hiemstra, H.; Sno, M. H. A. M.; Vijn, R. J.; Speckamp, W. N. *J. Org. Chem*. **1985**, *50*, 4014. (b) Keck, G. E.; Cressman, E. N. K.; Enholm, E. J. *J. Org. Chem*. **1989**, *54*, 4345.
(52) (a) Karstens, W. F. J.; Moolenaar, M. J.; Rutjes, F. P. J. T.; Grabowska, U.; Speckamp, W. N.; Hiemstra, H. *Tetrahedron Lett*. **1999**, *40*, 8629. (b) Hernández, A.; Marcos, M.; Rapoport, H. *J. Org. Chem*. **1995**, *60*, 2683.
(53) Lin, H.; Danishefsky, S. J. *Angew. Chem., Int. Ed*. **2003**, *42*, 36.
(54) (a) Earley, W. G.; Jacobsen, E. J.; Meier, G. P.; Oh, T.; Overman, L. E. *Tetrahedron Lett*. **1988**, *29*, 3781. (b) Earley, W. G.; Oh, T.; Overman, L. E. *Tetrahedron Lett*. **1988**, *29*, 3785. (c) Sheikh, Z.; Steel, R. W.; Tasker, A. S.; Johnson, A. P. *J. Chem. Soc., Chem. Commun*. **1994**, 763. (d) Dutton, J. K.; Steel, R. W.; Tasker, A. S.; Popsavin, V.; Johnson, A. P. *J. Chem. Soc., Chem. Commun*. **1994**, 765.
(55) (a) Dijkink, J.; Cintrat, J.-C.; Speckamp, W. N.; Hiemstra, H. *Tetrahedron Lett*. **1999**, *40*, 5919. (b) Vijn, R. J.; Hiemstra, H.; Kok, J. J.; Knotter, M.; Speckamp, W. N. *Tetrahedron* **1987**, *43*, 5019.
(56) Clarke, C.; Fleming, I.; Fortunak, J. M. D.; Gallagher, P. T.; Honan, M. C.; Mann, A.; Nübling, C. O.; Raithby, P. R.; Wolff, J. J. *Tetrahedron* **1988**, *44*, 3931.
(57) Herbert, R. B. In *Indoles, The Monoterpenoid Indole Alkaloids*, Vol. 25, Part Four; Saxton, J. E., Vol. Ed.; *The Chemistry of Heterocyclic Compounds*; Weissberger, A., Taylor, E. C., Eds.; John Wiley: New York, 1983.
(58) Lévy, J.; Soufyane, M.; Mirand, C.; Döé de Maindreville, M.; Royer, D. *Tetrahedron: Asymmetry* **1997**, *8*, 4127.
(59) (a) Kuehne, M. E.; Xu, F. *J. Org. Chem*. **1998**, *63*, 9434. (b) Kuehne, M. E.; Xu, F. *J. Org. Chem*. **1997**, *62*, 7950. For a review on strychnine synthesis with several examples of transannular cyclizations, see: (c) Bonjoch, J.; Solé, D. *Chem. Rev*. **2000**, *100*, 3455.
(60) Sumi, S.; Matsumoto, K.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2003**, *5*, 1891.
(61) Node, M.; Nagasawa, H.; Fuji, K. *J. Org. Chem*. **1990**, *55*, 517.
(62) Sanchez, J. D.; Ramos, M. T.; Avendano, C. *Tetrahedron Lett*. **2000**, *41*, 2745.
(63) Lutz, R. P. *Chem. Rev*. **1984**, *84*, 205.
(64) (a) Hart, D. J.; Yang, T.-K. *J. Org. Chem*. **1985**, *50*, 235. (b) Hart, D. J.; Yang, T.-K. *J. Chem. Soc., Chem. Commun*. **1983**, 135.
(65) Ent, H.; de Koning, H.; Speckamp, W. N. *J. Org. Chem*. **1986**, *51*, 1687.
(66) (a) Doedens, R. J.; Meier, G. P.; Overman, L. E. *J. Org. Chem*. **1988**, *53*, 685. (b) Jacobsen, E. J.; Levin, J.; Overman, L. E. *J. Am. Chem. Soc*. **1988**, *110*, 4329.
(67) Deng, W.; Overman, L. E. *J. Am. Chem. Soc*. **1994**, *116*, 11241.
(68) (a) Overman, L. E.; Sworin, M.; Bass, L. S.; Clardy, J. *Tetrahedron* **1981**, 4041. (b) Overman, L. E.; Mendelson, L. T.; Flippin, L. A. *Tetrahedron Lett*. **1982**, *23*, 2733. (c) Overman, L. E.; Jacobsen, E. J. *Tetrahedron Lett*. **1982**, *23*, 2741.
(69) (a) Overman, L. E.; Robertson, G. M.; Robichaud, A. J. *J. Am. Chem. Soc.* **1991**, *113*, 2598. (b) Overman, L. E.; Sugai, S. *Helv. Chim. Acta* **1985**, *68*, 745. (c) Overman, L. E.; Shim, J. *J. Org. Chem*. **1991**, *56*, 5005. (d) Fukaya, C.; Overman, L. E. *J. Am. Chem. Soc.* **1980**, *102*, 1454. (e) Fevig, J. M.; Marquis, R. W., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5085. (f) Burk, R.; Overman, L. E.; Sworin, M. *J. Org. Chem*. **1983**, *48*, 2685.
(70) Sakurai, O.; Horikawa, H.; Iwasaki, T. *J. Chem. Soc., Chem. Commun*. **1995**, 2527.
(71) (a) Agami, C.; Couty, F.; Lin, J.; Mikaeloff, A.; Poursoulis, M. *Tetrahedron* **1993**, *49*, 7239. (b) Agami, C.; Cases, M.; Couty, F. *J. Org. Chem*. **1994**, *59*, 7937.
(72) Luker, T.; Koot, W.-J.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem*. **1998**, *63*, 220.
(73) Evans, D. A.; Thomas, E. W.; Cherpeck, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 3695.

(74) Chihab-Eddine, A.; Daïch, A.; Jilale, A.; Decroix, B. *Heterocycles* **2002**, *58*, 449.
(75) Planas, L.; Pérard-Viret, J.; Royer, J.; Selkti, M.; Thomas, A. *Synlett* **2002**, 1629.
(76) Koseki, Y.; Sato, H.; Watanabe, Y.; Nagasaka, T. *Org. Lett.* **2002**, *4*, 885.
(77) Moolenar, M. J.; Speckamp, W. N.; Hiemstra, H.; Poetsch, E.; Casutt, M.; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2391.
(78) (a) Yamauchi, T.; Takahashi, H.; Higashiyama, K. *Chem. Pharm. Bull.* **1998**, *46*, 384. (b) Billard, T.; Langlois, B. R. *J. Org. Chem.* **2002**, *67*, 997.
(79) Andrés, C.; Gonzales, A.; Pedrosa, R.; Pérez-Encabo, A.; Garcia-Granda, S.; Salvado, M. A.; Gomez-Beltran, F. *Tetrahedron Lett.* **1992**, *33*, 4743.
(80) (a) Neelakantan, L. *J. Org. Chem.* **1971**, *36*, 2256. (b) Neelakantan, L.; Molin-Case, J. A. *J. Org. Chem.* **1971**, *36*, 2261. (c) Higashiyama, K.; Kyo, H.; Takahashi, H. *Synlett* **1998**, 489. (d) Takahashi, H.; Suzuki, Y.; Kametani, T. *Heterocycles* **1983**, *20*, 607.
(81) Khruscheva, N. S.; Loim, N. M.; Sokolov, V. I.; Makhaev, V. D. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2425.
(82) Canle, M.; Lawley, A.; McManus, E. C.; More O'Ferrall, R. A. *Pure Appl. Chem.* **1996**, *68*, 813.
(83) Cruz, A.; Vásquez-Badillo, A.; Ramos-Garcìa, I.; Contreras, R. *Tetrahedron: Asymmetry* **2001**, *12*, 711.
(84) Just, G.; Potvin, P.; Uggowitzer, P. *J. Org. Chem.* **1983**, *48*, 2923.
(85) O'Brien, P.; Warren, S. *Tetrahedron: Asymmetry* **1996**, *7*, 3431.
(86) Agami, C.; Couty, F.; Lequesne, C. *Tetrahedron Lett.* **1994**, *35*, 3309.
(87) Santes, V.; Ortiz, A.; Gutiérrez, A.; Farfan, N. *Synth. Commun.* **1999**, *29*, 1277.
(88) Agami, C.; Rizk, T. *Tetrahedron* **1985**, *41*, 537.
(89) Létinois, S.; Dumur, J.-C.; Hénin, F.; Muzart, J. *Tetrahedron Lett.* **1998**, *39*, 2327.
(90) Kumar, G. B.; Patel, H. V.; Shah, A. C.; Trenkle, M.; Cardin, C. J. *Tetrahedron: Asymmetry* **1996**, *7*, 3391.
(91) (a) Didier, E.; Fouque, E.; Taillepied, I.; Commerçon, A. *Tetrahedron Lett.* **1994**, *35*, 2349. (b) Bedürftig, S.; Weigl, M.; Wünsch, B. *Tetrahedron: Asymmetry* **2001**, *12*, 1293. (c) Hoppe, I.; Hoppe, D.; Wolff, C.; Egert, E.; Herbst, R. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 67. (d) Garcia-Valverde, M.; Pedrosa, R.; Vicente, M.; Garcia-Granda, S.; Guttiériez-Rodriguez, A. *Tetrahedron* **1996**, *52*, 10761. (e) Shiina, I.; Saitoh, K.; Fréchard-Ortuno, I.; Mukaiyama, T. *Chem. Lett.* **1998**, 3. (f) Keller, M.; Lehmann, C.; Mutter, M. *Tetrahedron* **1999**, *55*, 413. (g) Denis, J.-N.; Fkyerat, A.; Gimbert, Y.; Coutterez, C.; Mantellier, P.; Jost, S.; Greene, A. E. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1811. (h) Isobe, M.; Hirose, Y.; Shimokawa, K.; Nishikawa, T.; Goto, T. *Tetrahedron Lett.* **1990**, *31*, 5499. (i) Belvisi, L.; Gennari, C.; Poli, G.; Scolastico, C.; Salom, B.; Vassallo, M. *Tetrahedron* **1992**, *48*, 3945.
(92) Bernardi, A.; Cardani, S.; Pilati, T.; Poli, G.; Scolastico, C.; Villa, R. *J. Org. Chem.* **1988**, *53*, 1600.
(93) Seebach, D.; Sommerfeld, T. L.; Jiang, Q.; Venanzi, L. M. *Helv. Chim. Acta* **1994**, *77*, 1313.
(94) Seebach, D.; Aebi, J. D. *Tetrahedron Lett.* **1984**, *25*, 2545.
(95) Guerrier, L.; Royer, J.; Grierson, D. S.; Husson, H.-P. *J. Am. Chem. Soc.* **1983**, *105*, 7754.
(96) Katritzky, A. R.; Qiu, G.; Yang, B.; Steel, P. J. *J. Org. Chem.* **1998**, *63*, 6699.
(97) (a) Poerwono, H.; Higashiyama, K.; Takahashi, H. *J. Org. Chem.* **1998**, *63*, 2711. (b) Poerwono, H.; Higashiyama, K.; Yamauchi, T.; Takahashi, H. *Heterocycles* **1997**, *46*, 385.
(98) (a) Mehmandoust, M.; Marazano, C.; Das, B. C. *J. Chem. Soc., Chem. Commun.* **1989**, 1185. (b) Wong, Y.-S.; Marazano, C.; Gnecco, D.; Génisson, Y.; Chiaroni, A.; Das, B. C. *J. Org. Chem.* **1997**, *62*, 729. (c) Génisson, Y.; Mehmandoust, M.; Marazano, C.; Das, B. C. *Heterocycles* **1994**, *39*, 811. (d) Diez, A.; Vilaseca, L.; Lopez, I. Rubiralta, M. Marazano, C.; Grierson, D. S.; Husson, H.-P. *Heterocycles* **1991**, *32*, 2139. (e) Barbier, D.; Marazano, C. Riche, C.; Das, B. C.; Potier, P. *J. Org. Chem.* **1998**, *63*, 1767.
(99) (a) Lavilla, R.; Coll, O.; Nicolàs, M.; Bosch, J. *Tetrahedron Lett.* **1998**, *39*, 5089. (b) Lavilla, R.; Coll, O.; Nicolàs, M.; Sufi, B. A.; Torrents, J.; Bosch, J. *Eur. J. Org. Chem.* **1999**, 2997.
(100) Roussi, G.; Zhang, J. *Tetrahedron Lett.* **1991**, *32*, 1443.
(101) (a) Meyers, A. I.; Lefker, B. A.; Wanner, K. T.; Aitken, R. A. *J. Org. Chem.* **1986**, *51*, 1936. (b) Micouin, L.; Diez, A.; Castells, J.; Lopez, D.; Rubiralta, M.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1995**, *36*, 1693.
(102) (a) Fréville, S.; Bonin, M.; Célérier, J.-P.; Husson, H.-P.; Lhommet, G.; Quirion, J.-C.; Thuy, V. M. *Tetrahedron* **1997**, *53*, 8447. (b) Micouin, L.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1996**, *37*, 849.
(103) Royer, J.; Husson, H.-P. *Tetrahedron Lett.* **1987**, *28*, 6175.
(104) Katritzky, A. R.; Cui, X.-L.; Yang, B.; Steel, P. J. *J. Org. Chem.* **1999**, *64*, 1979.
(105) Higashiyama, K.; Inoue, H.; Takahashi, H. *Tetrahedron* **1994**, *50*, 1083.
(106) (a) Tararov, V. I.; Kadyrov, R.; Riermeier, T. H.; Börner, A. *Synthesis* **2002**, 375. (b) Shibasaki, M.; Terashima, S.; Yamada, S. *Chem. Pharm. Bull.* **1976**, *24*, 315.
(107) (a) Gosmann, G.; Guillaume D.; Husson, H.-P. *Tetrahedron Lett.* **1996**, *37*, 4369. (b) Katoh, T.; Kirihara, M.; Yoshino, T.; Terashima, S. *Tetrahedron Lett.* **1993**, *34*, 5751.
(108) Carrillo, L.; Badia, D.; Dominguez, E.; Anakabe, E.; Osante, I.; Tellitu, I.; Vicario, J. L. *J. Org. Chem.* **1999**, *64*, 1115.
(109) Tanaka, K.; Katsumara, S. *J. Am. Chem. Soc.* **2002**, *124*, 9660.
(110) Katritzky, A. R.; Aslan, D. C.; Oniciu, D. C. *Tetrahedron: Asymmetry* **1998**, *9*, 2245.
(111) Gámez-Montaño, R.; Chávez, M. L.; Roussi, G.; Cruz-Almanza, R. *Tetrahedron Lett.* **2001**, *42*, 9.
(112) (a) Suzuki, H.; Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **2001**, *42*, 3013. (b) Yamazaki, N.; Suzuki, H.; Kibayashi, C. *J. Org. Chem.* **1997**, *62*, 8280.
(113) (a) Tschantz, M. A.; Burgess, L. E.; Meyers, A. I. *Org. Synth.* **1995**, *73*, 221. (b) For a review, see: Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843.
(114) (a) Meyers, A. I.; Andres, C. J.; Resek, J. E.; McLaughlin, M. A.; Woodall, C. C.; Lee, P. H. *J. Org. Chem.* **1996**, *61*, 2586. (b) Ennis, M. D.; Hoffman, R. L.; Ghazal, N. B.; Old, D. W.; Mooney, P. A. *J. Org. Chem.* **1996**, *61*, 5813. (c) Allin, S. M.; James, S. L.; Elsegood, M. R. J.; Martin, W. P. *J. Org. Chem.* **2002**, *67*, 9464. (d) Allin, S. M.; Northfield, C. J.; Page, M. I.; Slawin, A. M. Z. *Tetrahedron Lett.* **1999**, *40*, 143. (e) Meyers, A. I.; Berney, D. *Org. Synth.* **1990**, *69*, 55. (f) Amat, M.; Pshenichnyi, G.; Bosch, J.; Molins, E.; Miravitlles, C. *Tetrahedron: Asymmetry* **1996**, *7*, 3091. (g) Amat, M.; Cantó, M.; Llor, N.; Ponzo, V.; Pérez, M.; Bosch, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 335. (h) Amat, M.; Bosch, J.; Hidalgo, J.; Cantó, M.; Pérez, M.; Llor, N.; Molins, E.; Miravitlles, C.; Orozco, M.; Luque, J. *J. Org. Chem.* **2000**, *65*, 3074. (i) Ragan, J. A.; Claffey, M. C. *Heterocycles* **1995**, *41*, 57. (j) Amat, M.; Cantó, M.; Llor, N.; Escolano, C.; Molins, E.; Espinosa, E.; Bosch, J. *J. Org. Chem.* **2002**, *67*, 5343. (k) Roth, G. P.; Leonard, S. F.; Tong, L. *J. Org. Chem.* **1996**, *61*, 5710. (l) Amat, M.; Llor, N.; Bosch, J. *Tetrahedron Lett.* **1994**, *35*, 2223.
(115) (a) Royer, J.; Husson, H.-P. *Heterocycles* **1993**, *36*, 1493. (b) Micouin, L.; Quirion, J.-C.; Husson, H.-P. *Synth. Commun.* **1996**, *26*, 1605. (c) Amat, M.; Llor, N.; Escolano, C.; Huguet, M.; Pérez, M.; Molins, E.; Bosch, J. *Tetrahedron: Asymmetry* **2003**, *14*, 293.
(116) (a) Baussanne, I.; Chiaroni, A.; Husson, H.-P.; Riche, C.; Royer, J. *Tetrahedron Lett.* **1994**, *35*, 3931. (b) O'Brien, P.; Warren, S. *Tetrahedron: Asymmetry* **1996**, *7*, 3431.
(117) Cho, C. S.; Chu, D. Y.; Lee, D. Y.; Shim, S. C.; Kim, T. J.; Lim, W. T. Heo, N. H. *Synth. Commun.* **1997**, *27*, 4141.
(118) (a) Wanner, K. T.; Weber, U. *Synthesis* **1994**, 387. (b) Goodman, M.; Zhang, J.; Gantzel, P.; Benedetti, E. *Tetrahedron Lett.* **1998**, *39*, 9589.
(119) (a) Bailey, J. H.; Byfield, A. T. J.; Davis, P. J.; Foster, A. C.; Leech, M.; Moloney, M. G.; Müller, M.; Prout, C. K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1977. (b) Thottathil, J. K.; Moniot, J. L.; Mueller, R. H.; Wong, M. K. Y.; Kissick, T. P. *J. Org. Chem.* **1986**, *51*, 3140. (c) Thottathil, J. K.; Przybyla, C.; Malley, M.; Gougoutas, J. Z. *Tetrahedron Lett.* **1986**, *27*, 1533.
(120) Hermitage, S. A.; Moloney, M. G. *Tetrahedron: Asymmetry* **1994**, *5*, 1463.
(121) Qui, W.; Gu, X.; Soloshonok, V. A., Carducci, M. D.; Hruby, V. J. *Tetrahedron Lett.* **2001**, *42*, 145.
(122) (a) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Merino, P. *J. Chem. Soc., Chem. Commun.* **1990**, 854. (b) Hikage, N.; Furukawa, H.; Takao, K.-I.; Kobayashi, S. *Tetrahedron Lett.* **1998**, *39*, 6241. (c) Hikage, N.; Furukawa, H.; Takao, K.-I.; Kobayashi, S. *Chem. Pharm. Bull.* **2000**, *48*, 1370. (d) Stratmann, O.; Hoppe, D.; Fröhlich, R. *J. Prakt. Chem.* **2000**, *342*, 828.
(123) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708.
(124) (a) Seebach, D.; Fadel, A. *Helv. Chim. Acta* **1985**, *68*, 1243. (b) Walter, M. W.; Adlington, R. M.; Baldwin, J. E.; Schofield, C. J. *J. Org. Chem.* **1998**, *63*, 5179. (c) Duffy, K. J.; Ridgers, L. H.; DesJarlais, R. L.; Tomaszek, T. A.; Bossard, M. J.; Thompson, S. K.; Keenan, R. M.; Veber, D. F. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1907. (d) Smith, A. B., III; Benowitz, A. B.; Favor, D. A.; Sprengeler, P. A.; Hirshmann, R. *Tetrahedron Lett.* **1997**, *38*, 3809.
(125) (a) Hiskey, R. G.; Jung, J. M. *J. Am. Chem. Soc.* **1963**, *85*, 578. (b) Karady, S.; Amato, J. S.; Weinstock, L. M. *Tetrahedron Lett.* **1984**, *25*, 4337.
(126) Shrader, W. D.; Marlowe, C. K. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2207.
(127) Ma, D.; Zhu, W. *J. Org. Chem.* **2001**, *66*, 348.
(128) (a) Seebach, D.; Boes, M.; Naef, R. Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390. (b) Beck, A. K.; Blank, S.; Job, K.; Seebach, D.; Sommerfeld, T. *Org. Synth.* **1993**, *72*, 62. (c) Papillon, J. P. N.; Taylor, R. J. K. *Org. Lett.* **2000**, *2*, 1987. (d) Seebach, D.; Vettiger, T.; Müller, H.-M.; Plattner, D. A.; Petter, W. *Liebigs Ann. Chem.* **1990**, 687. (e) Weber, T.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 155. (f) Seebach, D.; Naef, R. *Helv. Chim. Acta* **1981**, *64*, 2704.

(129) Robl, J. A.; Cimarusti, M. P.; Simpkins, L. M.; Weller, H. N.; Pan, Y. Y.; Malley, M.; DiMarco, J. D. *J. Am. Chem. Soc.* **1994**, *116*, 2348.
(130) Szilágyi, L.; Györgydeák, Z. *J. Am. Chem. Soc.* **1979**, *101*, 427.
(131) (a) Somogyi, L. *Liebigs Ann. Chem.* **1985**, 657. (b) Jeanguenat, A.; Seebach, D. *J. Chem. Soc., Perkin Trans 1* **1991**, 2291. (c) Patek, M.; Drake, B.; Lebl, M. *Tetrahedron Lett.* **1995**, *36*, 2227. (d) Inaba, A.; Inami, K.; Kimoto, Y.; Yanada, R.; Miwa, Y.; Taga, T.; Bessho, K. *Chem. Pharm. Bull.* **1995**, *43*, 1601. (e) Mulqueen, G. C.; Pattenden, G.; Whiting, D. A. *Tetrahedron* **1993**, *49*, 5359. (f) Pattenden, G.; Thom, S. M.; Jones, M. *Tetrahedron* **1993**, *49*, 2131.
(132) Agami, C.; Couty, F.; Prince, B.; Venier, O. *Tetrahedron Lett.* **1993**, *34*, 7061.
(133) (a) Tamura, S. Y.; Goldman, E. A.; Brunck, T. K.; Ripka, W. C.; Semple, J. E. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 331. (b) Allin, S. M.; Vaidya, D. G.; Page, M. I.; Slawin, A. M. Z.; Smith, T. *Tetrahedron Lett* **2000**, *41*, 2219. (c) Bachand, B.; DiMaio, J.; Siddiqui, M. A. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 913. (d) Geyer, A.; Moser, F. *Eur. J. Org. Chem.* **2000**, 1113. (e) Baldwin, J. E.; Lee, V.; Schofield, C. J. *Heterocycles* **1992**, *34*, 903. (f) Baldwin, J. E.; Christie, M. A. *J. Am. Chem. Soc.* **1978**, *100*, 4597.
(134) (a) Kukolja, S. *J. Am. Chem. Soc.* **1971**, *93*, 6269. (b) Daniels, N.; Johnson, G.; Ross, B. C. *J. Chem. Soc., Chem. Commun.* **1983**, 1006. (c) Bachi, M. D.; Frydman, N.; Sasson, S.; Stern, C.; Vaya, J. *Tetrahedron Lett.* **1977**, 641.
(135) (a) Alexakis, A.; Tranchier, J.-P.; Lensen, N.; Mangeney, P. *J. Am. Chem. Soc.* **1995**, *117*, 10767. (b) Rezgui, F.; Mangeney, P.; Alexakis, A. *Tetrahedron Lett.* **1999**, *40*, 6241. (c) Gosmini, R.; Mangeney, P.; Alexakis, A.; Commerçon, M.; Normant, J.-F. *Synlett* **1991**, 111. (d) Alexakis, A.; Lensen, N.; Mangeney, P. *Tetrahedron Lett.* **1991**, *32*, 1171. (e) Alexakis, A.; Lensen, N.; Tranchier, J.-P.; Mangeney, P.; Feneau-Dupont, J.; Declercq, J. P. *Synthesis* **1995**, 1038. (f) Ferrand, A.; Bruno, M.; Tommasino, M. L.; Lemaire, M. *Tetrahedron: Asymmetry* **2002**, *13*, 1379. (g) Halland, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 8331. (h) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 661.
(136) Mukaiyama, T. *Tetrahedron* **1981**, *37*, 4111.
(137) Wasserman, H. H.; Henke, S. L.; Luce, P.; Nakanishi, E.; Schulte, G. *J. Org. Chem.* **1990**, *55*, 5821.
(138) (a) Yee, N. K. *Org. Lett.* **2000**, *2*, 2781. (b) Rinnová, M.; Nefzi, A.; Houghten, R. A. *Tetrahedron Lett.* **2002**, *43*, 2343. (c) Rinnová, M.; Vidal, A.; Nefzi, A. Houghten, R. A. *J. Comb. Chem.* **2002**, *4*, 209. (d) Rinnová, M.; Nefzi, A.; Houghten, R. A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3175. (e) Polt, R.; Seebach, D. *J. Am. Chem. Soc.* **1989**, *111*, 2622. (f) Ma, D.; Tian, H. *Tetrahedron: Asymmetry* **1996**, *7*, 1567. (g) Frutos, R. P.; Stehle, S.; Nummy, L.; Yee, N. *Tetrahedron: Asymmetry* **2001**, *12*, 101.
(139) Naef, R.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 135.
(140) (a) Juaristi, E.; Rizo, B.; Natal, V.; Escalante, J.; Regla, I. *Tetrahedron: Asymmetry* **1991**, *2*, 821. (b) Juaristi, E.; Anzorena, J. L.; Boog, A.; Madrigal, D.; Seebach, D.; Garcia-Baez, E. V.; Garcia-Barradas, O.; Gordillo, B. Kramer, A.; Steiner, I.; Zürcher, S. *J. Org. Chem.* **1995**, *60*, 6408.
(141) Zhu, J.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1989**, *30*, 5137.
(142) (a) Katritzky, A. R.; He, H.-Y.; Wang, J. *J. Org. Chem.* **2002**, *67*, 4951. (b) Katritzky, A. R.; Suzuki, K.; He, H.-Y. *J. Org. Chem.* **2002**, *67*, 8224.
(143) (a) Froelich, O.; Desos, P.; Bonin, M.; Quirion, J.-C.; Husson, H.-P.; Zhu, J. *J. Org. Chem.* **1996**, *61*, 6700. (b) Cutri, S.; Bonin, M.; Micouin, L.; Froelich, O.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **2000**, *41*, 1179. (c) Cutri, S.; Bonin, M.; Micouin, L.; Husson, H.-P. *J. Org. Chem.* **2003**, *68*, 2645.
(144) Kayakiri, H.; Kasahara, C.; Oku, T.; Hashimoto, M. *Tetrahedron Lett.* **1990**, *31*, 225.
(145) Schultz, A. G.; Pettus, L. *J. Org. Chem.* **1997**, *62*, 6855.
(146) Schultz, A. G.; Dai, M. *Tetrahedron Lett.* **1999**, *40*, 645.
(147) Hager, M. W.; Liotta, D. C. *J. Am. Chem. Soc.* **1991**, *113*, 5117.
(148) Martín-López, M. J.; Bermejo, F. *Tetrahedron* **1998**, *54*, 12379.
(149) (a) Lee, T. B. K.; Wong, G. S. K. *J. Org. Chem.* **1991**, *56*, 872. (b) Grieco, P. A.; Carroll, W. A. *Tetrahedron Lett.* **1992**, *33*, 4401. (c) Pallavicini, M.; Valoti, E.; Villa, L. Resta, I. *Tetrahedron: Asymmetry* **1994**, *5*, 363. (d) Node, M.; Hao, X.-J.; Nishide, K.; Fuji, K. *Chem. Pharm. Bull.* **1996**, *44*, 715. (e) Fuji, K.; Kawabata, T.; Ohmori, T.; Shang, M.; Node, M. *Heterocycles* **1998**, *47*, 951.
(150) Pei, X.-F.; Greig, N. H.; Flippen-Anderson, J. L.; Bi, S.; Brossi, A. *Helv. Chim. Acta* **1994**, *77*, 1412.
(151) Vojkovsky, T.; Weichsel, A.; Patek, M. *J. Org. Chem.* **1998**, *63*, 3162.
(152) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797.
(153) Kowalski, P.; Bojarski, A. J.; Mokrosz, J. L. *Tetrahedron* **1995**, *51*, 2737.
(154) (a) Bailey, P. D.; Hollinshead, S. P.; McLay, N. R.; Morgan, K.; Palmer, S. J.; Prince, S. N.; Reynolds, C. D.; Wood, S. D. *J. Chem. Soc., Perkin Trans. 1* **1993**, 431. (b) Bailey, P. D. *Tetrahedron Lett.* **1987**, *28*, 5181.
(155) Cox, E. D.; Hamaker, L. K.; Li, J.; Yu, P.; Czerwinski, K. M.; Deng, L.; Bennett, D. W.; Cook, J. M.; Watson, W. H.; Krawiec, M. *J. Org. Chem.* **1997**, *62*, 44.
(156) For other recent examples of tryptophane-based Pictet−Spengler cyclizations, see: (a) Madrigal, A.; Grande, M.; Avendaño, C. *Tetrahedron: Asymmetry* **2000**, *11*, 3515. (b) Yu, S.; Berner, O. M.; Cook, J. M. *J. Am. Chem. Soc.* **2000**, *122*, 7827. (c) Li, J.; Wang, T.; Yu, P.; Peterson, A.; Weber, R.; Soerens, D.; Grubisha, D.; Bennett, D.; Cook, J. M. *J. Am. Chem. Soc.* **1999**, *121*, 6998. (d) Magnus, P.; Mugrage, B.; DeLuca, M.; Cain, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 786. (e) Magnus, P.; Mugrage, B.; DeLuca, M.; Cain, G. A. *J. Am. Chem. Soc.* **1990**, *112*, 5220. (f) O'Malley, G. J.; Cava, M. P. *Tetrahedron Lett.* **1987**, *28*, 1131. (g) Yu, J.; Wearing, X. Z.; Cook, J. M. *Tetrahedron Lett.* **2003**, *44*, 543.
(157) Jiang, W.; Sui, Z.; Chen, X. *Tetrahedron Lett.* **2002**, *43*, 8941.
(158) Miyazawa, N.; Ogasawara, K. *Tetrahedron Lett.* **2002**, *43*, 4773.
(159) Dai, W.-M.; Zhu, H. J.; Hao, X.-J. *Tetrahedron Lett.* **1996**, *37*, 5971.
(160) Grigg, R.; MacLachlan, W. S.; MacPherson, D. T.; Sridharan, V.; Suganthan, S.; Thornton-Pett M.; Zhang, J. *Tetrahedron* **2000**, *56*, 6585.
(161) Bringmann, G.; Weirich, R.; Reuscher H.; Jansen, J. R.; Kinzinger, L.; Orthmann, T. *Liebigs Ann. Chem.* **1993**, 877.
(162) Spengle, J.; Schedel, H.; Sieler, J.; Quaedflieg, P. J. L. M.; Broxterman, Q.; Duchateau, A. L. L.; Burger, K. *Synthesis* **2001**, 1513.
(163) (a) Tomioka, K.; Kubota, Y.; Koga, K. *Tetrahedron* **1993**, *49*, 1891. (b) Tepe, J. J.; Madalengoitia, J. S.; Slunt, K. M.; Werbovetz, K. W.; Spoors, P. G.; Macdonald, T. L. *J. Med. Chem.* **1996**, *39*, 2188.
(164) (a) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895. (b) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407.
(165) (a) Soe, T.; Kawate, T.; Fukui, N.; Hino, T.; Nakagawa, M. *Heterocycles* **1996**, *42*, 347. (b) Soe, T.; Kawate, T.; Fukui, N.; Hino, T.; Nakagawa, M. *Tetrahedron Lett.* **1995**, *36*, 1857. (c) Kawate, T.; Yamanaka, M.; Nakagawa, M. *Heterocycles* **1999**, *50*, 1033.
(166) (a) Waldmann, H.; Schmidt, G.; Jansen, M.; Geb, J. *Tetrahedron* **1994**, *50*, 11865. (b) Waldmann, H.; Schmidt, G.; Jansen, M.; Geb, J. *Tetrahedron Lett.* **1993**, *34*, 5867.
(167) (a) Schmidt, G.; Waldmann, H.; Henke, H.; Burkard, M. *Chem.—Eur. J.* **1996**, *2*, 1566. (b) Waldmann, H.; Schmidt, G.; Henke, H.; Burkard, M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2402.
(168) (a) Comins, D. L.; Thakker, P. M.; Baevsky, M. F.; Badawi, M. M. *Tetrahedron* **1997**, *53*, 16327. (b) Comins, D. L.; Badawi, M. M. *Tetrahedron Lett.* **1991**, *32*, 2995.
(169) (a) Gremmen, C.; Willemse, B.; Wanner, M. J.; Koomen, G.-J. *Org. Lett.* **2000**, *2*, 1955. (b) Gremmen, C.; Wanner, M. J.; Koomen, G.-J. *Tetrahedron Lett.* **2001**, *42*, 8885.
(170) Khuong-Huu, Q.; Nemlin, J.; Kervagoret, J.; Pancrazi, A. *Tetrahedron* **1992**, *48*, 6689.
(171) For the use of chiral nonracemic aldehydes with *N*-protected tryptophan methyl ester, see: (a) De la Figuera, N.; Alkorta, I.; Garcia-Lopez, T.; Herranz, R.; Gonzalez-Muniz, R. *Tetrahedron* **1995**, *51*, 7841. With amino acid derived acyliminiums and chiral aldehydes: (b) Zhang, X.; Jiang, W.; Sui, Z. *J. Org. Chem.* **2003**, *68*, 4523. With *N*-protected tryptophan methyl ester and amino acid derived acyliminiums on a solid phase: (c) Wang, H.; Ganesan, A. *Org. Lett.* **1999**, *1*, 1647. In the liquid phase: (d) Wang, H.; Ganesan, A. *Tetrahedron Lett.* ***1997***, *38*, 4327.
(172) (a) Singh, K.; Deb, P. K. *Tetrahedron Lett.* **2000**, *41*, 4977. (b) Singh, K.; Deb, P. K. *Heterocycles* **1999**, *51*, 1509.
(173) Katritzky, A. R.; Cobo-Domingo, J.; Yang, B.; Steel, P. J. *Tetrahedron: Asymmetry* **1999**, *10*, 255.
(174) Tomioka, K.; Kubota, Y.; Koga, K. *Tetrahedron Lett.* **1989**, *30*, 2953.
(175) Annunziata, R.; Ferrari, M.; Papeo, G.; Resmini, M.; Sisti, M. *Synth. Commun.* **1997**, *27*, 23.
(176) (a) Allin, S. M.; James, S. L.; Elsegood, M. R. J.; Martin, W. P. *J. Org. Chem.* **2002**, *67*, 9464. (b) Allin, S. M.; Northfield, C. J.; Page, M. I.; Slawin, A. M. Z. *Tetrahedron Lett.* **1998**, *39*, 4905. (c) Allin, S. M.; James, S. L.; Martin, W. P.; Smith, T. A. D. *Tetrahedron Lett.* **2001**, *42*, 3943. (d) Allin, S. M.; James, S. L.; Martin, W. P.; Smith, T. A. D.; Elsegood, M. R. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3029.
(177) (a) Pedrosa, R.; Andrés, C.; Iglesias, J. M. *J. Org. Chem.* **2001**, *66*, 243. (b) Liénard, P.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron* **1993**, *49*, 3995.
(178) Mangeney, P.; Gosmini, R.; Raussou, S.; Commerçon, M.; Alexakis, A. *J. Org. Chem.* **1994**, *59*, 1877.
(179) Lee, J. Y.; Lee, Y. S.; Chung, B. Y.; Park, H. *Tetrahedron* **1997**, *53*, 2449.
(180) (a) Vercauteren, J.; Lavaud, C.; Lévy, J.; Massiot, G. *J. Org. Chem.* **1984**, *49*, 2278. (b) Bailey, P. D.; Hollinshead, S. P. *J. Chem. Soc., Perkin Trans. 1* **1988**, 739.
(181) Ohba, M.; Kubo, H.; Fujii, T.; Ishibashi, H.; Sargent, M. V.; Arbain, D. *Tetrahedron Lett.* **1997**, *38*, 6697.
(182) Huizenga, R. H.; Pandit, U. K. *Tetrahedron* **1992**, *48*, 6521.

(183) Oppolzer, W.; Bienaymé, H.; Genevois-Borella A. *J Am. Chem. Soc.* **1991**, *113*, 9660.
(184) Fontaine, H.; Baussanne, I.; Royer, J. *Synth. Commun.* **1997**, *27*, 2817.
(185) Katritzky, A. R.; Metha, S.; He, H.-Y. *J. Org. Chem.* **2001**, *66*, 148.
(186) García, E.; Arrasate, S.; Ardeo, A.; Lete, E.; Sotomayor, N. *Tetrahedron Lett.* **2001**, *42*, 1511.
(187) Grigg, R.; Thornton-Pett, M.; Yoganathan, G. *Tetrahedron* **1999**, *55*, 8129.
(188) (a) Zawadzka, A.; Leniewski, A.; Maurin, J. K.; Wojtasiewicz, K.; Czarnocki, Z. *Org. Lett.* **2001**, *3*, 997. (b) Zawadzka, A.; Leniewski, A.; Maurin, J. K.; Wojtasiewicz, K.; Siwicka, A.; Blachut, D.; Czarnocki, Z. *Eur. J. Org. Chem.* **2003**, 2443.
(189) Corey, E. J.; Gin, D. Y. *Tetrahedron Lett.* **1996**, *37*, 7163.
(190) (a) Brown, R. T.; Dauda, B. E. N.; Jameson, S. B.; Santos, C. A. M. *Tetrahedron Lett.* **2000**, *41*, 8861.
(191) (a) Danieli, B.; Lesma, G.; Mauro, M.; Palmisano, G.; Passarella, D. *Tetrahedron* **1994**, *50*, 8837. (b) Ihara, M.; Taniguchi, N.; Fukumoto, K. *J. Chem. Soc., Perkin. Trans. 1* **1997**, 365. (c) Kametani, T.; Suzuki, T.; Sato, E.; Nishimura, M.; Unno, K. *J. Chem. Soc., Chem. Commun.* **1982**, 1201.
(192) Lee, Y. S.; Cho, D. J.; Kim, S. N.; Choi, J. H.; Park, H. *J. Org. Chem.* **1999**, *64*, 9727.
(193) Ducrot, P.; Thal, C. *Tetrahedron Lett.* **1999**, *40*, 9037.
(194) Wee, A. G.; Yu, Q. *Tetrahedron Lett.* **2000**, *41*, 587.
(195) Wee, A. G.; Yu, Q. *J. Org. Chem.* **2001**, *66*, 8935.
(196) Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 9202.
(197) (a) Ripoche, I.; Gelas, J.; Grée, D.; Grée, R.; Troin, Y. *Tetrahedron Lett.* **1995**, *36*, 6675. (b) Ripoche, I.; Bennis, K.; Canet, J.-L.; Gelas, J.; Troin, Y. *Tetrahedron Lett.* **1996**, *37*, 3991. (c) Ripoche, I.; Canet, J.-L.; Gelas, J.; Troin, Y. *Eur. J. Org. Chem.* **1999**, 1517. (d) Ciblat, S.; Besse, P.; Canet, J.-L.; Troin, Y.; Veschambre, H.; Gelas, J. *Tetrahedron: Asymmetry* **1999**, *10*, 2225. (e) Ciblat, S.; Besse, P.; Papastergiou, V.; Veschambre, H.; Canet, J.-L.; Troin, Y. *Tetrahedron: Asymmetry* **2000**, *11*, 2221. (f) Ciblat, S.; Canet, J.-L.; Troin, Y. *Tetrahedron Lett.* **2001**, *42*, 4815. (g) Carbonnel, S.; Fayet, C.; Gelas, J.; Troin, Y. *Tetrahedron Lett.* **2000**, *41*, 8293. (h) Rougnon Glasson, S.; Canet, J.-L.; Troin, Y. *Tetrahedron Lett.* **2000**, *41*, 9797. (i) Carbonnel, S.; Troin, Y. *Heterocycles* **2002**, *57*, 1807.
(198) (a) Yang, T.-K.; Teng, T.-F.; Lin, J.-H.; Lay, Y.-Y. *Tetrahedron Lett.* **1994**, *35*, 3581. (b) Castro, P.; Overman, L. E.; Zhang, X.; Mariano, P. S. *Tetrahedron Lett.* **1993**, *34*, 5243.
(199) Rutjes, F. P. J. T.; Veerman, J. J. N.; Meester, W. J. N.; Hiemstra, H.; Schoemaker, H. F. *Eur. J. Org. Chem.* **1999**, 1127.
(200) Veenstra, S. J.; Hauser, K.; Schilling, W.; Betschart, C.; Ofner, S. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 3029.
(201) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352.
(202) (a) Khim, S. K.; Wu, X.; Mariano, P. S. *Tetrahedron Lett.* **1996**, *37*, 571. (b) Wu, X.-D.; Khim, S.-K.; Zhang, X.; Cederstrom, E. M.; Mariano, P. S. *J. Org. Chem.* **1998**, *63*, 841.
(203) Miguel, D.; Diez, A.; Blache, Y.; Luque, J.; Orozco, M.; Remuson, R.; Gelas-Mialhe, Y.; Rubiralta, M. *Tetrahedron* **1995**, *51*, 7527.
(204) Cellier, M.; Gelas-Mialhe, Y.; Husson, H.-P.; Perrin, B.; Remuson, R. *Tetrahedron: Asymmetry* **2000**, *11*, 3913.
(205) (a) Skiles, J. W.; Giannousis, P. P.; Fales, K. R. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 963. (b) Gillard, J.; Abraham, A.; Anderson, P. C.; Beaulieu, P. L.; Bogri, T.; Bousquet, Y.; Grenier, L.; Guse, I.; Lavallée, P. *J. Org. Chem.* **1996**, *61*, 2226.
(206) Meyers, A. I.; Miller, D. B.; White, F. H. *J. Am. Chem. Soc.* **1988**, *110*, 4778.
(207) (a) Heathcock, C. H.; Davidsen, S. K.; Mills, S.; Sanner, M. A. *J. Am. Chem. Soc.* **1986**, *108*, 5650. (b) Heathcock, C. H.; Davidsen, S. K.; Mills, S.; Sanner, M. A. *J. Org. Chem.* **1992**, *57*, 2531.
(208) (a) Agami, C.; Comesse, S.; Kadouri-Puchot, C. *J. Org. Chem.* **2002**, *67*, 2424. (b) Agami, C.; Bihan, D.; Hamon, L.; Puchot-Kadouri, C. *Tetrahedron* **1998**, *54*, 10309. (c) Agami, C.; Comesse, S.; Kadouri-Puchot, C. *J. Org. Chem.* **2000**, *65*, 4435.
(209) Chalard, P.; Remuson, R.; Gelas-Mialhe, Y.; Gramain, J.-C.; Canet, I. *Tetrahedron Lett.* **1999**, *40*, 1661.
(210) Chalard, P.; Remuson, R.; Gelas-Mialhe, Y.; Gramain, J.-C. *Tetrahedron: Asymmetry* **1998**, *9*, 4361.
(211) Gardette, D.; Gelas-Mialhe, Y.; Gramain, J.-C.; Perrin, B.; Remuson, R. *Tetrahedron: Asymmetry* **1998**, *9*, 1823.
(212) (a) Overman, L. E.; Bell, K. L.; Ito, F. *J. Am. Chem. Soc.* **1984**, *106*, 4192. (b) Overman, L. E.; Lin, N.-H. *J. Org. Chem.* **1985**, *50*, 3669. (c) Lett, R. M.; Overman, L. E.; Zablocki, J. *Tetrahedron Lett.* **1988**, *29*, 6541. (d) Tietze, L. F.; Wünsch, J. R.; Noltemeyer, M. *Tetrahedron* **1992**, *48*, 2081.
(213) Caderas, C.; Lett, R.; Overman, L. E.; Rabinowitz, M. H.; Robinson, L. A.; Sharp, M. J.; Zablocki, J. *J. Am. Chem. Soc.* **1996**, *118*, 9073.
(214) Endoma, M. A.; Butora, G.; Claeboe, C. D.; Hudlicky, T.; Abboud, K. A. *Tetrahedron Lett.* **1997**, *38*, 8833.
(215) Hong, C. Y.; Kado, N.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 11028.
(216) Kamatani, A.; Overman, L. E. *Org. Lett.* **2001**, *3*, 1229.
(217) Consonni, A.; Danieli, B.; Lesma, G.; Passarella, D.; Piacenti, P.; Silvani, A. *Eur. J. Org. Chem.* **2001**, 1377.
(218) (a) Ayer, W. A.; Dawe, R.; Eisner, R. A.; Furuichi, K. *Can. J. Chem.* **1976**, *54*, 473. (b) Yue, C.; Nicolay, J.-F.; Royer, J.; Husson, H.-P. *Tetrahedron* **1994**, *50*, 3139.
(219) Vidal, L.; Royer, J.; Husson, H.-P. *Tetrahedron Lett.* **1995**, *36*, 2991.
(220) Hernández, A. S.; Thaler, A.; Castells, J.; Rapoport, H. *J. Org. Chem.* **1996**, *61*, 314.
(221) Gauthier, I.; Royer, J.; Husson, H.-P. *J. Org. Chem.* **1997**, *62*, 6704.
(222) (a) Klaver, W. J.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1987**, *28*, 1581. (b) Klaver, W. J.; Hiemstra, H.; Speckamp, W. N. *J. Am. Chem. Soc.* **1989**, *111*, 2588. (c) Beddoes, R. L.; Davies, M. P. H.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1992**, 538.
(223) Mechelke, M. F.; Meyers, A. I. *Tetrahedron Lett.* **2000**, *41*, 4339.
(224) Yue, C.; Royer, J.; Husson, H.-P. *J. Org. Chem.* **1992**, *57*, 4211.
(225) Harrison, J. R.; O'Brien, P.; Porter, D. W.; Smith, N. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3623.
(226) (a) Kuehne, M. E.; Xu, F.; Brook, C. S. *J. Org. Chem.* **1994**, *59*, 7803. (b) Deiters, A.; Chen, K.; Eary, C. T.; Martin, S. F. *J. Am. Chem. Soc.* **2003**, *125*, 4541.
(227) Pedrosa, R.; Andrés, C.; Iglesias, J. M.; Pérez-Encabo, A. *J. Am. Chem. Soc.* **2001**, *123*, 1817.
(228) Schneider, C.; Reese O. *Angew. Chem., Int. Ed.* **2000**, *39*, 2948.
(229) Sun, P.; Sun, C.; Weinreb, S. M. *J. Org. Chem.* **2002**, *67*, 4337.
(230) Abe, H.; Aoyagi, S.; Kibayashi, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3017.
(231) Inouye, Y.; Tazawa, N.; Watanabe, A.; Aoki, Y.; Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2866.
(232) Downham, R.; Ng, F. W.; Overman, L. E. *J. Org. Chem.* **1998**, *63*, 8096.
(233) Mecozzi, T.; Petrini, M.; Profeta, R. *Tetrahedron: Asymmetry* **2003**, *14*, 1171.
(234) Chihab-Eddine, A.; Daïch, A.; Jilale, A.; Decroix, B. *Tetrahedron Lett.* **2001**, *42*, 573.
(235) Dinsmore, C. J.; Zartman, C. B.; Baginsky, W. F.; O'Neill, T. J.; Koblan, K. S.; Chen, I.-W.; McLoughlin, D. A.; Olah, T. V.; Huff, J. R. *Org. Lett.* **2000**, *2*, 3473.
(236) (a) Micouin, L.; Diez, A.; Castells, J.; Lopez, D.; Rubiralta, M.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1995**, *36*, 1693. (b) Saito, M.; Kawamura, M.; Hiroya, K.; Ogasawara, K. *Chem. Commun.* **1997**, 765.
(237) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, 1986.
(238) Ayer, W. A.; Dawe, R.; Eisner, R. A.; Furuichi, K. *Can. J. Chem.* **1976**, *54*, 473.
(239) (a) Overman, L. E.; Robinson, L. A.; Zablocki, J. *J. Am. Chem. Soc.* **1992**, *114*, 368. (b) Lett, R. M.; Overman, L. E.; Zablocki, J. *Tetrahedron Lett.* **1988**, *29*, 6541. (c) Caderas, C.; Lett, R.; Overman, L. E.; Rabinowitz, M. H.; Robinson, L. A.; Sharp, M. J.; Zablocki, J. *J. Am. Chem. Soc.* **1996**, *118*, 9073.
(240) Clauss, R.; Hunter, R. *J. Chem. Soc., Perkin Trans. 1* **1997**, 71.
(241) (a) Yoshioka, M.; Tsuji, T.; Uyeo, S.; Yamamoto, S.; Aoki, T.; Nishitani, Y.; Mori, S.; Satoh, H.; Hamada, Y.; Ishitobi, H.; Nagata, W. *Tetrahedron Lett.* **1980**, *21*, 351. (b) Schmincke, H.; Hoppe, D. *Tetrahedron* **1989**, *45*, 701.
(242) (a) Kałuza, Z. *Tetrahedron Lett.* **1998**, 39, 8349. (b) Kałuza, Z.; Łysek, R. *Tetrahedron: Asymmetry* **1997**, *8*, 2553. (c) Furman, B.; Thürmer, R.; Ka-łuza, Z.; Łysek, R.; Voelter, W.; Chmielewski, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1121.
(243) (a) Sato, M.; Hisamishi, H.; Kitazawa, N.; Kaneko, C.; Furuya, T.; Suzaki, N.; Inukai, N. *Tetrahedron Lett.* **1990**, *31*, 3605. (b) Sato, M.; Kitazawa, N.; Nagashima, S.; Kaneko, C. Inoue, N.; Furuya, T. *Tetrahedron* **1991**, *47*, 7271.
(244) (a) Pedrosa, R.; Andres, C.; Iglesias, J. M. *J. Org. Chem.* **2001**, *66*, 243. (b) Mino, T.; Hata, S.; Ohtaka, K.; Sakamoto, M.; Fujita, T. *Tetrahedron Lett.* **2001**, *42*, 4837.
(245) (a) Noé, E.; Séraphin, D.; Zhang, Q.; Djaté, F.; Hénin, J.; Laronze, J.-Y.; Lévy, J. *Tetrahedron Lett.* **1996**, *37*, 5701. (b) Baldwin, J. E.; Melman, A.; Lee, V.; Firkin, C. R.; Whitehead, R. C. *J. Am. Chem. Soc.* **1998**, *120*, 8559. (c) Bentley, N.; Singh, G. Howarth, O. W. *Tetrahedron* **1993**, *49*, 4315. (d) Sun, H.; Moeller, K. D. *Org. Lett.* **2002**, *4*, 1547.
(246) (a) Stragies, R.; Blechert, S. *J. Am. Chem. Soc.* **2000**, *122*, 9584. (b) Mizutani, N.; Chiou, W.-H.; Ojima, I. *Org. Lett.* **2002**, *4*, 4575. (c) Kohn, W. D.; Zhang, L. *Tetrahedron Lett.* **2001**, *42*, 4453.
(247) Khalil, E. M.; Ojala, W. H.; Pradhan, A.; Nair, V. D.; Gleason, W. B.; Mishra, R. K.; Johnson, R. L. *J. Med. Chem.* **1999**, *42*, 628.
(248) Holmes, C. P.; Chinn, J. P.; Look, G. C.; Gordon, E. M.; Gallop, M. A. *J. Org. Chem.* **1995**, *60*, 7328.
(249) Kalyanam, N.; Manjunatha, S. G. *Heterocycles* **1991**, *32*, 1131.
(250) Fülöp, F.; Tari, J.; Bernáth, G.; Sohár, P.; Dancsó, A.; Argay, G.; Kálmán, A. *Liebigs Ann./Recl.* **1997**, 1165.
(251) Murer, P.; Rheiner, B.; Juaristi, E.; Seebach, D. *Heterocycles* **1994**, *39*, 319.

(252) Merlin, P.; Braekman, J.-C.; Daloze, D. *Tetrahedron* **1991**, *47*, 3805.
(253) (a) Yue, C.; Royer, J.; Husson, H.-P. *J. Org. Chem*. **1990**, *55*, 1140. (b) Yue, C.; Gauthier, I.; Royer, J.; Husson, H.-P. *J. Org. Chem*. **1996**, *61*, 4949.
(254) Pandey, G.; Das, P.; Reddy, P. Y. *Eur. J. Org. Chem*. **2000**, 657.
(255) Sugiura, M.; Hagio, H.; Hirabayashi, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 12510.
(256) Aubele, D. L.; Floreancig, P. E. *Org. Lett*. **2002**, *4*, 3443.
(257) Forns, P.; Diez, A.; Rubiralta, M. *J. Org. Chem*. **1996**, *61*, 7882.
(258) (a) Forns, P.; Diez, A.; Rubiralta, M.; Solans, X.; Font-Bardia, M. *Tetrahedron* **1996**, *52*, 3563. (b) Rubiralta, M.; Torrens, A.; Reig, I. Grierson, D. S.; Husson, H.-P. *Heterocycles* **1989**, *29*, 2121. (c) Yamada, S.; Hino, T.; Ogawa, K. *Chem. Pharm. Bull*. **1963**, *11*, 674.
(259) (a) Robl, J. A. *Tetrahedron Lett*. **1994**, *35*, 393. (b) Moeller, K. D.; Rothfus, S. L.; Wong, P. L. *Tetrahedron* **1991**, *47*, 583.
(260) (a) Metais, E.; Overman, L. E.; Rodriguez, M. I.; Stearns, B. A. *J. Org. Chem*. **1997**, *62*, 9210. (b) Overman, L. E.; Rodriguez-Campo, I. M. *Synlett* **1992**, 995.
(261) Tietze, L. F.; Wuensch, J. R.; Noltemeyer, M. *Tetrahedron* **1992**, *48*, 2081.
(262) Marson, C. M.; Pink, J. H.; Smith, C. *Tetrahedron Lett*. **1995**, *36*, 8107.
(263) (a) Lee, Y. S.; Min, B. J.; Park, Y. K.; Lee, J. Y.; Lee, S. J.; Park, H. *Tetrahedron Lett*. **1999**, *40*, 5569. (b) Lee, Y. S.; Min, B. J.; Park, Y. K.; Lee, J. Y.; Lee, S. J.; Park, H. *Tetrahedron* **1999**, *55*, 12991.
(264) (a) Flynn, G. A.; Giroux, E. L.; Dage, R. C. *J. Am. Chem. Soc.* **1987**, *109*, 7914. (b) Flynn, G. A.; Burkholder, T. P.; Huber, E. W.; Bey, P. *Biorg. Med. Chem. Lett.* **1991**, *1*, 309. (c) Rabi-Barakey, A.; Ben-Ishai, D. *Tetrahedron* **1994**, *50*, 10771.
(265) Sánchez, J. D.; Ramos, M. T.; Avendaño, C. *J. Org. Chem*. **2001**, *66*, 5731.
(266) Heredia, M. L.; de la Cuesta, E.; Avendaño, C. *Tetrahedron* **2002**, *58*, 6163.
(267) (a) Gillaizeau-Gauthier, I.; Royer, J.; Husson, H.-P. *Eur. J. Org. Chem*. **2002**, 1484. (b) Somfai, P.; Ahman, J. *Tetrahedron Lett*. **1992**, *33*, 3791. (c) Skrinjar, M.; Nilsson, C.; Winstrand, L.-G. *Tetrahedron: Asymmetry* **1992**, *3*, 1263. (d) Sardina, F. J.; Howard, M. H.; Koskinen, A. M. P.; Rapoport, H. *J. Org. Chem*. **1989**, *54*, 4654. (e) Hernandez, A.; Rapoport, H. *J. Org. Chem*. **1994**, *59*, 1058. (f) Shono, T.; Matsumura, Y.; Uchida, K.; Tagami, K. *Chem. Lett*. **1987**, 919.
(268) Kigoshi, H.; Hayashi, N.; Uemura, D. *Tetrahedron Lett*. **2001**, *42*, 7469.
(269) (a) Klaver, W. J.; Moolenaar, M. J.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1988**, *44*, 3805. (b) Klaver, W. J.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1988**, *44*, 6729.
(270) (a) Beyersbergen van Henegouwen, W. G.; Fieseler, R. M.; Rutjes, F. P. J. T.; Hiemstra, H. *J. Org. Chem*. **2000**, *65*, 8317. (b) Beyersbergen van Henegouwen, W. G.; Hiemstra, H. *J. Org. Chem*. **1997**, *62*, 8862.
(271) Beyersbergen van Henegouwen, W. G.; Fieseler, R. M.; Rutjes, F. P. J. T.; Hiemstra, H. *Angew. Chem., Int. Ed*. **1999**, *38*, 2214.
(272) Cornille, F.; Fobian, Y. M.; Slomczynska, U.; Beusen, D. D.; Marshall, G. R.; Moeller, K. D. *Tetrahedron Lett*. **1994**, *35*, 6989.
(273) Ge, P.; Kalman, T. I. *Bioorg. Med. Chem. Lett*. **1997**, *7*, 3023.
(274) Robl, J. A.; Sun, C.-Q.; Stevenson, J.; Ryono, D. E.; Simpkins, L. M.; Cimarusti, M. P.; Dejneka, T.; Slusarchyk, W. A.; Chao, S.; Stratton, L.; Misra, R. N.; Bednarz, M. S.; Asaad, M. M.; Cheung, H. S.; Abboa-Offei, B. E.; Smith, P. L.; Mathers, P. D.; Fox, M.; Schaeffer, T. R.; Seymour, A. A.; Trippodo, N. C. *J. Med. Chem*. **1997**, *40*, 1570.
(275) Wasserman, H. H.; Henke, S. L.; Nakanishi, E.; Schulte, G. *J. Org. Chem*. **1992**, *57*, 2641.
(276) Avery, M. A.; Bonk, J. D.; Chong, W. K. M.; Mehrotra, S.; Miller, R.; Milhous, W.; Goins, D. K.; Venkatesan, S.; Wyandt, C.; Khan, I.; Avery, B. A. *J. Med. Chem*. **1995**, *38*, 5038.
(277) Peyrane, F.; Fourrey, J.-L.; Clivio, P. *Chem. Commun*. **2003**, 736.
(278) Wijnberg, B. P.; Speckamp, W. N. *Tetrahedron Lett.* **1980**, *21*, 1987.
(279) (a) Kumar, G. Biju; Shah, A. C.; Pitali, T. *Tetrahedron Lett.* **1997**, *38*, 3297. (b) Thottathil, J. K.; Przybyla, C.; Malley, M.; Gougoutas, J. Z. *Tetrahedron Lett.* **1986**, *27*, 1533.

CR020083X