1-Azaallylic Anions in Heterocyclic Chemistry

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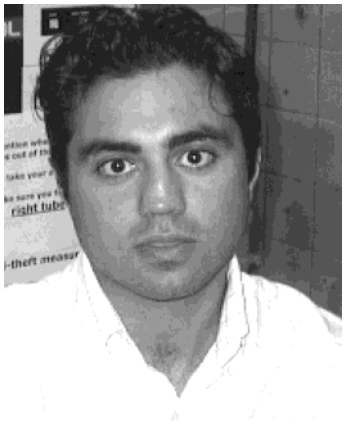


Nicola Giubellina was born in 1974 in Vercelli, Italy. He studied at the University of Piemonte Orientale in Novara, Italy, where he received his diploma in pharmaceutical chemistry in 1999. During the same year he spent a few months at the University of Turin, under the guidance of Professor Giovanni Appendino, continuing the development of new biologically active phorboid derivatives started during his thesis. In 2000 he moved to Ghent University, Ghent, Belgium, where he enrolled in the study of antileishmaniae saponins. He is currently active in the fourth year of a Ph.D. program under the supervision of Professor Norbert De Kimpe. His research interests include the synthesis of small- and medium-sized azaheterocyclic systems using 3-halo-1-azaallylic anions as building blocks.

Norbert De Kimpe obtained the diploma of chemical agricultural engineer in 1971, the Ph.D. degree in 1975, and the habilitation degree in 1985, all from Ghent University, Ghent, Belgium. He performed postdoctoral research work at the University of Massachusetts, Harbor Campus, at Boston (1979) and at the Centre National de Recherche Scientifique (CNRS) in Thiais, Paris, France (1983), where he worked on unstable nitrogen-substituted sulfenyl derivatives and electron-deficient carbenium ions, respectively. He continued his scientific career at the Belgian National Fund for Scientific Research, where he went through all stages up to the position of Research Director. During this time, he was affiliated with the Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences at Ghent University, where he has held teaching positions since 1987. He is now Professor of Organic Chemistry at the latter institution. He was a guest professor at the Centre Universitaire de Recherche sur la Pharmacopée et la Médecine Traditionelle in Butare, Rwanda, Central Africa, and at the Universities of Perpignan (France), Helsinki (Finland), Leuven (Belgium), Siena (Italy), Barcelona (Spain), Sofia (Bulgaria), Buenos Aires (Argentina), and Pretoria (South Africa). He was awarded the degree of doctor honoris causa from the Russian Academy of Sciences in Novosibirsk, Russia, in 1998. He is the author of 330 articles in international peer-reviewed journals. His research interests include (1) the synthesis of heterocyclic compounds, with focus on agrochemicals, pharmaceuticals, and natural products, (2) flavor chemistry, and (3) the bioassay-guided isolation of physiologically active natural products from medicinal plants.

1. Introduction

Since their first use in the early 1960s[1−3] 1-azaallylic anions have gained a predominant role in organic synthesis due to their ability to form new C−C bonds with a lack of side reaction products.[4] The present review discloses relevant applications of the chemistry of 1-azaallylic anions leading to basic heterocyclic systems such as aziridines, azetidines, pyrrolidines, pyrroles, piperidines, pyridines, oxiranes, oxolanes, ... and higher functionalized rings, currently used in pharmaceutical chemistry and agrochemistry. The literature has been reviewed up to early 2003. 1-Azaallylic anions **2a**−**e** generated from imines **1a**, hydrazones **1b,c**, oximes **1d**, and oxime derivatives, e.g., oxime ethers **1e** (R = alkyl), will be treated in detail in separate sections (Scheme 1). However, some 1-azaallylic anions derived from miscellaneous compounds will also be considered (e.g., anions **3**−**5**, Chart 1). First structural information for 1-azaallylic anions and their regio- and stereochemical preferences will be given, followed by an overview of the different methods available for the synthesis of heterocycles of different ring sizes.

Deprotonation of imines, hydrazones, and oximes with stoichiometric amounts of sterically hindered strong bases, such as lithium diisopropylamide (LDA),

Scheme 1

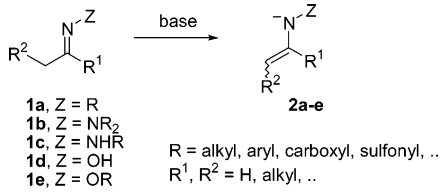
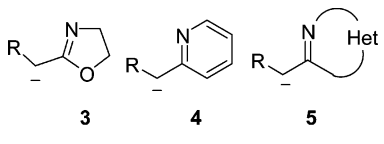


Chart 1



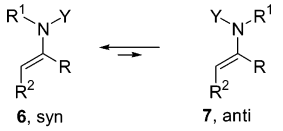
lithium 2,2,6,6-tetramethylpiperidide (LiTMP), or Grignard reagents, is performed in solvents with low dielectric constant (tetrahydrofuran, diethyl ether) to give smoothly 1-azaallylic anions. The synthetic utility of these delocalized anions can easily be understood. 1-Azaallylic anions react with electrophiles (alkyl halides, carbonyl compounds, imines, nitriles, epoxides, ...) almost exclusively at the β-carbon (*C*-alkylation), while *N*-alkylations have scarcely been observed so far. In addition, monoalkylated products can easily be obtained, although examples of dialkylated compounds are known, e.g., acetaldimine alkylations. There is no proton transfer from, for example, diisopropylamine, formed after deprotonation, to the generated anions. Finally, there is almost no condensation of 1-azaallylic anions with the starting imine, with itself, or with the end product. Thus, 1-azaallylic anions are suitable reagents for condensation reactions in organic synthesis, and in particular in heterocyclic synthesis due to the ambident nature of the building block.

2. 1-Azaallylic Anions (Imine Anions)

2.1. Structural Data

Among the 1-azaallylic systems, anions derived from imines (Schiff bases, azomethines) represent the most extensively studied. It is remarkable to note how the commonly used nomenclature of describing the position of the *N*-substituent R^1 (Chart 2), at the same side of the C−C π bond (*syn*) or at the opposite side (*anti*), has generated some problems of interpretation.[5,6]

Chart 2



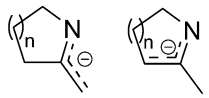
Y = Li, MgX, K, Na, BR_3^-, ZnX, Cu (I), $Al(alk)_3^-$, ...

1-Azaallylic anions are generated from the deprotonation of the corresponding imines via the use of nonnucleophilic bases, such as lithium dialkylamides (lithium diisopropylamide, lithium diethylamide, LiTMP, ...), rarely alkylmagnesium halides (e.g., ethylmagnesium bromide), potassium amides (potassium diisopropylamide), and sodium hydride (vide infra). 1-Azaallylic anions can also be derived from direct lithiation at 10 °C in THF in the presence of a hydrogen acceptor (aromatic hydrocarbon, i.e., phenanthrene).[7] Less common is the formation of 1-azaallylic anions via Michael addition of a *C*-nucleophile toward 1-azadienes (vide infra). Another exception can include the use of a substoichiometric quantity of lithium dialkylamides in the conversion of *N*-aziridinylimines to alkenes. The base can then be regenerated after proton transfer to the alkenyllithium.[8] The deprotonations are conveniently performed in aprotic solvents, such as THF or Et_2O, to give a quantitative amount of 1-azaallylic anions. Among all the possible isomers, the one with a *syn*-C−N, (*E*)-C−C stereochemistry is the more stabilized, as described by almost all authors (vide infra).

2.2. The *Syn* Effect

In the context of imine metalation, the "*syn* effect" refers to the following assumptions: (1) a kinetic preference of imines to metalate the acidic methylene adjacent to the *N*-alkyl substituent, (2) a thermodynamic preference of the resulting lithioimines to orient the *N*-alkyl moiety *syn* to the carbanionic carbon, or (3) a kinetic preference of lithioimines to react with electrophiles, so as to afford products with the newly introduced substituent and the *N*-alkyl moieties *syn* to each other.[9] As mentioned before, metalated 1-azaallylic anions have a *syn* (*Z*)-C−N stereochemistry preference. This configuration has been described and confirmed by ab initio calculations,[10−13] NMR studies,[14−20] X-ray analysis,[21,22] and experimental evidence.[23−26] The experimental evidence was rationalized via ab initio computational studies.[10] Energy barriers of 4.7 and 6.2 kcal/mol were estimated with a 4-31G basis set in favor of the *syn* isomer, calculated for acetaldimine and *N*-methylacetaldimine anions, respectively. At first, the *syn* effect was related to homoaromaticity and a chelation effect, although one can assume that such a large preference for the *syn* isomer cannot be completely explained by these two factors. It was concluded that the *syn* preferences may be derived from σ-orbital effects and dipolar (electrostatic) stabilizations, together with electrostatic repulsion between the electrons at C-3 and the lone pair electrons at nitrogen, in the unfavored *anti* conformation. Studies on the ^{13}C NMR shielding for a series of aldimine and ketimine anions confirmed the *syn* geometry.[17] Deprotonation of a series of aldimines, which are *anti* configurated at the imino form, received an upfield shift for C-4, the one attached to the nitrogen atom, rationalized with the change from the *anti* to the *syn* configuration (Chart 2; R = H; $R^1 = CH_2Ph$; R^2 = H, CH_3). The latter is explained by a γ-effect of steric origin, when the R^1 group and the C-3 are situated on the same side of the space. When ketimines were lithiated, the shift at C-4 failed to attribute stereochemical evidence. The calculation of the pK_a values of aldimines and ketimines in a THF solution revealed that the pK_a value for the deprotonation of the α-carbon to the imino function should be lower than the pK_a of LDA (35.7), which can perform a complete deprotonation of imines. A pK_a value around 30 in DMSO for α-protons of *N*-benzylketimines derived from acetone was estimated.[11] It should be mentioned that proton abstraction of imines by lithium dialkylamides is extraordinarily slow, compared to that of the corresponding keto analogues. This is a clear advantage, considering that the deprotonation of imines still proceeds smoothly without competitive proton transfer. Further studies on the deprotonation of a series of ketimines and aldimines indicated that lithiation is favored on a scale from primary to tertiary carbon atoms. Ab initio calculation at the 4-31G level to evaluate the previous experiments confirmed the scale reported.[11] An exception to the *syn* configuration stability is repre-

Chart 3



8 **9**

n = 1, 2, ..

sented by endocyclic ketimines. Experimental and theoretical results suggested that endocyclic ketimines preferred to deprotonate *exo*, resulting in *anti* anions **8** (Chart 3). These experimental observations were explained by the NCC angle strain in the *syn endo* anions **9**,[13] measured as 120° or less, in contrast with the *exo* angle, which is reliable to the ideal NCC = 133° for acyclic imine anions.[10,11,17] It is worth noting how well the 1-azaallyl moiety approaches the angles for allyl anions (CCC = 132°) and propene (CCC = 125°).

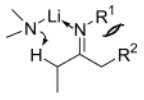
2.3. C–C Stereochemistry

Metalation of imines gives preferentially the (*E*)-C−C isomers under kinetic conditions.[15,16] The *E*/*Z* isomerism can be affected by addition of hexamethylphosphor(V) triamide (HMPA) as cosolvent.[16] In the case of *N*-(propylidene)cyclohexylamine a 44:56 *E*/*Z* mixture of 1-azaallylic anions is formed. This mixture isomerizes thermodynamically to a mixture where the *E* isomer is prevalent (*E*:*Z* = 82:18). The influence of HMPA on the stereochemistry of aldimine anions can be explained by the strong chelating effect of this solvent, which can promote the interconversion of different aggregates (vide infra) in free anion pairs, the lithium ion pair isomerization being estimated as only 10 kcal/mol. The activation barrier for the C−C rotation on imine anions has been established between 16.9 and 28.2 kcal/mol; considering that the C−N isomerization can be accomplished with 19.1 and 16.4 kcal/mol from *syn* to *anti* and vice versa, it becomes clear how 1-azaallylic anions have been described with an amide character rather than as carbanions.[12] Analyzing a series of metalated 1-azaallylic anions (lithium, aluminum, zinc, magnesium), it was found that only lithium azaallylic and trialkyl(azaallylic)aluminate anions have a relatively high rotational barrier, while the other metalated anions show a much lower energy barrier (about 14 kcal/mol), lowering the stereoselectivity of the anion formation.[19] These findings confirmed that lithium 1-azaallylic anions are the reagents of choice in deprotonation of imines.[19]

2.4. Regioselectivity

Regioselectivity in unsymmetrical ketimines varies with the nature of the *N*-substituent, the structure of the base, and the experimental conditions. All these variables can account for high selectivity on primary versus secondary carbon atoms or vice versa.[27,28] Imines derived from methyl ketones and cyclic ketones can undergo regioselective deprotonation at −78 °C with LDA in THF to give the less substituted 1-azaallylic anions, regardless of the *N*-substituent and the C=N geometry.[27] However, regioselective deprotonation of highly substituted reagents requires a more accurate choice of the *N*-substituent, the base, and the conditions for the deprotonation.[27] It was suggested that kinetic metalation of alkylimines occurs *anti* to the *N*-alkyl substituent, followed by a rapid equilibration and alkylation of the *syn*-oriented carbanion to give the *syn* product.[28,29] The regioselectivity of the *anti* deprotonation is lowered by a bulky *N*-substituent (*tert*-butyl, phenyl, ...) or the use of the less hindered LDEA (lithium diethylamide) instead of LDA.[28] Exceptions to the regioselective deprotonation *anti* to the nitrogen substituent were explained by 1,3-allylic interactions between the R^1 group at nitrogen and R^2 at the α-position of the ketimine, which destabilize the transition state (see **10**, Chart 4).

Chart 4



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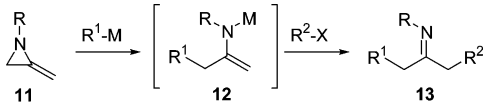
Difficulties in the regiochemical control of the deprotonation of unsymmetrical imines (vide supra) have encouraged the development of more efficient alternative methods. One can include the ring opening reaction of 2-methyleneaziridines with organometallic reagents (Scheme 2). The ring opening of the

Scheme 2



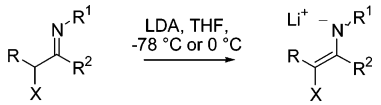
11 **12** **13**

M = metal, X = leaving group

aziridines is highly regiospecific, when Grignard reagents are used in tetrahydrofuran solutions with cupper(I) iodide as catalyst.[30] Although the latter procedure is still not evaluated, it should be available for heterocyclic chemistry. If R^2 is an alkyl halide bearing a certain functionality (N, O, S, ...), the alkylation would result in the formation of highly functionalized derivatives, which could be further elaborated to give the target heterocycles.

Another example of regioselective deprotonation of imines is given by the use of 3-halo-1-azaallylic anions **15** (X = Cl, Br, F).[31] In particular, treating α-chloroimines **14** (X = Cl) with lithium bases at 0 °C (or −78 °C) in THF smoothly results in the regiospecific deprotonation at the more acidic α-carbon (Scheme 3).[32,33] The previously mentioned 3-halo-1-

Scheme 3



14, X = Cl, Br, F **15**

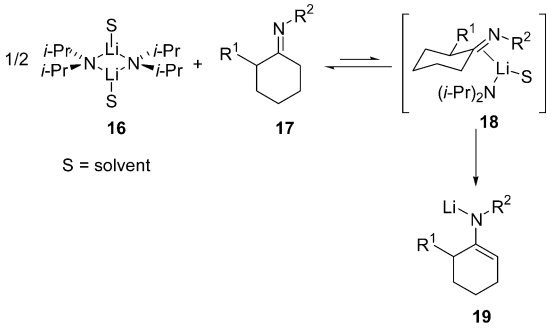
azaallylic anions represent attractive building blocks in the generation of heterocycle systems (vide infra). In a similar way, regioselective deprotonation of α-fluoroimines could be achieved under more restricted reaction conditions.[34] In contrast, depro-

tonations of α-bromoimines are more difficult to handle, due to their instability.

2.5. Reactivity of 1-Azaallylic Anions

Experimentally observed stereochemistry in reactions with 1-azaallylic anions can be accounted for with a mechanism that involves a kinetically controlled reaction featuring a dimer as the reactive species. The same dimeric structure was proven upon X-ray crystallography. MNDO and other computational methods have been used to address dimer versus monomer intuitions, stereoselectivity, and all the issues that could not be adequately explained by spectroscopic and kinetic methods.[6,13,35−38] It was evidenced how modifications of the solvent and sterical hindrance of the base and of the *N*-substituent changed the dimeric aggregate to an open dimer or monomer structure. The different possible conformations can match with the discordant stereoselectivity observed in the experimental procedures. In addition, colligative effects need to be invoked to explain the stereochemistry of reactions of metalated imines with electrophiles. In particular, 1-azaallylic anions in solvents with low polarity (such as THF) tend to give aggregates.[12] Some conclusions arise from rate studies on the metalation of imines derived from cyclohexanones performed with LDA in THF, TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine), and DMEA (*N*,*N*-dimethylethylamine). *N*-Isopropylimines appear to metalate via a mechanism involving deaggregation of the LDA dimer to give reactive monomers without participation of additional donor solvent (Scheme 4). *N*-Isopropylimine metalation or

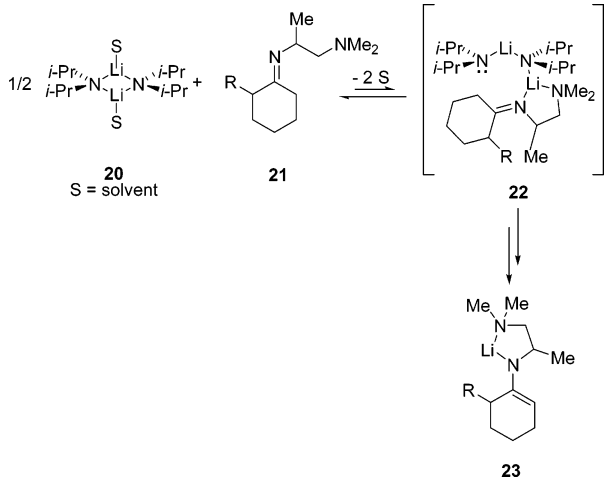
Scheme 4



N,*N*-dimethylhydrazones provided no evidence that the dimethylamino−lithium interaction facilitated the metalation.[39] Instead, open dimers of LDA are suggested to be the critical reactive intermediates in a mechanism shown to constitute a complex-induced proximity effect (CIPE). The term "complex-induced proximity effect" was introduced to describe those instances in which reagent−substrate precomplexation facilitates the subsequent reaction with a proximate electrophilic moiety.[40] Kinetic studies revealed that *N*-isopropylimines **17** (Scheme 4; R^1 = H, Me; R^2 = *i*-Pr) and *N*,*N*-dimethylhydrazones **17** (R^1 = H, Me; R^2 = NMe_2) appear to react via a transient η^2-π-complexed intermediate, **18**, irrespective of the donor solvent (Scheme 4).

In contrast, for rate studies on imines bearing pendent Me_2N moieties, a mechanism was suggested involving a rate-limiting solvent-free open dimer, **22**, exclusively in TMEDA/hexane (or DMEA/hexane) mixtures (Scheme 5).[39] Rate equations for metalations in THF/hexane mixtures are qualitatively and quantitatively indistinguishable from their *N*-isopropyl counterpart.[39]

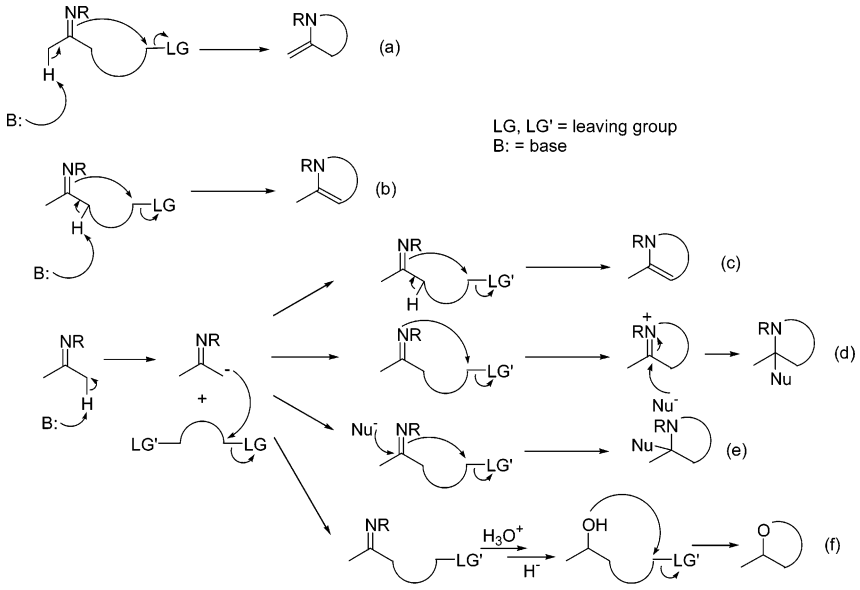
Scheme 5



Ab initio and semiempirical PM3 calculations performed on lithioimines as a model system for molecules in which lithium is η^3 bound to the aza-π-allylic system, such as the growing poly(2-vinylpyridine)chain end, give reasonable results in comparison with previous calculations and X-ray crystal data.[13] Lithioimines exhibit bonding in which the lithium atom resides above the azaallylic orbital and is bonded in an η^3 manner. In a weakly polar solvent, the molecule exists as an equilibrium mixture of two cyclic dimers of similar energy. It was confirmed that changes in structure and bonding occur upon addition of strongly coordinating solvents. A third open dimer, similar to the asymmetric unit of lithiohydrazones in the solid state, may occur as a minor species in the presence of a strongly coordinating or chelating solvent (i.e., HMPA). Steric hindrance also may affect the structure and bonding of these compounds, and in polar solvents hindered lithioimines may exist as an equilibrium mixture of solvated monomers and dimers. In conclusion, theoretical and experimental analyses showed a variety of aggregation structures that may account for the relatively low stereoselectivity in alkylation reactions of imines.[13,37]

Reactions in which 1-azaallylic anions, generated from imines, are used for the synthesis of suitable intermediates that are capable of forming a heterocyclic ring are considered here. Because of the fact that 1-azaallylic anions are ambident anions, capable of reacting with (mostly) the carbanionic center and the amide moiety, the introduction of a functionalized unit via an electrophile in such 1-azaallylic anions offers the potential for ring closing reactions. However, various variants are possible. When a leaving group is present in the starting imine, deprotonation at the α- or α′-position of the imine and subsequent *N*-alkylation by substitution of the leaving group result in the formation of *N*-heterocyclic compounds with an exo- or endocyclic double bound (see reactions

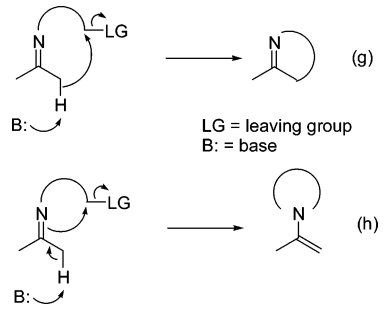
Scheme 6



a and b in Scheme 6). The introduction of such a leaving group in the imine can be accomplished via 1-azaallylic anions themselves. Biselectrophiles, bearing two leaving groups in their structure, can react with a 1-azaallylic anion, forming imines containing a leaving group. Similar to reaction b deprotonation results in *N*-alkylation and cyclization to the *N*-heterocyclic compound (see reaction c). The imines containing a leaving group in their structure can also cyclize via direct substitution of the leaving group by the nitrogen of the imino function, resulting in iminium salts which react with nucleophiles toward the *N*-heterocycles (see reaction d). Vice versa, the addition of a nucleophile across the imino function, followed by cyclization through the substitution of the leaving group by the nitrogen anion, leads to the same *N*-heterocyclic compounds as in reaction d (see reaction e). Although in the latter two pathways, d and e, the formation of a 1-azaallylic anion is not used in the final cyclization step, the 1-azaallylic chemistry is essential for the formation of the suitable intermediate necessary to form the heterocycle. Therefore, these types of reactions are also included in this review. A reaction sequence which is closely related to pathway e is the formation of the imine with a leaving group present in the structure by reaction of a 1-azaallylic anion with a biselectrophile, as in reaction e, but then followed by hydrolysis of the imino function and reduction of the corresponding keto function with hydride. Final cyclization by substitution of the leaving group by the alcohol leads then to the corresponding *O*-heterocycles (see reaction f). In summary pathways a−f are examples where the use of 1-azaallylic anions are essential to form a heterocyclic structure by reaction of the nucleophilic nitrogen of the imino group, or the masked alcohol, with an electrophilic functionality present in the imine.

Another possibility to form *N*-heterocyclic compounds is the formation of a 1-azaallylic anion of imines which contains a leaving group in the chain attached to the nitrogen of the imine. Reaction of the carbanionic center with the electrophilic chain on the nitrogen results in *N*-heterocyclic compounds (see reaction g in Scheme 7). The 1-azaallylic anion could potentially also react via *N*-alkylation to form *N*-heterocycles (see reaction h).

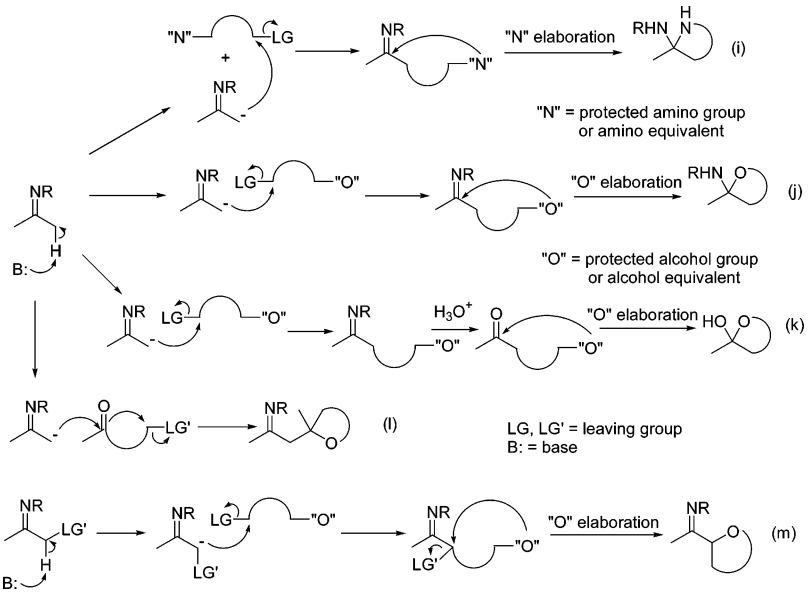
Scheme 7



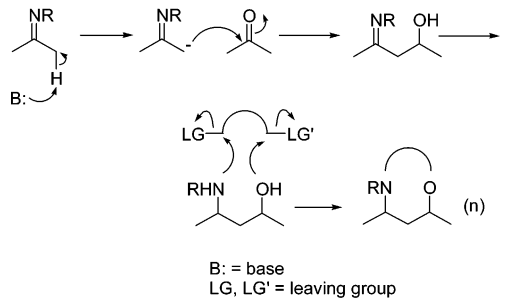
An important use of 1-azaallylic anions is the introduction of a nucleophilic function in the structure of the imine. The nucleophilic function can be an amino group introduced via reaction of the 1-azaallylic anion with an electrophile containing a protected amino group or amino equivalent. Addition of that amino group with the electrophilic imino function results in *N*-heterocyclic compounds (see reaction i in Scheme 8). The nucleophile can also be an alcohol function introduced via the 1-azaallylic anion by reaction with an electrophile containing a protected alcohol or alcohol equivalent. Further cyclization by again addition across the imino function by the generated alcohol results in *O*-heterocyclic compounds (see reaction j). The introduced alcohol function could also react with the corresponding keto function formed after hydrolysis of the imino group (see reaction k), or with another electrophilic function present in the imine, all leading to *O*-heterocycles (see reactions l and m).

A strategy leading to heterocycles containing both nitrogen and oxygen consists of first the introduction of an alcohol function by addition of the 1-azaallylic anion across a keto function, followed by reduction of the imino group to the amine. The thus formed

Scheme 8



Scheme 9



amino alcohol can then react with a biselectrophile to form the *N*,*O*-heterocyclic compound (see reaction n in Scheme 9).

2.6. Synthesis of Three- and Four-Membered Heterocyclic Compounds

2.6.1. Synthesis of Oxiranes

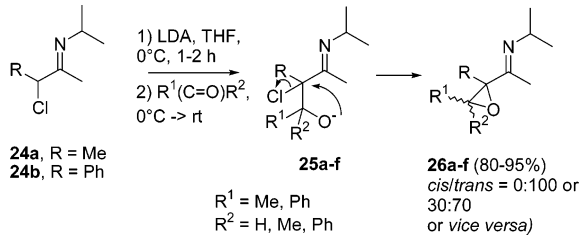
Oxiranes are accessible by condensation reactions of 3-chloro-1-azaallylic anions and the analogous heteroarylazaallylic anions (anions derived from 2-methyloxazolines, 2-methylpyridines, ...) (vide infra).

α-Chloroketimines **24** were converted to 3-chloro-1-azaallylic anions by reaction with lithium diisopropylamide in tetrahydrofuran at 0 °C, and by addition of ketones, such as acetone, 2-butanone, and benzophenone, or aldehydes, namely, benzaldehyde, the addition reactions gave adducts **25**, which easily underwent ring closure to generate 2-imidoyloxiranes **26** via a Darzens-type reaction (Scheme 10).[41]

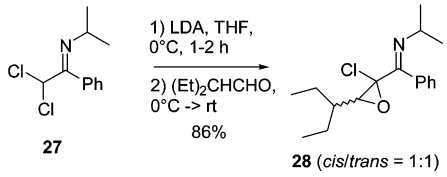
The same Darzens reaction was observed starting from α,α-dichloroketimines. When *N*-(2,2-dichloro-1-phenylethylidene)isopropylamine (**27**) was reacted with 2-ethylbutanal, a 1:1 mixture of *cis*- and *trans*-2-chloro-2-imidoyloxiranes **28** was obtained (Scheme 11).[42]

Oxiranylimines **29** can suffer base-induced dimerization to give aziridine **31** as the sole diastereoisomer (Scheme 12).[43]

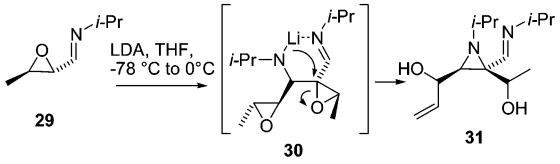
Scheme 10



Scheme 11



Scheme 12

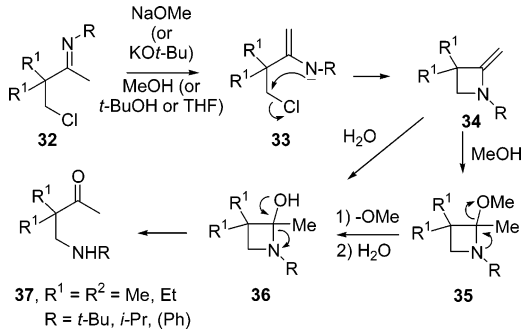


2.6.2. Synthesis of Azetidines

A methodology for the preparation of β-(alkylamino) ketones **37** can include the presence of an azetidine as the reactive intermediate (Scheme 13). For instance, during the synthesis of β-(alkylamino)-carbonyl **37** compounds, generated from *N*-alkylated β-chloroimines **32** with alkoxide bases (sodium methoxide, potassium *tert*-butoxide) in alcohols (methanol, *tert*-butyl alcohol), an azetidine intermediate was formed either in situ or upon acid workup. As a proof, using β-chlorinated *N*-arylimines, 2-methoxy-1-phenylazetidines **35** (R = Ph) could be isolated.[44,45]

In this matter, *N*-benzyl-α-chloroaldimines do not give rise to azetidines as they suffer base-induced 1,4-dehydrochlorination to 2-aza-1,3-dienes.[46,47] Moreover, treating α-chloro- and α-bromoimines with

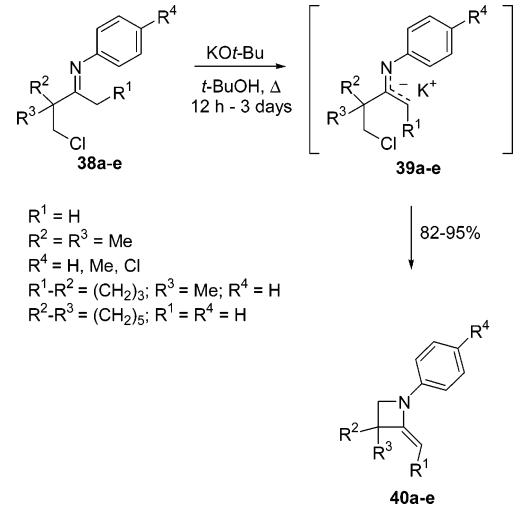
Scheme 13



N-bases (triethylamine, DABCO, DBU) in alcohols led, via the corresponding 1-azaallylic anion enamine, to 1-alkoxy-1-aminocyclopropanes, α-alkoxyimines, and rearranged α-aminoacetals in various ratios depending on the reaction conditions.[48]

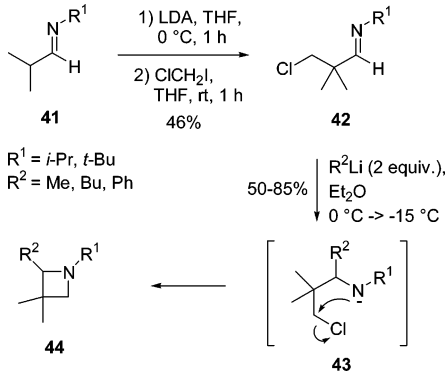
In addition, refluxing of *N*-aryl-*β*-chloroimines **38** with potassium *tert*-butoxide in *tert*-butyl alcohol led to the formation of 2-methyleneazetidines **40a**−**e** in 82−95% yield. The synthesis was rationalized in the formation of the 1-azaallylic anion upon deprotonation at the α′-position of the imine and subsequent ring closure to the strained heterocyclic compounds.[45] It is noteworthy that only *N*-aryl-2-methyleneazetidines could be prepared and that aqueous workup destabilized the end products, partially being converted in the corresponding *β*-(arylamino) ketones **37** (vide supra). This methodology was useful for the formation of bicyclic and spiro compounds (Scheme 14; $R^1-R^2 = (CH_2)_3$ and $R^2-R^3 = (CH_2)_5$, respectively). In the case of *N*-alkyl derivatives, under no circumstances were 2-methyleneazetidines prepared as these compounds are very sensitive to hydrolysis during workup. Even nonaqueous workup did not allow the synthesis of these strained compounds.[45] Reactions of *β*-haloimines lacking the α,α-disubstitution failed to give azetidines (vide supra), disclosing a limitation during this procedure.[45]

Scheme 14



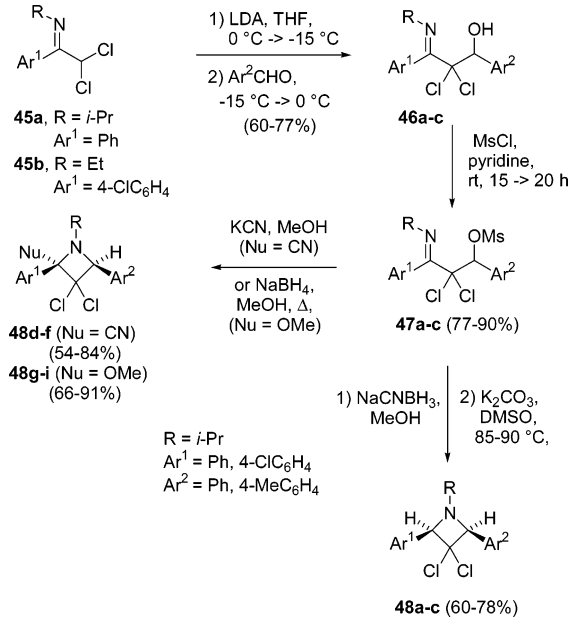
A synthetic entry to 1-alkyl-2-substituted azetidines **44** has been developed via ring closure of *β*-chloroimines with alkyllithiums.[49] These *β*-chloroimines can be synthesized via alkylation of lithium 1-azaallylic anions, derived from *N*-alkylisobutyraldimines **41** (R = *t*-Bu, *i*-Pr) with chloroiodomethane at 0 °C (Scheme 15).

Scheme 15



An approach to 3,3-dichloroazetidines **48** started from the synthesis of α,α-dichloro-*β*-hydroxyketimines **46** by lithiation of α,α-dichloroarylketimines **45** (Ar^1 = Ph, 4-ClC_6H_4) and reaction with aromatic aldehydes (Ar^2 = Ph, 4-MeC_6H_4) via aldol-type condensation. After mesylation of the *β*-hydroxyimines with mesyl chloride in pyridine, the *cis*-azetidines **48** were generated either via a nucleophile-induced one-step cyclization or in a two-step sequence consisting of a reduction with sodium cyanoborohydride followed by a ring closure under basic conditions (Scheme 16).[42] Exclusively *cis*-2,4-diaryl-3,3-dichloroazetidines **48** were observed.

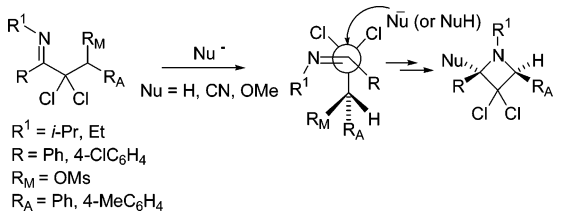
Scheme 16



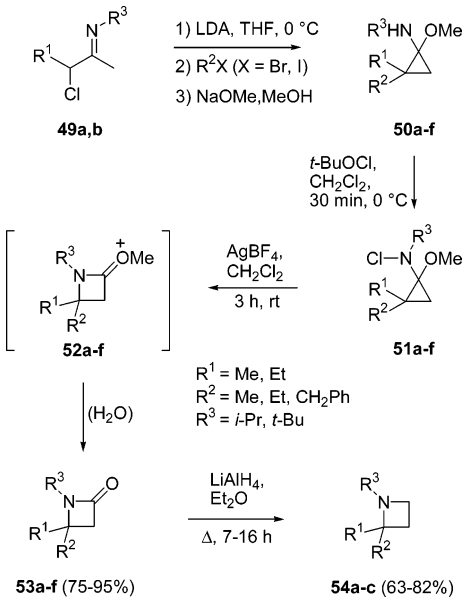
The observed stereoselectivity was described via an Evans-type model, where the nucleophile forming the new bond and the larger aryl substituent R_A are situated most remote from each other (Scheme 17).

1-Azaallylic anions can be a useful tool in the synthesis of 4,4-disubstituted *β*-lactams **53**, via regiospecific electrophile- and silver-induced ring expansion of 2,2-disubstituted 1-methoxycyclopropylamines **50** (Scheme 18). The synthesis of 1-methoxycyclopropylamines started from (1) the deprotonation

Scheme 17



Scheme 18



of the corresponding α-chloroketimine **49**, (2) reaction of the regiospecifically formed 1-azaallylic anion with alkyl halide, and (3) Favorskii-type cyclopropanation together with the addition of methoxide across the imino function of intermediate cyclopropylidenamine. *N*-Chlorination of the carbinolamine **50** and silver tetrafluoroborate-induced ring expansion produced 4,4-disubstituted *β*-lactams **53**, which can be reduced to the corresponding azetidines **54** via lithium aluminum hydride in diethyl ether under reflux for 7−16 h.[50]

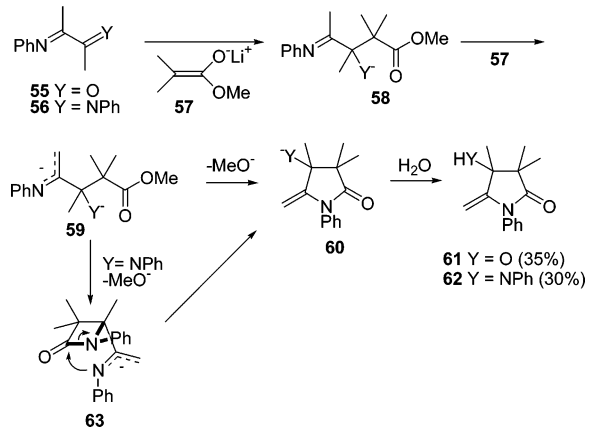
2.7. Synthesis of Five- and Six-Membered Heterocyclic Compounds

2.7.1. Synthesis of Pyrrolidines and Pyrrolines

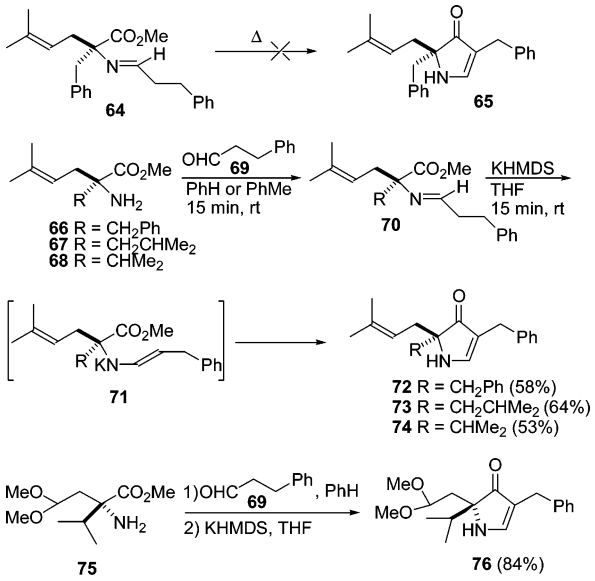
5-Methylenepyrrolidin-2-ones **61** and **62** were synthesized on the basis of the reaction of dielectrophilic imines **55** and **56** with lithium ester enolates **57** (Scheme 19).[51,52] Hereby an ester function was introduced at the *β*-position of the imine, after which the excess of the lithium ester enolate **57** acted as a base to deprotonate the intermediate imino ester **58** at the α′-position. Final cyclization of the 1-azaallylic anion **59** via nitrogen by addition to the ester yielded 4-functionalized 5-methylenepyrrolidin-2-ones **61** and **62**. In the case of the α-diimine **56** the reaction seems to proceed via the *β*-lactam **63** as intermediate. The absence of protons in the α-position of the ester seems to be essential, as otherwise enolization of the ester prevented cyclization to the related *γ*-lactam when the excess of enolate was used.[51,52]

A method for yielding (poly)pyrrolinones consists of the intramolecular acylation of metalated imines,

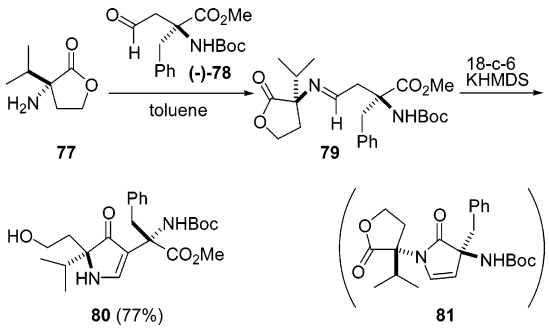
Scheme 19



Scheme 20



Scheme 21



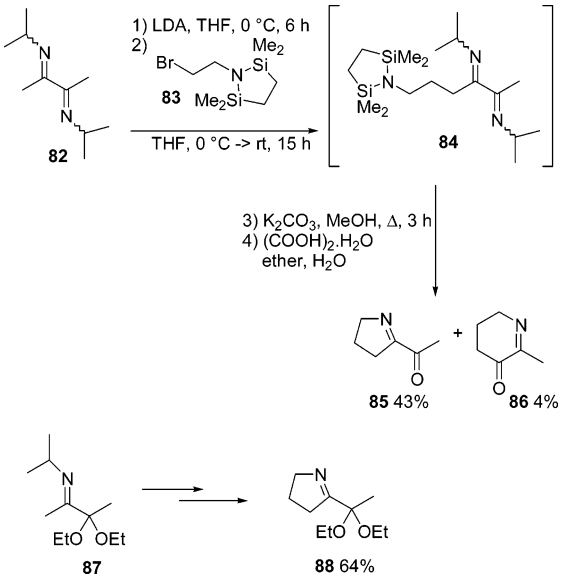
synthesized from α-amino esters.[53−56] Whereas heating of the imine **64** did not give the prenylated pyrrolinone **65**, the more reactive metalloimine derivatives **71**, prepared by treatment of the imines **70** with potassium hexamethyldisilazide (KHMDS), could be cyclized to the prenylated pyrrolinones **72**−**74** and dimethoxyethylated pyrrolinones **76** (Scheme 20). In addition to α-amino ester derivatives, also α-amino-lactones **77** have been used as starting material, leading to hydroxyalkylated pyrrolinones **80** (Scheme 21).[57,58] In the latter case, if other amide bases were used such as LDA, LiTMP, and LiHMDS, the unsaturated lactam **81** was found as a major side product

(ca. 40%), as a result of the addition of the metalloimine nitrogen to the methoxycarbonyl group.

Similar reactions toward pyrrolinones have been described via deprotonation of the corresponding iminium salts of α-amino esters.[59]

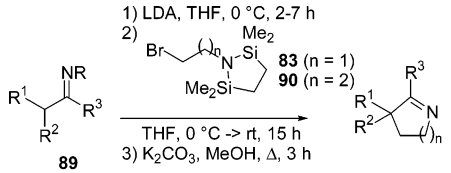
The principal rice flavor component, 2-acetyl-1-pyrroline (**85**), was prepared by α-deprotonation with LDA and α-alkylation of α-diimine **82** with the stabase-protected *ω*-bromoethylamine **83**, resulting in the functionalized intermediate imine **84** (Scheme 22). This intermediate underwent cleavage of the

Scheme 22



N−silyl bonds, upon which it cyclized to **85** and minor amounts (4%) of the structural isomer **86** by transimination.[60] This methodology, starting from the α,α-diethoxyketimine **87**, also led to the more stable diethyl acetal **88** of 2-acetyl-1-pyrroline. Diverse other five-membered and six-membered cyclic imines, including several alkaloids such as myosmine (**93**), anabaseine (**94**), and apoferrorosamine (**95**), were also synthesized via this strategy (Scheme 23).[61]

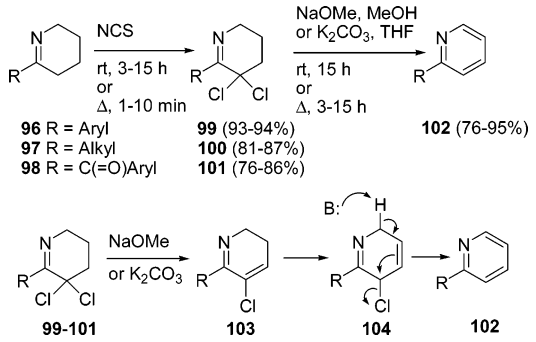
Scheme 23



91 R = *t*-Bu, $R^1 = R^2$ = Et, R^3 = H, n = 1 (62%)
92 R = *t*-Bu, $R^1 = R^2$ = Et, R^3 = H, n = 2 (58%)
93 R = *i*-Pr, $R^1 = R^2$ = H, R^3 =  , n = 1 (56%)
94 R = *i*-Pr, $R^1 = R^2$ = H, R^3 =  , n = 2 (88%)
95 R = *i*-Pr, $R^1 = R^2$ = H, R^3 =  , n = 1 (78%)

The six-membered cyclic imines **96**−**98**, namely, 2,3,4,5-tetrahydropyridines, which are accessible from the cyclization of imines **89**, after deprotonation into 1-azaallyl anions, with ethylenetetramethyldisilyl-protected 3-bromopropylamine **90**, are α,α-dichlorinated to cyclic dichloroketimines **99**−**101** (Scheme

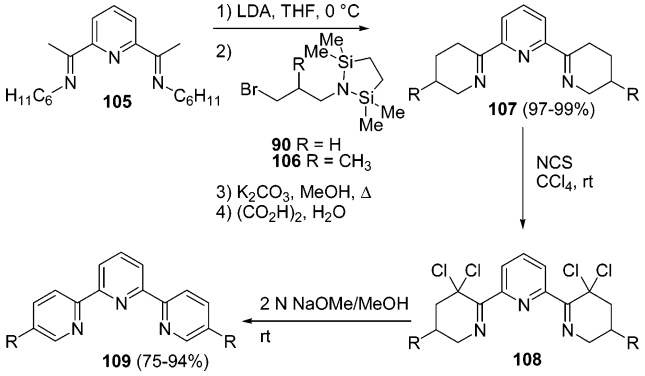
Scheme 24



24).[62] A high degree of regioselectivity is achieved in the reaction of the aliphatic tetrahydropyridines **97** toward 6-alkyl-5,5-dichloro-2,3,4,5-tetrahydropyridines **100**.[62] Treatment of the α,α-dichloroimines **99**−**101** with sodium methoxide in methanol resulted in 1,2- and further 1,4-dehydrochlorination, via an intermediate 1-aza-1,3-diene, **103**, providing the pyridines **102**. This same method of α,α-dihalogenation and subsequent dehydrohalogenation has also been used in the synthesis of 3-halopyrroles from the corresponding 1-pyrrolines.[63]

This strategy to form pyridines from 2,3,4,5-tetrahydropyridines was used to prepare symmetric terpyridines **109**.[64] Cyclization of the bisimine **105** with the ethylenetetramethyldisilyl-protected 3-bromopropylamines **90** and **106** provided the tetrahydropyridines **107**, via α-alkylation, *N*-deprotection, and transimination (Scheme 25). Subsequent tetrachlo-

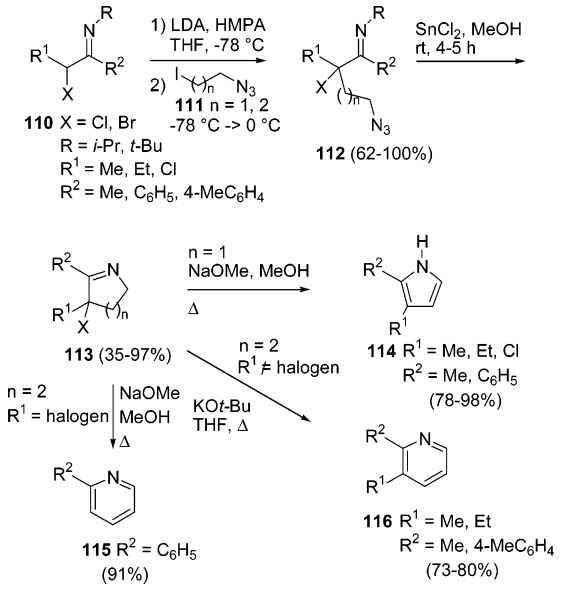
Scheme 25



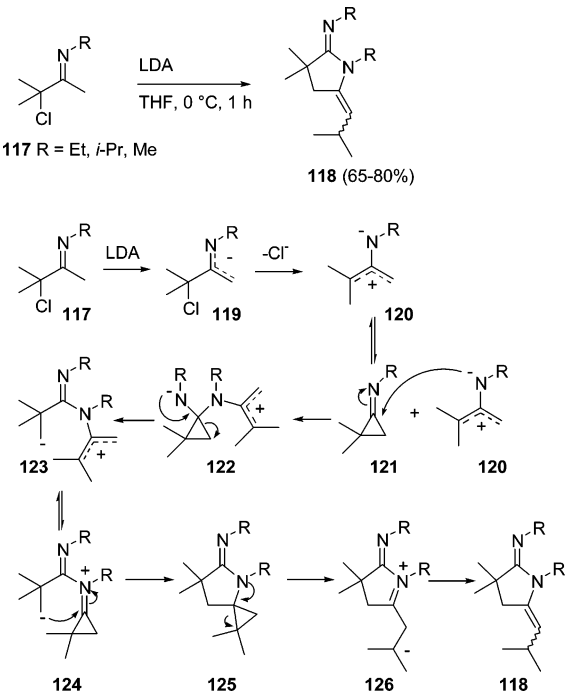
rination with *N*-chlorosuccinimide and further conversion by the action of sodium methoxide in methanol yielded the terpyridines **109**.

The reaction of 3-halo-1-azaallylic anions, regiospecifically generated from α-halogenated ketimines **110**, with *ω*-iodoazides **111** led to *ω*-azido-α-haloketimines **112** (Scheme 26).[65] Treatment of these imines **112** with tin(II) chloride in methanol afforded halogenated 1-pyrrolines **113** ($n = 1$) and 2,3,4,5-tetrahydropyridines **113** ($n = 2$). Further transformation under basic conditions led to 2,3-disubstituted pyrroles **114** and pyridines **115** and **116**. In the case of α,α-dichloroketimines **113** (R^1 = Cl), the second chloro atom can be kept in pyrroles as 3-chloropyrroles **114** (R^1 = Cl), while in the case of pyridines the second chloro atom is used in the second dehydrochlorination step to provide 2-substituted pyridines **115**.

Scheme 26



Scheme 27



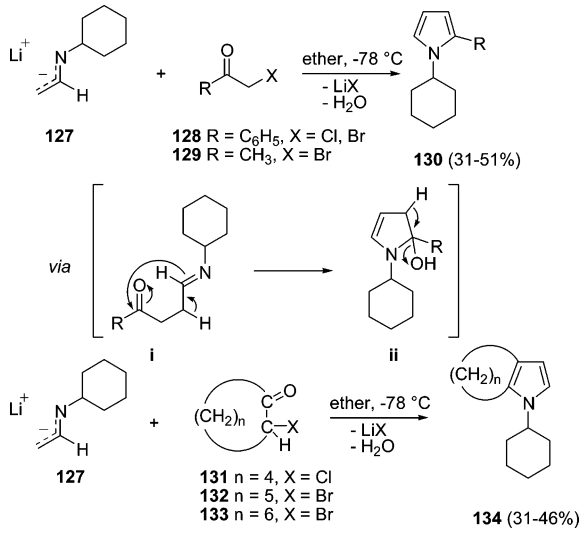
The reaction of *N*-(3-chloro-3-methyl-2-butylidene)-amines **117** with 2 equiv of lithium diisopropylamide in tetrahydrofuran at 0 °C afforded unexpectedly 2-(*N*-alkylimino)-3,3-dimethyl-1-isopropyl-5-(2-methyl-propylidene)pyrrolidines **118** (Scheme 27).[66] This reaction was explained as starting with a base-induced Favorskii-type ring contraction, affording cyclopropylidenamines **121** (*N*-analogues of cyclopropanones), followed by a "dimerization" process involving addition of zwitterion **120** across the imino bond of the cyclopropylidenamine **121** and subsequent opening of the resulting aminal anion **122** to the most stable carbanion **123**. The ring-closed isomeric species **124**, i.e., cyclopropylideniminium ions in equilibrium with **123**, suffered nucleophilic addition, affording spiro intermediate **125**. The next step involved an "abnormal" ring opening, forming the least stable carbanionic species **126**, which is protonated and converted into the functionalized amidines **118**.[66]

The corresponding oxygen compound, i.e., 3-chloro-3-methyl-2-butanone, reacted under similar conditions to give 2,2-dimethyl-5-[*N*-(isopropyl)amino]-6-(2,2-dimethyl-1-hydroxycyclopropyl)-4-hexen-3-one as the principal reaction product, resulting from addition of two molecules of the Favorskii-derived cyclopropanone with *N*-(2-propylidene)isopropylamine, i.e., the oxidation product of LDA.[67,68]

2.7.2. Synthesis of Pyrroles

Besides the above-mentioned synthesis of the 2,3-disubstituted pyrroles **114** via halogenated 1-pyrrolines **113**, some other more direct methods for the synthesis of pyrroles are known making use of 1-azaallylic anions. One of the first reports on the synthesis of a heterocyclic compound from a 1-aza-allylic anion is the formation of pyrroles **130** and **134** from the reaction of lithioazaenolate **127** with α-halogenated ketones **128** and **129** and **131**−**133** in ether at −78 °C (Scheme 28).[69] The mechanism is

Scheme 28

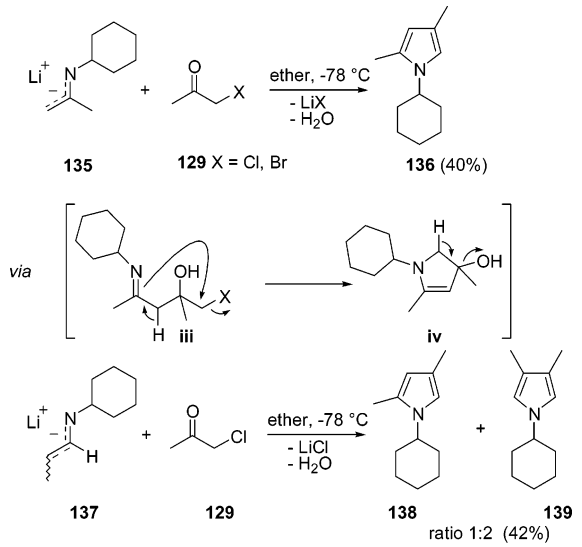


explained as an S_N2 reaction of the metalated imine with the halomethyl group, followed by cyclization via the enamine form and elimination of water from intermediate **ii**.

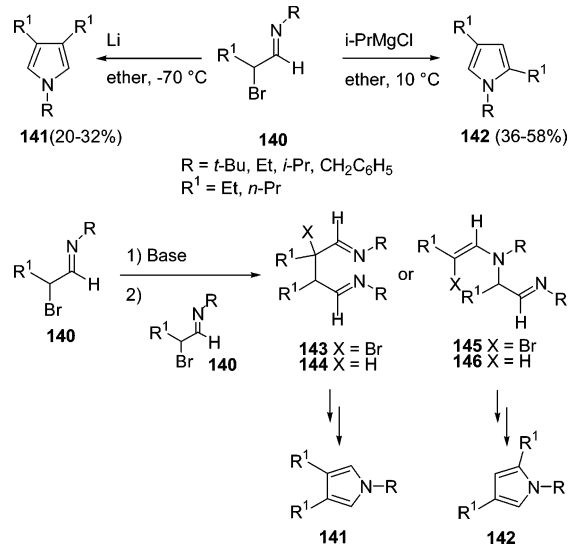
Lithiated isopropylidenecyclohexylamine **135** reacted in a different way, with initial nucleophilic addition of the anion across the carbonyl group, followed by substitution of the chloro substituent in **iii** and aromatization by dehydration (Scheme 29).[69,70] The use of lithiated propylidenecyclohexylamine **137** illustrates both mechanisms by the formation of a mixture of both types of 1,2,4- and 1,3,4-trisubstituted pyrroles **138** and **139**.

α-Bromoaldimines **140** reacted with 2 equiv of isopropylmagnesium chloride in ether at 10 °C to afford 1,2,4-trisubstituted pyrroles **142**,[71,72] while the isomeric 1,3,4-trisubstituted pyrroles **141** were obtained by reaction with lithium in ether at −70 °C (Scheme 30).[71] In both cases, the main products were contaminated by the respective isomer **141** or **142**.

Scheme 29



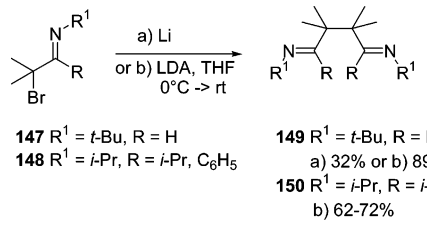
Scheme 30



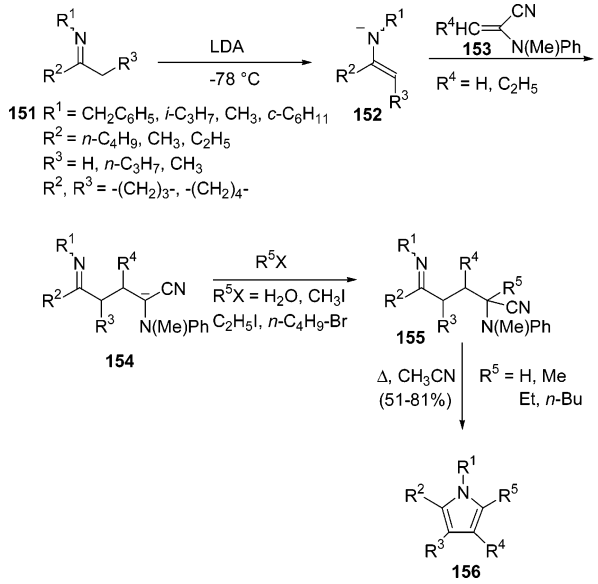
The synthesis of these pyrroles **141** and **142** can be explained by an ionic mechanism that leads, after formation of a carbanion and *C*- or *N*-alkylation, to intermediates **143** and **145**, which can further cyclize to the corresponding pyrroles **141** and **142**. However, particularly in the case of the symmetric pyrroles **141**, a radical mechanism could be a valuable alternative. This would include a dimerization of imines **140** via an electron-transfer process to give the reduced adducts **144**, which cyclize to pyrroles **141**. Similar diimines **149** and **150** have been synthesized, probably through this radical mechanism, via captodative intermediates, starting from imines **147** and **148**, after treatment with lithium and lithium diisopropylamide, respectively (Scheme 31).[71,73] It was also demonstrated that α-bromo- as well as α-chloroaldimines gave 1,3,4-trisubstituted pyrroles, exclusively, via diimines **144** by reaction with sodium in liquid ammonia.[72]

Michael addition of 1-azaallyl anions **152** with 2-(*N*-methylanilino)acrylonitriles **153**, followed by protonation or alkylation and heating in a polar solvent such as acetonitrile, furnished the pyrroles **156** (Scheme 32).[74] By this method pentasubstituted

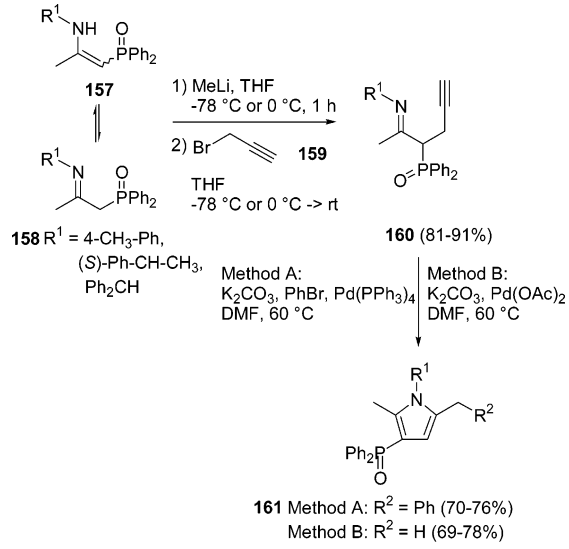
Scheme 31



Scheme 32



Scheme 33



pyrroles could be synthesized, with good control of the regiochemistry of the substituents. When unsymmetrical imines were used, however, problems arose from nonselective deprotonation at higher temperatures, leading to a mixture of regioisomeric pyrroles.[74]

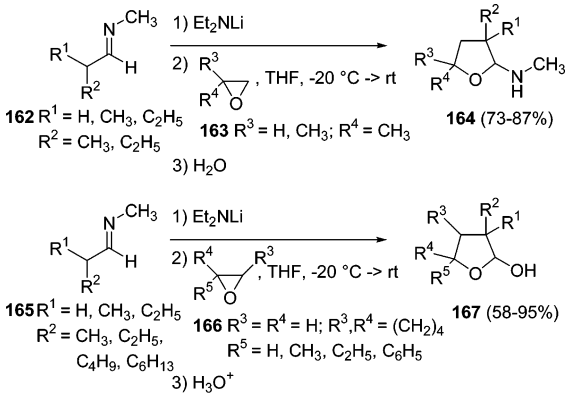
Deprotonation of the mixture of *β*-enamino- and *β*-iminophosphane oxides **157** and **158** with methyllithium and alkylation with propargyl bromide (**159**) gave the α,α-difunctionalized imines **160**.[75] Due to the presence of the anion-stabilizing phosphane oxide moiety in the starting imine **158**, the deprotonation occurred with complete regioselectivity at the internal carbon. The α-propargyl-*β*-iminophosphane ox-

ides **160** were cyclized to the phosphinylated pyrroles **161** via a palladium-catalyzed heterocyclization reaction (Scheme 33).

2.7.3. Synthesis of Tetrahydrofurans

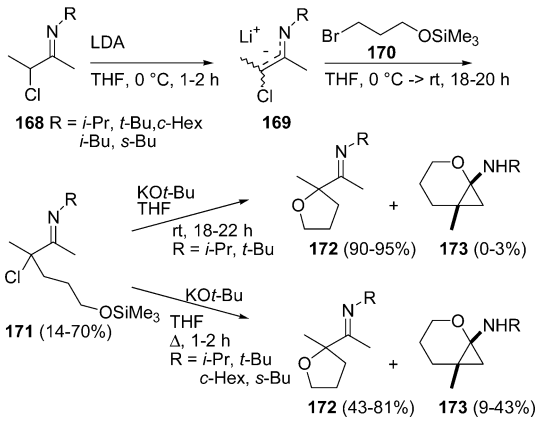
Several methodologies have been described toward the synthesis of oxygen-containing five-membered heterocycles via 1-azaallylic anions. In the first pathway, the anion of imines **162** and **165** attacked the epoxides **163** and **166**, resulting in an *O*-anion which reacted via a nucleophilic addition across the imino function (Scheme 34). After aqueous workup or acid hydrolysis this led to the corresponding aminals **164** or hemiacetals **167**.[76]

Scheme 34

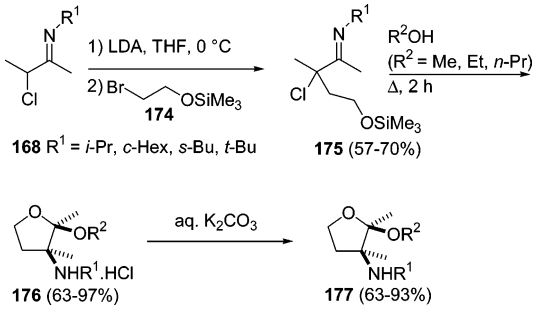


Regiospecific deprotonation of α-chloroketimines **168** with lithium diisopropylamide, followed by alkylation with 3-bromopropyl trimethylsilyl ether (**170**), afforded the δ-trimethylsilyloxy-α-chloroketimines **171** (Scheme 35).[77,78] Reaction of the α-chloroketimines **171** with potassium *tert*-butoxide furnished mostly the 2-functionalized tetrahydrofurans **172**, next to a substantial amount of 1-(alkylamino)-6-methyl-2-oxabicyclo[4.1.0]heptanes **173**, the latter being the trapping products of the Favorskii intermediates, i.e., cyclopropylidenamines (nitrogen analogues of cyclopropanones). The furans **172** resulted from deprotection of the trimethylsilyl ether and subsequent intramolecular nucleophilic substitution. When the δ-trimethylsilyloxy-α-chloroketimines **171** were reacted with methanol in the presence of bases, 2-alkoxy-3-aminotetrahydropyrans were formed, as well as tetrahydrofurans **172** (vide infra, Scheme 66).[78]

Scheme 35

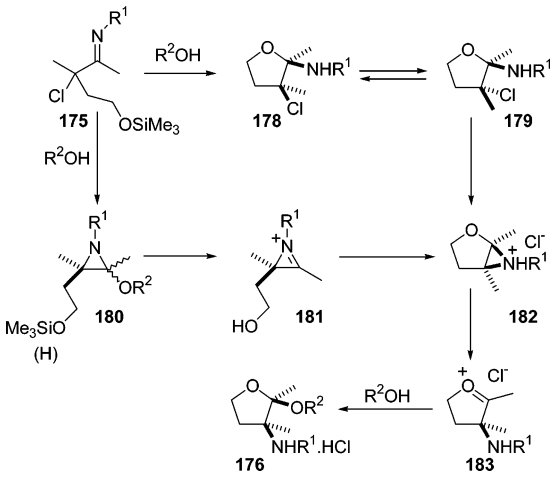


Scheme 36



The γ-trimethylsilyloxy-α-chloroketimines **175** cyclized with alcohols to afford *cis*-2-alkoxy-3-aminotetrahydrofurans **177** in a stereospecific way after treatment with base (Scheme 36).[79] The mechanism was explained in terms of two possible routes involving either a *trans*-2-amino-3-chlorotetrahydrofuran, **179**, or intermediate 2-alkoxyaziridines **180** and azirinium ions **181** (Scheme 37). Both routes lead to a bicyclic aziridinium ion, **182**, which opens up to the final tetrahydrofurans **176** via a hydrogen-bond-guided stereospecific attack of the alcohol to the transient oxonium ion **183**.

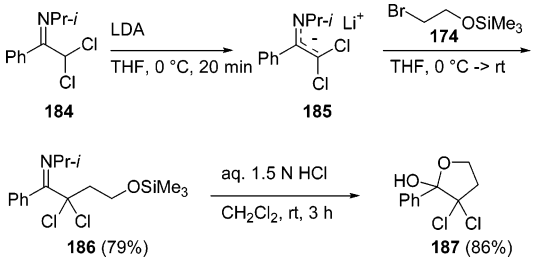
Scheme 37



Deprotonation of *N*-(2,2-dichloro-1-phenylethylidene)isopropylamine (**184**) with lithium diisopropylamide produced the 3,3-dichloro-1-azaallylic anion **185**, which reacted with 2-bromoethyl trimethylsilyl ether (**174**), resulting in the α,α-dichloroimine **186**, the acidic hydrolysis of which gave 3,3-dichloro-2-hydroxy-2-phenyloxolane **187** (Scheme 38).[80]

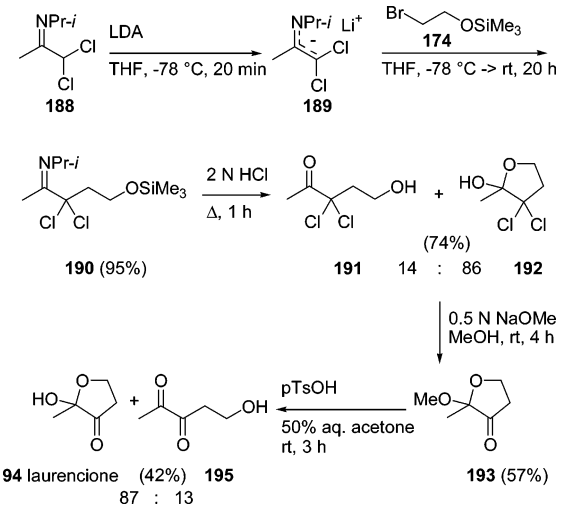
Using the same methodology, the synthesis of the marine natural product laurencione (**194**) was accomplished.[81] Regiospecific deprotonation of the α,α-

Scheme 38



dichloroketimine **188**, prepared from 1,1-dichloroacetone and isopropylamine in the presence of titanium(IV) chloride, resulted in the 3,3-dichloro-1-azaallylic anion **189** (Scheme 39). Further alkylation

Scheme 39

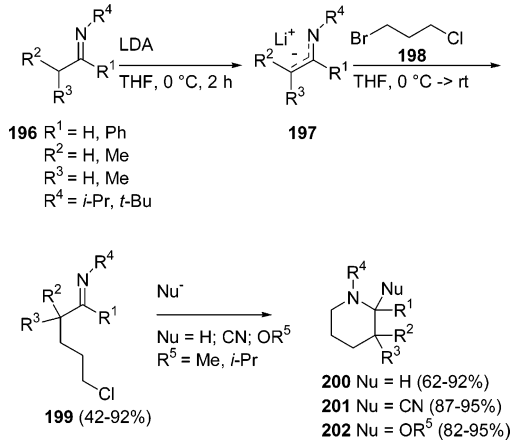


with **174** and acidic hydrolysis generated 2,2-dichloro-5-hydroxypentan-2-one (**191**) as an equilibrium mixture with its cyclic form **192**. The reaction of this mixture of compounds **191** and **192** with sodium methoxide in methanol afforded 2-methoxy-2-methyldihydrofuran-3(2*H*)-one (**193**), i.e., laurencione methyl ether, as a result of base-induced intramolecular nucleophilic substitution affording an intermediate α-chloroepoxide which rearranged into **193** via a transient pseudocarbenium ion. **193** was converted into **194** by reaction with *p*-TsOH in aqueous acetone.[82]

2.7.4. Synthesis of Piperidines and Piperidinones

Reaction of δ-chloroimines **199**, prepared by base-induced α-alkylation of imines **196** with α,γ-dihalopropanes **198**,[83] with nucleophiles such as complex metal hydrides, potassium cyanide, alcohols, and alkoxides furnished piperidines **200**, 2-cyanopiperidines **201**, and 2-alkoxypiperidines **202**, respectively (Scheme 40).[84] The presence of a leaving group in the carbon chain made the imines **199** synthetic blocks for the construction of *N*-heterocycles. The

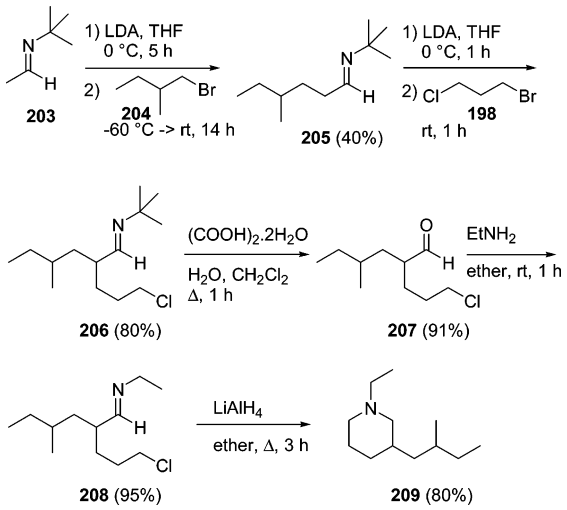
Scheme 40



nucleophile added across the carbon−nitrogen double bond followed by ring closure of the intermediate adduct.

Using the previous ω-haloimine chemistry, the synthesis of stenusine (**209**), the spreading agent of the staphynilid beetle *Stenus comma*, was accomplished.[85] First, alkylation of *N*-*tert*-butylaldimine **203** via its 1-azaallylic anion with 1-bromo-2-methylbutane (**204**), followed by separation from some dialkylated product, and second alkylation with 1-bromo-3-chloropropane (**198**) resulted in the corresponding δ-chloroaldimine **206** (Scheme 41). After

Scheme 41

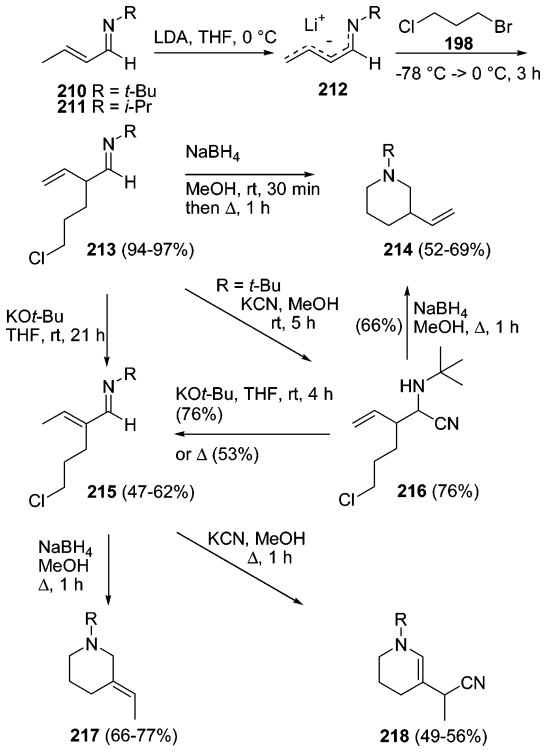


hydrolysis and conversion to the corresponding *N*-ethylaldimine **208**, cyclization to **209** was accomplished with lithium aluminum hydride, giving a 1:1 mixture of two diastereoisomers. In the same way the 1-*tert*-butyl analogue of stenusine was also synthesized.[85] An enantioselective synthesis of various stenusine enantiomers was performed via SAMP-hydrazone chemistry (vide infra).

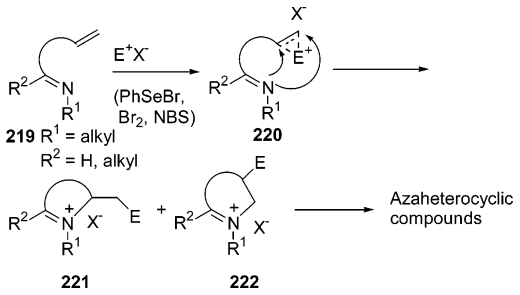
The preparation of δ-chloroimines can also be accomplished from α,β-unsaturated imines.[86] Reaction of conjugated 1-azaenolates **212** derived from *N*-(2-buten-1-ylidene)alkylamines **210** and **211** with **198** yielded the β,γ-unsaturated imines **213** (Scheme 42). Reductive cyclization gave 1-alkyl-3-vinylpiperidines **214**, which were also accessible via the α-aminonitrile **216**. The conjugated enimines **215** were prepared by basic treatment of the β,γ-unsaturated imines **213** or the α-aminonitrile **216**, and converted into 3-ethylidenepiperidines **217** and 5-(1-cyanoethyl)-1,2,3,4-tetrahydropyridines **218**, the latter being formed by a Michael addition of cyanide and subsequent ring closure (MIRC reaction). As such this methodology is very suitable for the synthesis of a whole variety of piperidine derivatives.

An important method to synthesize azaheterocycles starting from imines concerns electrophile-induced cyclization reactions. Olefinic primary or secondary amines do not cyclize readily, while *N*-protected olefinic primary amines do. Imines can be used as a protective group for the amino function in the electrophile-induced cyclization of substrates **219** with electrophilic reagents such as phenylselenenyl bro-

Scheme 42



Scheme 43

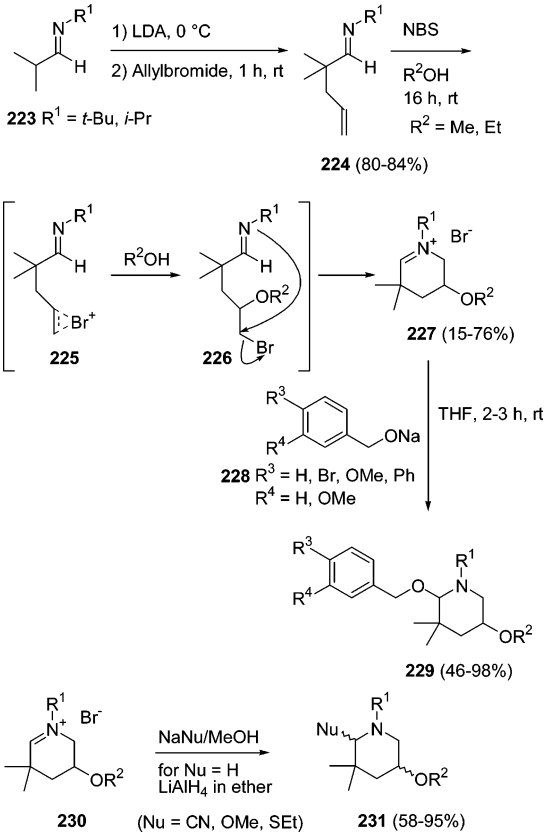


mide, bromine, or *N*-bromosuccinimide (Scheme 43).[87−92]

The intermediate iminium salts **221** and/or **222** react with nucleophiles (H^-, RO^-, CN^-), resulting in different types of azaheterocycles such as pyrrolidines and piperidines, depending on the reaction conditions used in the electrophile-induced cyclization step. The starting alkenylimines **219** are prepared via alkylation of the corresponding 1-azaallylic anion, generated from the imine after deprotonation with LDA, with the corresponding allyl halide. For instance, the alkylation of *N*-(isobutylidene)amines **223** with allyl bromide after deprotonation with LDA at 0 °C afforded the required 4-alkenylimines **224** (Scheme 44). Reaction of imines **224** with *N*-bromosuccinimide in an alcoholic solvent gave rise to the formation of the iminium salts **227**, which reacted with a range of benzyl alcoholates **228** in the corresponding alcohol to give the 2,5-dialkoxypiperidines **229**.[91] The use of other nucleophiles such as lithium aluminum hydride, sodium cyanide, sodium ethylthiolate, and sodium methoxide gave rise to other 2-functionalized 5-alkoxypiperidines **231**.

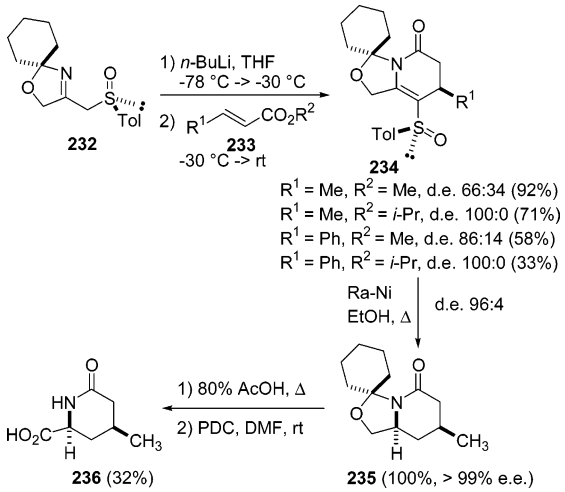
Lithiation of the (3-oxazolin-4-yl)methyl sulfoxide **232** using *n*-BuLi and addition of a suitable Michael

Scheme 44



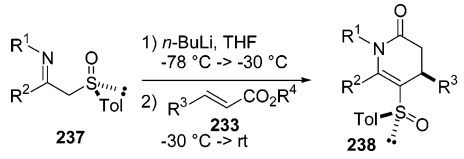
acceptor, **233**, to the lithium azaenolate (Hua's reaction) afforded the chiral 4-substituted 5,6-dehydropiperidin-2-one **234** (Scheme 45). Removal of the chiral auxiliary and reduction of the enamine function with Raney nickel, deprotection of the *N*,*O*-acetal moiety, and final oxidation afforded L-(2*S*,4*S*)-4-methyl-6-oxopipecolic acid (**236**).[93,94]

Scheme 45



Generalization of the Hua methodology in the synthesis of 4-substituted 5-(*p*-tolylsulfinyl)-5,6-dehydropiperidin-2-ones **238** was accomplished by the addition of azaenolates derived from different α-sulfinylketimines **237** to (*E*)-α,*β*-unsaturated esters **233** (Scheme 46).[94]

Scheme 46

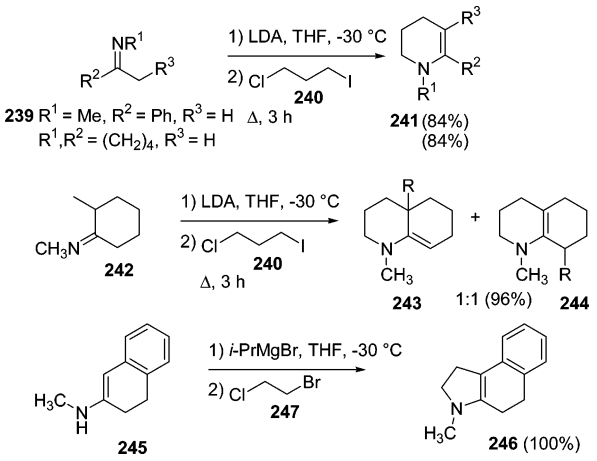


R^1 = 4-MeOC$_6$H$_4$, R^2 = Ph, R^3 = Me, R^4 = Me d.e. 80:20 (58%)
R^1 = 4-MeOC$_6$H$_4$, R^2 = Ph, R^3 = Me, R^4 = *i*-Pr d.e. 100:0 (46%)
R^1 = 4-MeOC$_6$H$_4$, R^2 = Ph, R^3 = Ph, R^4 = *i*-Pr d.e. 100:0 (68%)
R^1 = CH_2Ph, R^2 = H, R^3 = Me, R^4 = Me d.e. 86:14 (40%)
R^1 = CH_2Ph, R^2 = H, R^3 = Me, R^4 = *i*-Pr d.e. 100:0 (69%)
R^1 = CH_2Ph, R^2 = *n*-Pr, R^3 = Me, R^4 = Me d.e. 88:12 (62%)
R^1 = CH_2Ph, R^2 = *n*-Pr, R^3 = Me, R^4 = *i*-Pr d.e. 100:0 (50%)
R^1 = CH_2Ph, R^2 = *n*-Pr, R^3 = Ph, R^4 = *i*-Pr d.e. 100:0 (36%)

2.7.5. Synthesis of Tetrahydropyridines and Pyridines

Evans developed a methodology for the synthesis of cyclic enamines based on the reaction of diverse imine anions with dielectrophiles.[95] Deprotonation of the imines **239** and reaction with α,ω-dihaloalkanes **240**, followed by heating, resulted in the cyclic enamines **241** (Scheme 47). In the case of the *N*-

Scheme 47

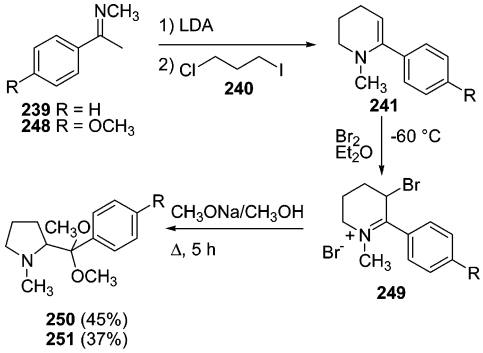


methylimine **242**, derived from 2-methylcyclohexanone, no regioselectivity was observed in the first alkylation. In the case of the tetrahydropyridine derivatives, only 1 equiv of base was needed, whereas for the pyrrolines **246** 2 equiv of base was necessary. This is due to the relatively slow intermolecular alkylation step. The cyclic enamines **241** could be brominated to yield the α-brominated iminium salts **249**, which underwent ring contraction under the action of sodium methoxide in methanol, affording the α-aminoacetals **250** and **251** (Scheme 48).[96]

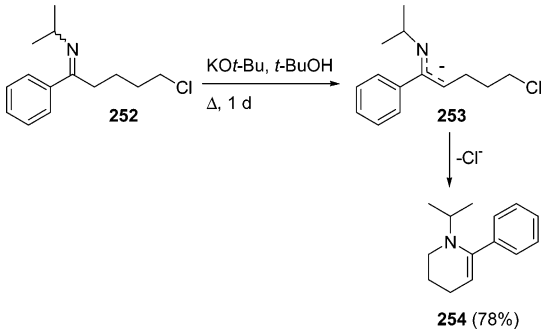
δ-Chloroketimines, carrying no substituent at the α-position, such as *N*-(1-phenyl-5-chloro-1-pentylidene)isopropylamine (**252**), were converted into 1,2,3,4-tetrahydropyridines **254** by treatment with potassium *tert*-butoxide in *tert*-butanol under reflux (Scheme 49).[44]

Using the same methodology, the synthesis of 1,5-disubstituted 1,2,3,4-tetrahydropyridines is also possible.[97] This involves alkylation of aldimines **255**−**257** with 1-bromo-3-chloropropane **198**, followed by cyclization upon treatment with sodium isopropoxide in 2-propanol, a base which avoids side reactions such as nucleophilic substitution and 1,2-dehydrochlori-

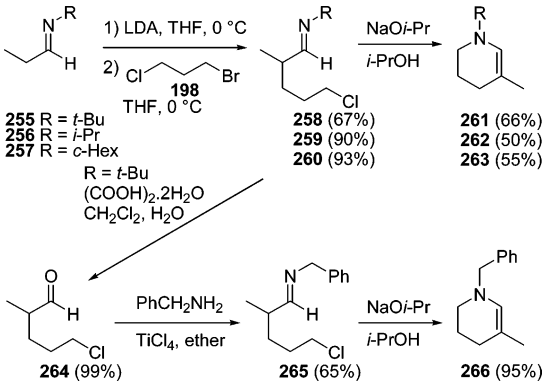
Scheme 48



Scheme 49



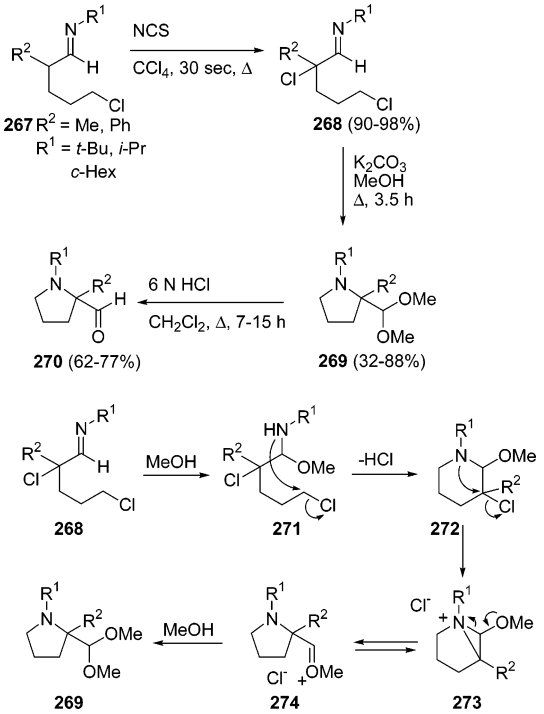
Scheme 50



nation (Scheme 50). Due to the competing reactivity of the benzylic methylene function, *N*-benzylimines cannot be conveniently and selectively alkylated for this purpose. Adjusting the pathway by performing the alkylation with *N*-(1-propylidene)-*tert*-butylamine (**255**), hydrolysis to the δ-chloroaldehyde **264** and imination with benzylamine yielded the appropriate derivative **265**, which could be further cyclized with sodium isopropoxide in 2-propanol.

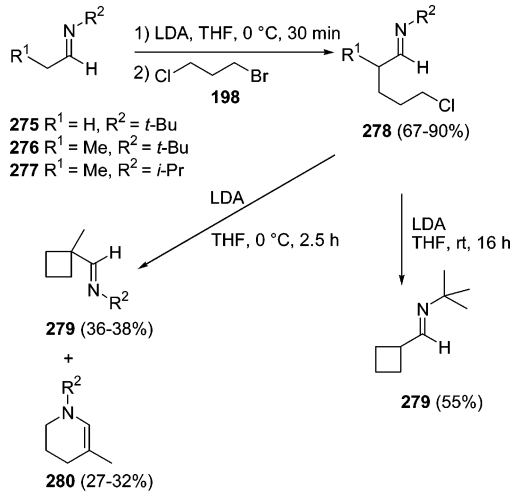
Treatment of these δ-chloroimines **267** with *N*-chlorosuccinimide in carbon tetrachloride resulted in α-halogenation. Further reaction with potassium carbonate in methanol under reflux led to 1,2-dialkyl-2-(1,1-dimethoxymethyl)pyrrolidines **269** (Scheme 51).[98] This rearrangement can be explained by addition of methanol across the imino function, which led to piperidine **272** via intramolecular substitution of the ω-chloro atom. This 3-chloro-2-methoxypiperidine **272** rearranged by displacement of the chloro atom by the nitrogen lone pair with formation of the bicyclic piperidinium salt **273**, which suffered ring opening by reaction with methanol to give the ring contraction product **269**.

Scheme 51



Contrary to ϵ-chloroaldimines, φ-chloroaldimines and α-unsubstituted δ-chloroaldimines, which upon treatment with LDA give carbon alkylation, forming the corresponding cyclopentane-, cyclohexane-, and cyclobutanecarboxaldehydes after hydrolysis, the introduction of an extra α-methyl substituent in the δ-chloroaldimines **276** and **277** led after deprotonation with LDA to a mixture of cyclobutanecarboxaldimines **279** and the cyclic enamines **280** (Scheme 52).[99]

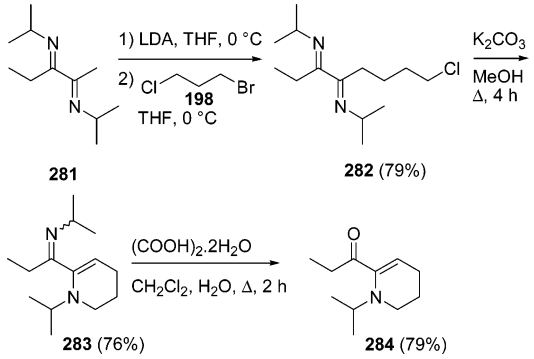
Scheme 52



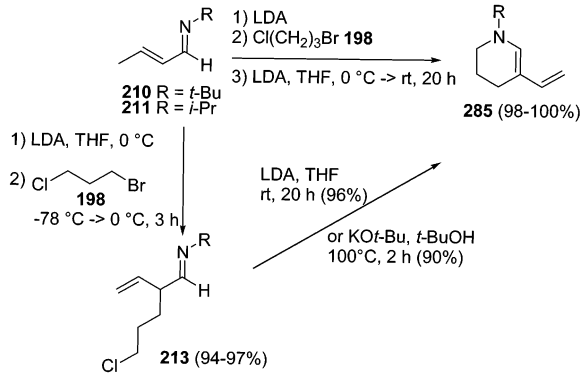
Introduction of the 3-chloropropyl functionality in the α-diimine **281** and base-induced cyclization yielded 6-propionyl-1-isopropyl-1,2,3,4-tetrahydropyridine (**284**) upon acidic hydrolysis (Scheme 53).[100]

Cyclization of the earlier mentioned δ-chloroaldimines **213** was also possible by reaction with bases, affording the corresponding cyclic enamines **285** (Scheme 54).[86] The one-pot alkylation of enimines

Scheme 53



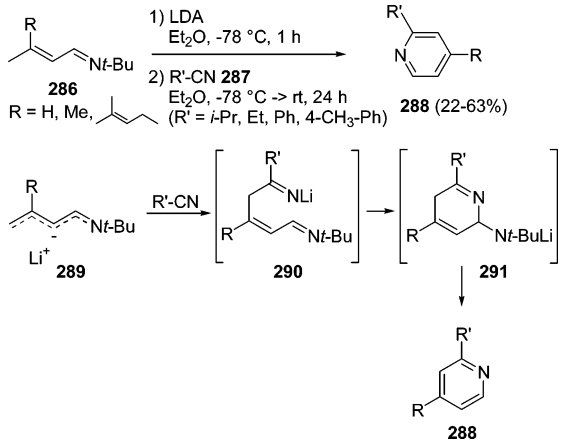
Scheme 54



210 and **211** with **198** and ring closure with LDA led to 5-ethenyl-1,2,3,4-tetrahydropyridines **285**, which can also be obtained by treatment of the δ-chloroaldimines **213** with LDA or potassium *tert*-butoxide. The aminodienes **285** proved to be suitable dienes for Diels−Alder reactions with *N*-phenylmaleimide, furnishing octahydro-1*H*-pyrrolo[3,4-*h*]quinoline-1,3-diones.[86]

Alkylpyridines **288** were prepared by the reaction of the lithiated α,β-unsaturated aldimines **286** with nitriles **287** (Scheme 55).[101] The pyridine was formed

Scheme 55

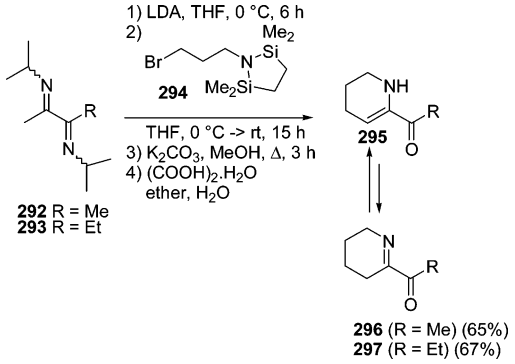


by addition of the lithiated aldimine **286** to the nitrile **287**, followed by intramolecular cyclization of the resulting diimine **290**, as in the synthesis of pyrroles **142** (vide supra),[71] and elimination of the *tert*-butylamino group.

The earlier mentioned strategy for the synthesis of **85** (vide supra) also led to the Maillard flavor

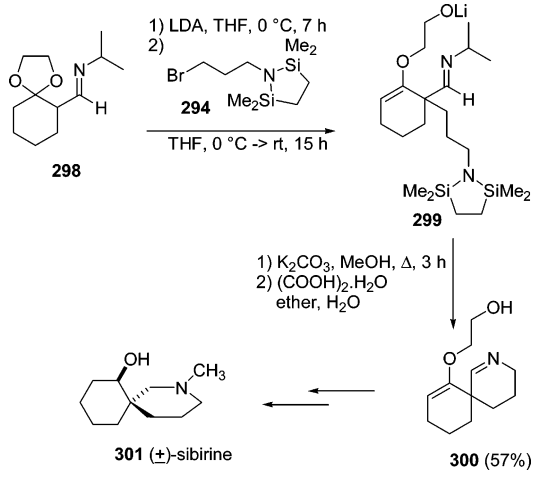
compounds 6-acetyl- and 6-propionyl-1,2,3,4-tetrahydropyridine **295**, which occur in tautomeric equilibrium with α-keto imines **296** and **297** (Scheme 56).[60] In this case, stabase-protected *ω*-bromopropylamine **294** was used as alkylating agent.

Scheme 56

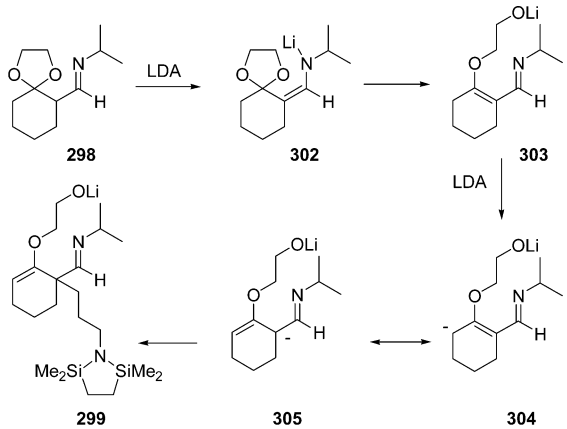


An application of this stabase-mediated alkylation and cyclization process is the preparation of the spirocyclic alkaloid (±)-sibirine (**301**).[102] α-Deprotonation of imine **298** with excess LDA and subsequent alkylation with 1-(3-bromopropyl)-2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane (**294**) afforded the aldimine **299** (Scheme 57). In this case a large excess of LDA was necessary because an unexpected additional acetal ring opening occurred (Scheme 58). Whereas acetal functions are normally stable under basic conditions, the acetal moiety proved here to be reactive under the conditions forming the 1-azaallylic anion. After the initial deprotonation of the imine **298** and formation of the intermediate **303**, further deprotonation occurred at the *γ*-position, and α-alkylation by the stabase electrophile **294** furnished the aldimine **299**. Deprotection of the amine moiety by methanolysis afforded the cyclic imine **300** after spontaneous cyclization. Via several functional group transformations compound **300** was converted stereoselectively to (±)-sibirine **301**.[102]

Scheme 57

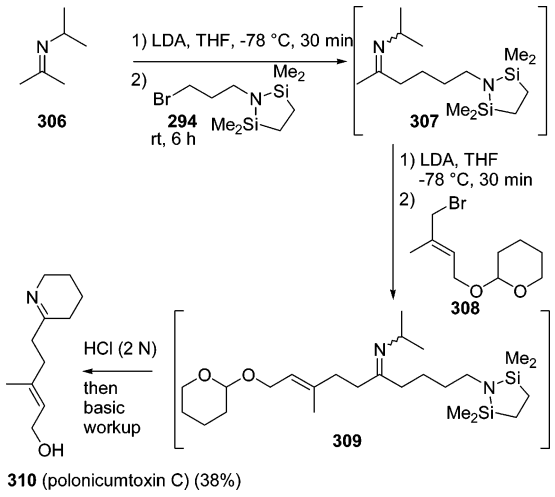


Scheme 58



Via the same C_3-stabase protocol the tetrahydropyridine alkaloid polonicumtoxin C (**310**) was synthesized in a one-pot procedure.[103] Deprotonation of *N*-isopropylideneisopropylamine (**306**) with LDA and treatment with *N*,*N*-diprotected *γ*-bromopropylamine **294** gave the intermediate *δ*-aminated ketimine **307** (Scheme 59). Further deprotonation of the α′-methyl group with LDA and alkylation with the (*E*)-allyl bromide **308** afforded the intermediate functionalized ketimine **309**, which, after hydrolytic removal of the three protecting groups in one step, transiminated to **310**.[103]

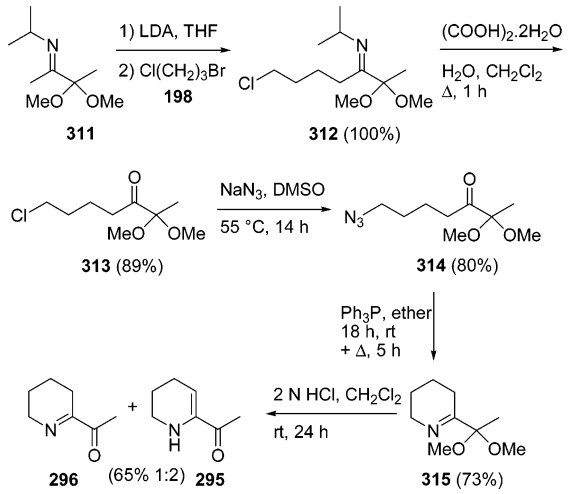
Scheme 59



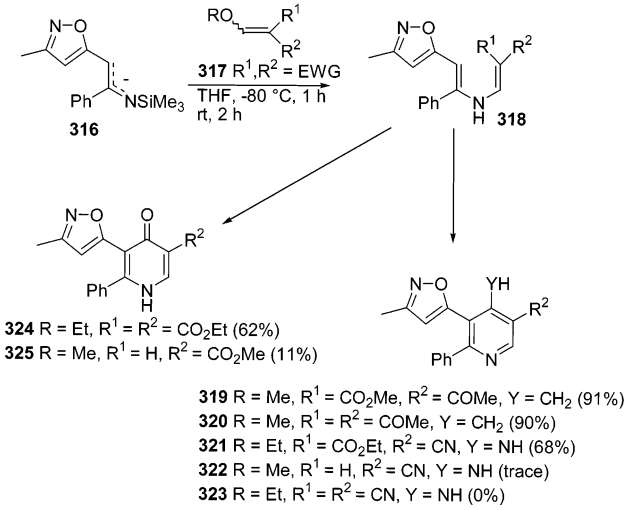
An alternative synthesis of the Maillard flavor compound 6-acetyl-1,2,3,4-tetrahydropyridine **295** is accomplished through alkylation of the α,α-dialkoxyimines **311** with 1,3-dihalopropanes **198**, affording the *δ*-haloimines **312** (Scheme 60). Selective hydrolysis of the imino function of compound **312** cleanly led to α-keto acetal **313**, which was azidated to give azide **314**. Final intramolecular aza-Wittig reaction, giving the acetal **315**, and acid hydrolysis yielded the bread flavor component **295**, in tautomeric equilibrium with its imino isomer **296**.[104]

Reaction of the *N*-silyl-1-azaallyl anion **316** with electron-poor alkoxyalkenes **317** (R^1 and/or R^2 are electron-withdrawing groups) afforded the corresponding 4-methylpyridines **319** and **320**, 4-aminopyridines **321**−**323**, and 4-pyridones **324** and **325** (Scheme 61).[105] This reaction can be explained by an initial attack of the nitrogen atom of the 1-azaallyl anion **316** to the electrophilic 3-positioned carbon atom of the alkoxyalkene **317** to give the intermediate *N*-adducts **318** after desilylation and dealkoxylation. Further cyclization by reaction of the enamine

Scheme 60



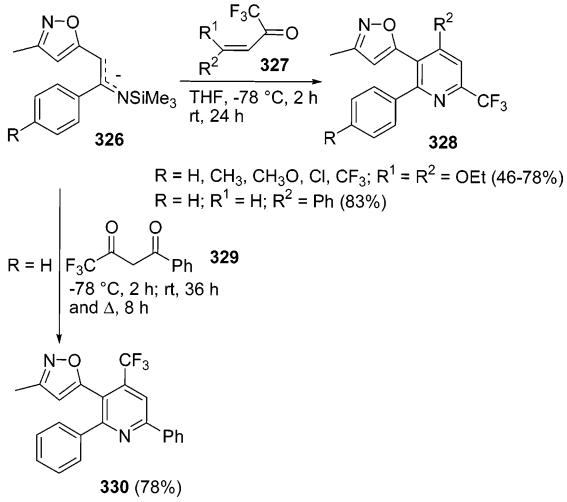
Scheme 61



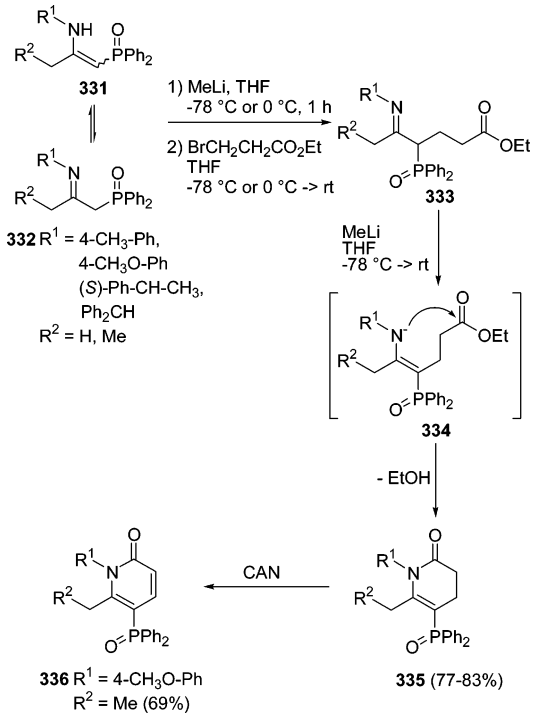
nucleophilic carbon with the keto function and cyano group, respectively, gave the corresponding 4-methylpyridines **319** and **320** and 4-aminopyridines **321**–**323**. Cyclization of the *N*-adduct intermediates **318** via reaction with the ester function resulted in the synthesis of the corresponding 4-pyridones **324** and **325**. However, the reactions to give the derivatives **322** and **323** failed as only the corresponding *N*-adduct intermediates **318** were formed.

The *N*-silyl-1-azaallyl anion **326** also reacted with trifluoroacetylketene diethyl ketal (**327a**) and (*E*)-1,1,1-trifluoro-4-phenylbut-3-en-2-one (**327b**) to afford the corresponding 2-(trifluoromethyl)pyridine derivatives **328** and not the regioisomeric 4-(trifluoromethyl)pyridines (Scheme 62).[106] Apparently in these cases the 1-azaallylic anion **326** added via 1,2-addition of the nitrogen to the active carbonyl of the electrophile **327**, followed by ring closure via intramolecular Michael addition. This regiochemistry was proven by study of experimental NMR data with data from the literature and also from the synthesized 4-(trifluoromethyl)pyridine **330**, formed by reaction of **326** and 4,4,4-trifluoro-1-phenylbutane-1,3-dione (**329**).[106] Reaction of the *N*-silyl-1-azaallyl anion **326** and 1,3-diphenyl-2-propen-1-one also afforded analogous 2,3,4,6-tetrasubstituted pyridines.[107]

Scheme 62



Scheme 63

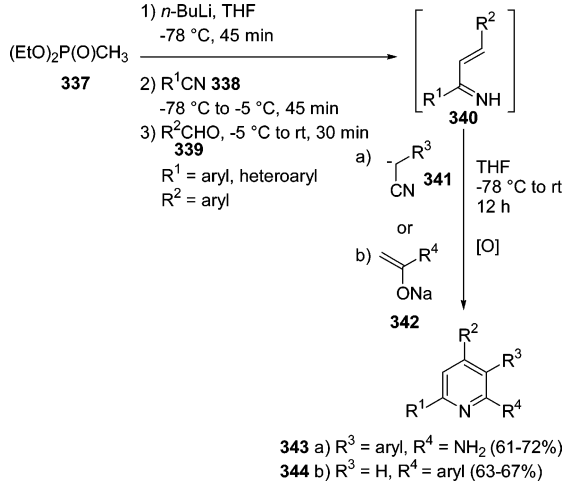


Alkylation of phosphane oxides **331**/**332** (vide supra) with ethyl bromopropionate after treatment with methyllithium afforded the α,α-difunctionalized imines **333** (Scheme 63).[75] These imines were cyclocondensed with methyllithium under the loss of ethanol, to give the 5-phosphinylated 3,4-dihydropyridin-2-ones **335**. Further oxidation of the 3,4-dihydropyridin-2-one **335** was possible with cerium(IV) ammonium nitrate in acetonitrile, giving 2-pyridone **336**. The use of other biselectrophiles, such as isocyanate, isothiocyanates, ethyl chloroformate, and diethyl azodicarboxylate, for the alkylation of functionalized phosphane oxides or enaminophosphonates has led to diverse types of heterocyclic compounds, i.e., 4-aminoquinolines,[108–110] pyrimidine-2,4-diones,[111] and imidazol-2-ones.[112]

The α,*β*-unsaturated imines **340**, prepared in a one-pot procedure by subsequent treatment of diethyl lithiomethylphosphonate (**337**) with nitriles **338**,

followed by addition of carbonyl compounds **339**, were reacted with anions of aryl-substituted acetonitriles **341** and sodium enolates of methyl aryl ketones **342**, yielding the corresponding 2,3,4,6-tetrasubstituted and 2,4,6-trisubstituted pyridines **343** and **344** (Scheme 64).[113] The mechanism of the reaction was

Scheme 64

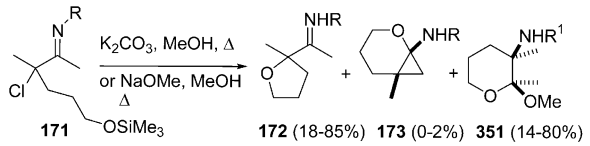


explained as an initial attack of the α,β-unsaturated imine **340** by the CH-nucleophiles **341** and **342**, giving the intermediate 1-azaallylic anions **345** and **348**, in equilibrium with stabilized anions **346** and **349** (Scheme 65). The cyclization of the 1-azaallylic anions **345** and **348** resulted in the formation of the intermediate tetrahydropyridines **347** and **350**, followed by oxidation into pyridines **343** and **344**.

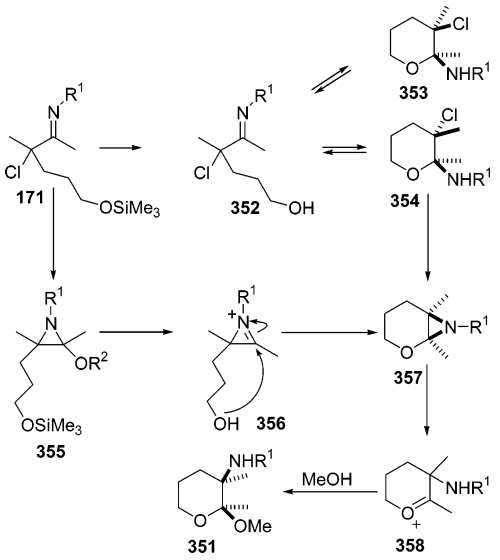
2.7.6. Synthesis of Tetrahydropyrans

Reaction of the δ-trimethylsilyloxy-α-chloroketimines **171** (vide supra) with methanol under reflux in the presence of bases such as sodium methoxide or potassium carbonate gave *cis*-3-(*N*-alkylamino)-2,3-dimethyl-2-methoxytetrahydropyran derivatives **351**, as well as tetrahydrofurans **172** (Scheme 66).[78] This conversion into 2,3-disubstituted tetrahydropyrans **351** bears similarity with the formation of *cis*-2-alkoxy-3-aminotetrahydrofurans **177** from γ-trimethylsilyloxy-α-chloroketimines **175**, where no competitive intramolecular nucleophilic substitution occurred because of ring strain (vide supra).[79] Again the mechanism was explained via two equally plausible pathways. The first mechanistic route consists of an oxygen desilylation and addition of the alcohol function across the imino bond to give tetrahydropyranyl ethers **354**, whereas the second proposal starts with the attack of methanol (or methoxide) across the imino bond with subsequent ring closure to α-alkoxyaziridines **355** (Scheme 67). Both mechanisms lead to the same bicyclic aziridine **357**, which suffers ring opening to the oxonium ion **358**, which undergoes a stereospecific attack of the alcohol to provide *cis*-3-alkylamino-2-methoxytetrahydropyrans **351**.[78]

Scheme 66



Scheme 67

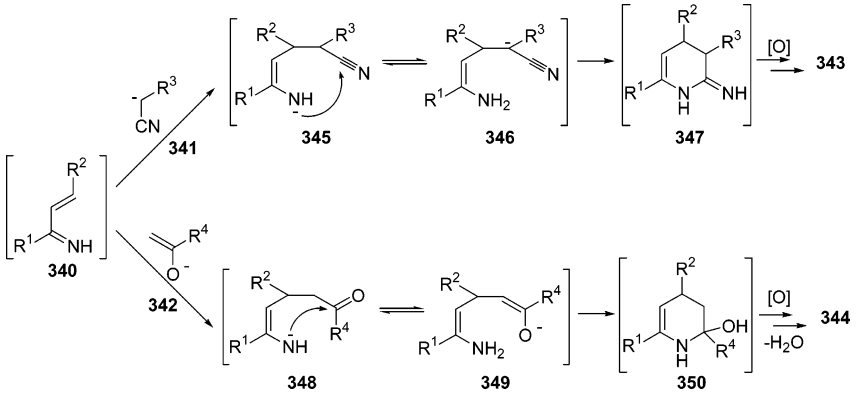


2.8. Synthesis of Higher Membered Heterocyclic Compounds

2.8.1. Synthesis of Azepines, Oxazocines, and Oxazonines

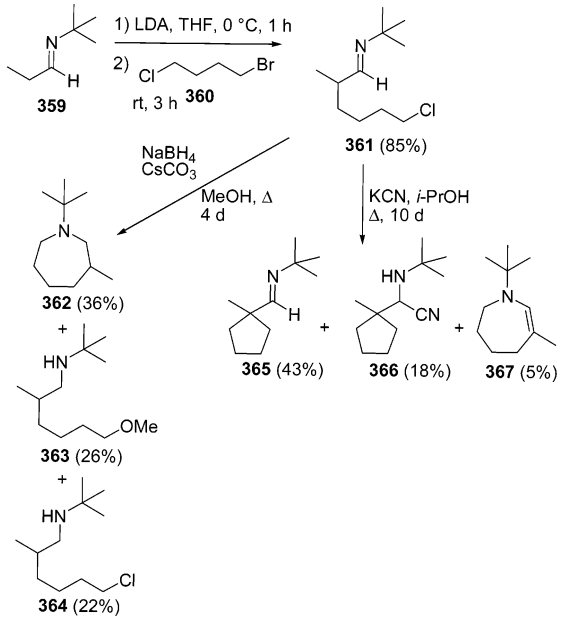
In analogy with the reaction of δ-chloroaldimines **199** for the synthesis of piperidines **200**−**202** (vide supra, Scheme 40), the formation of azepine deriva-

Scheme 65



tives from ϵ-chloroaldimines is also described.[114] The ϵ-chloroaldimine **361** is prepared by alkylation of aldimine **359** with 1-bromo-4-chlorobutane **360**,[99] and cyclized by reaction with nucleophiles such as sodium borohydride and potassium cyanide (Scheme 68).

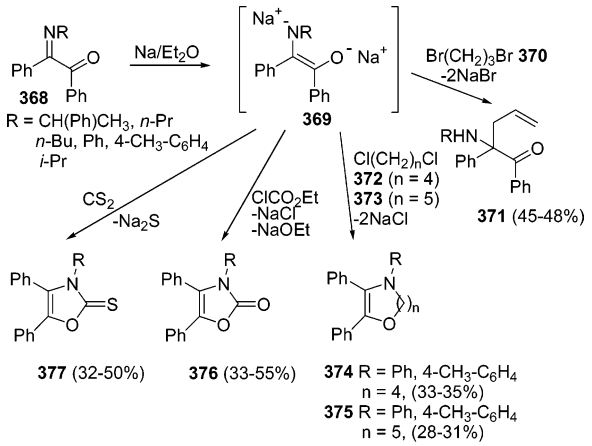
Scheme 68



This resulted in the corresponding azepine derivatives **362** and **367** in only moderate yield due to side reactions, including nucleophilic substitution and intramolecular carbon alkylation, and also incomplete reactions. It seems that such azepine derivatives from ϵ-haloimines are rather difficult to access, even when cesium carbonate is used as the base.

The electron transfer from sodium to 2-imino-1,2-diphenylethanone **368** resulted in the dianion **369**, which was reacted with a biselectrophile to yield five-, eight-, and nine-membered heterocycles each containing one oxygen and one nitrogen atom (Scheme 69).[115] Treatment of the dianion with carbon disulfide

Scheme 69

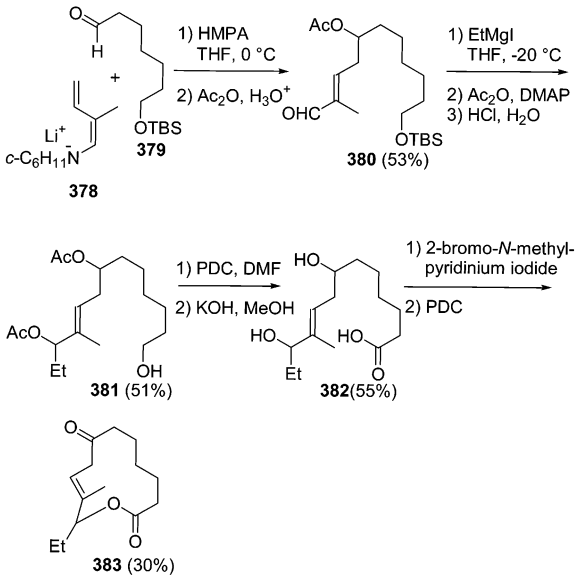


or ethyl chloroformate gave the corresponding 4-oxazoline-2-thione **377** and 4-oxazolin-2-one **376**. Addition of 1,4-dichlorobutane (**372**) to the dianions **369** resulted in 2,3,4-triaryl-5,6,7,8-tetrahydro-4*H*-1,4-oxazocines **374**, while 1,5-dichloropentane (**373**) gave 2,3,4-triaryl-4,5,6,7,8,9-hexahydro-1,4-oxazonines **375**. When the dianions **369** from imino ketones **368** were similarly treated with 1,3-dibromopropane (**370**), the expected 1,4-oxazepines were not obtained and 2-anilino-1,2-diphenyl-4-penten-1-ones **371** were formed.[115]

2.8.2. Synthesis of Macrocyclic Compounds

The reaction of the conjugated *N*-cyclohexyl-1-azaallylic anion **378** with aldehyde **379** gave alkylation at the γ-carbon (Scheme 70). After several functional group manipulations the hydroxy acid **382** was formed, which was lactonized to **383** with 2-bromo-*N*-methylpyridinium iodide followed by oxidation with pyridinium dichromate.[116]

Scheme 70



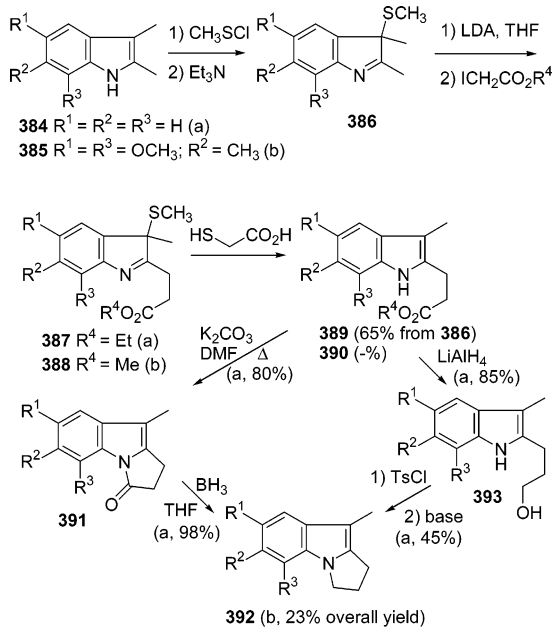
2.9. Synthesis of Bicyclic and Polycyclic Compounds

2.9.1. Synthesis of Bicyclic and Polycyclic Compounds with an Annelated N-Containing Five-Membered Ring

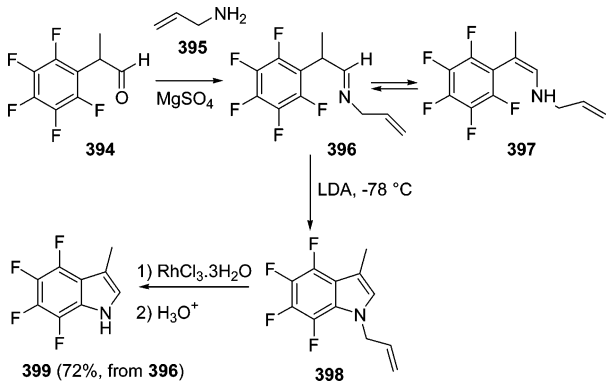
Deprotonation of carbocyclic enamines **245** and reaction with 1-bromo-2-chloroethane (**247**) resulted in the tricyclic enamines **246** (vide supra, Scheme 47).[95] Deprotonation of 2-methyl-3-(methylthio)indolenines **386** with LDA and reaction with the appropriately substituted two-carbon unit resulted in the synthesis of the pyrrolo[1,2-*a*]indoles **392** (Scheme 71).[117] After the alkylation with an alkyl iodoacetate, reduction with mercaptoacetic acid, followed by cyclization and reduction of the amide **391**, gave rise to pyrrolo[1,2-*a*]indoles **392**. The latter could also be obtained by reduction of the ester **389** to the alcohol **393** and base-catalyzed cyclization after tosylation.

Reaction of 2-(pentafluorophenyl)propanal (**394**) with allylamine (**395**) followed by cyclization of the equilibrium mixture of imine **396** and enamine **397** using lithium diisopropylamide, and further deprotection of the *N*-allylindole nitrogen with rhodium(III)

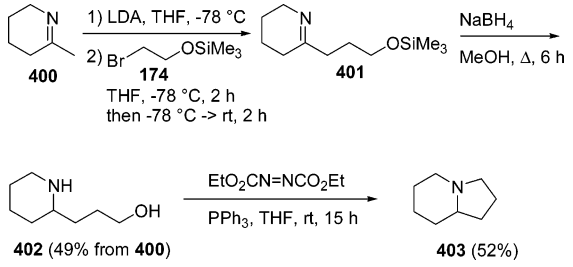
Scheme 71



Scheme 72



Scheme 73

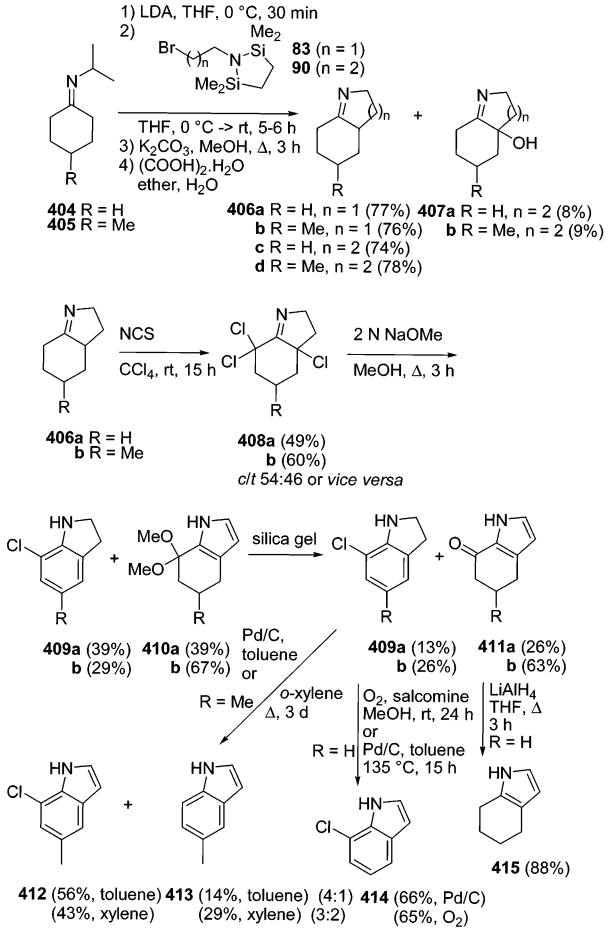


chloride, gave 3-methyl-4,5,6,7-tetrafluoroindole (**399**) (Scheme 72).[118]

The synthesis of indolizidine **403** (*δ*-coniceine) could be achieved by regioselective deprotonation of 6-methyl-2,3,4,5-tetrahydropyridine (**400**) at −78 °C and subsequent reaction with **174** (Scheme 73).[119] Reaction at higher temperature resulted in increasing *N*-alkylation. Further deprotection of the alcohol and reduction of the double bond of the piperideine **401** with sodium borohydride and Mitsunobu cyclization furnished **403**.

Using the same strategy as in the synthesis of **85**, α-alkylation of imines **404** and **405** with *N*,*N*-disilyl-protected *ω*-bromoamines **83** and **90**, deprotection, and transimination gave the hexahydro-2*H*-indoles

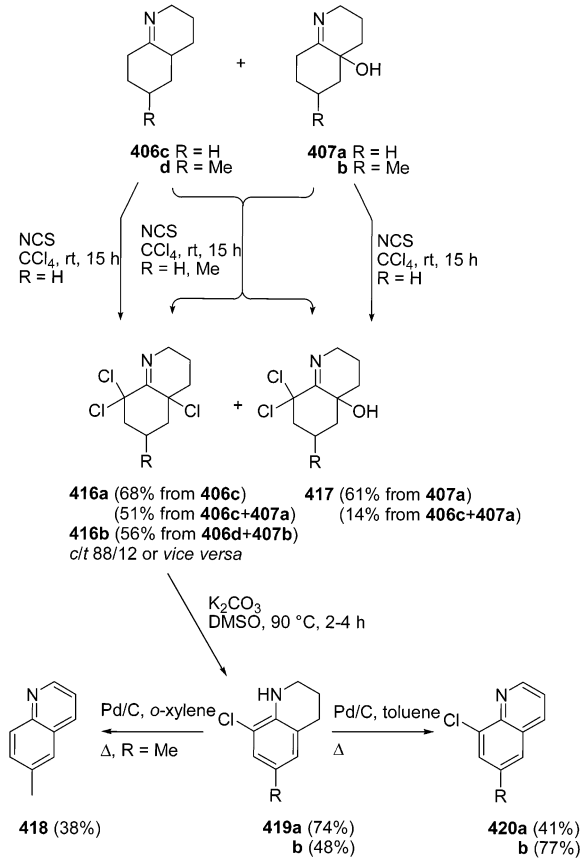
Scheme 74



406a,b and octahydroquinolines **406c,d**, which proved to be very sensitive to oxygen, giving the α-hydroxylated imines **407a,b** (Scheme 74).[120] These bicyclic imines **406a**−**d** could be further converted into indolines, tetrahydroindoles, quinolines, and tetrahydroquinolines. Treatment of bicyclic ketimines **406a** and **406b** with excess *N*-chlorosuccinimide in CCl_4 at room temperature afforded 3a,7,7-trichloro-3,3a,4,5,6,7-hexahydro-2*H*-indoles **408a** and **408b**. These trichlorinated bicyclic imines **408a** and **408b** were converted into indolines **409a** and **409b** and tetrahydroindoles **410a** and **410b** by reaction with base. Reaction of 3a,7,7-trichloro-3,3a,4,5,6,7-hexahydro-2*H*-indoles **408a** with excess sodium methoxide in methanol gave rise to either aromatization of the azaheterocyclic moiety or aromatization of the six-membered carbocyclic part. Under these conditions 7-chloroindolines **409a** and **409b** and 7,7-dimethoxy-4,5,6,7-tetrahydroindoles **410a** and **410b** were formed, the latter being converted to 7-oxo-4,5,6,7-tetrahydroindoles **411a** and **411b** after flash chromatography. 7-Oxo-4,5,6,7-tetrahydroindole (**411a**) was converted into 4,5,6,7-tetrahydroindole (**415**) with lithium aluminum hydride in tetrahydrofuran. Indoline **409a** was oxidized either with oxygen in methanol in the presence of salcomine or with palladium on carbon (10%). Oxidation of **409b** also occurred with formation of the dehalogenated 5-methylindole **413**.[120] In a similar way the 2,3,4,4a,5,6,7,8-octahydroquinolines **406c** and **406d** afforded, after trichlorination, reaction with excess

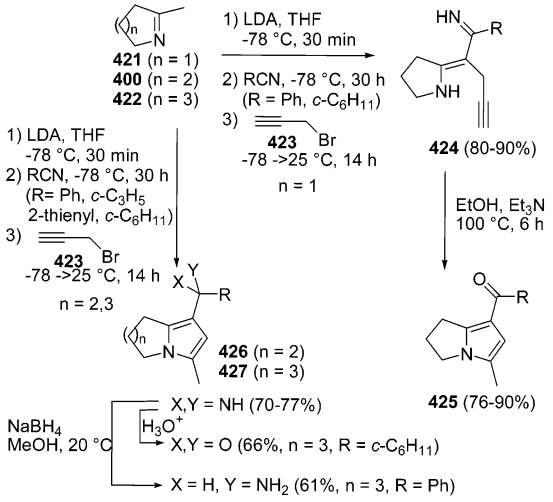
potassium carbonate in dimethyl sulfoxide at 90 °C, and oxidation with palladium on carbon in toluene, the 8-chloroquinolines **420a** and **420b** and the dechlorinated quinoline **418** upon oxidation under reflux in *o*-xylene (Scheme 75).

Scheme 75



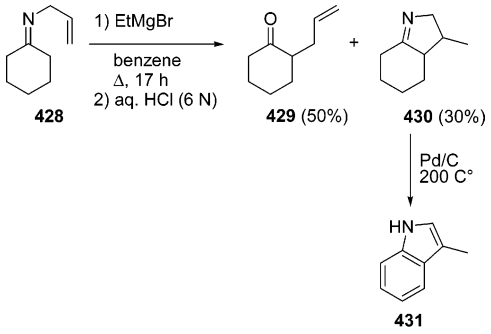
A short synthesis of *N*-bridgehead pyrroles **425**−**427** was accomplished by addition of the 1-azaallyl anion derived from cyclic imines **400** and **421** and **422** to nitriles, followed by regioselective trapping of the resulting diazapentadienyl anion with prop-2-ynyl bromide (**423**) and cycloamination (Scheme 76).[121] In this way indolizidines **426**, azaazulenes **427**, and pyrrolizidines **425** were synthesized in good yield.

Scheme 76



When ethylmagnesium bromide was treated with imine **428**, formed from cyclohexanone and allylamine, in benzene under reflux, 2-allylcyclohexanone (**429**) and 3,3a,4,5,6,7-hexahydro-3-methyl-2*H*-indole (**430**) were obtained (Scheme 77).[122] The former

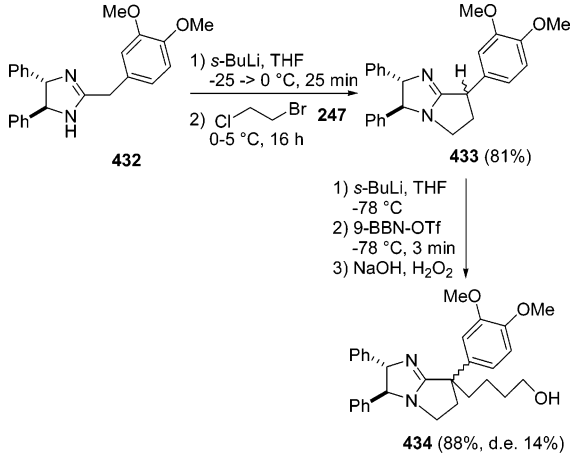
Scheme 77



product resulted from Claisen-type rearrangement after α-deprotonation of the imine **428** with ethylmagnesium bromide, and was isolated in 50% yield. **430** was isolated as a side product (30% yield), and the structure was further proven by aromatization to scatole (**431**).[122]

The bicyclic amidine **433** was obtained by alkylation of the dianion from imidazoline **432** with **247** as biselectrophile (Scheme 78).[123] Alkylation via alkylative ring opening of THF mediated by 9-BBN triflate led to the introduction of a quaternary benzylic center.

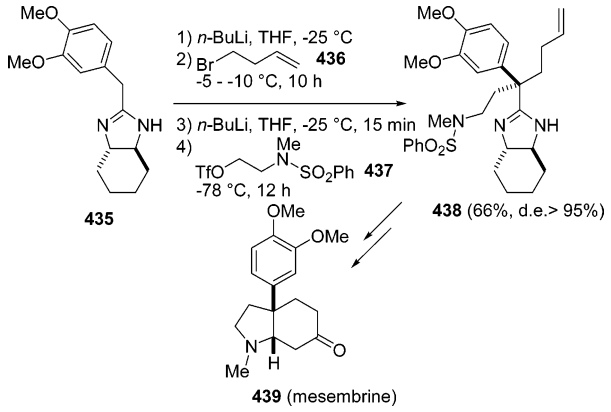
Scheme 78



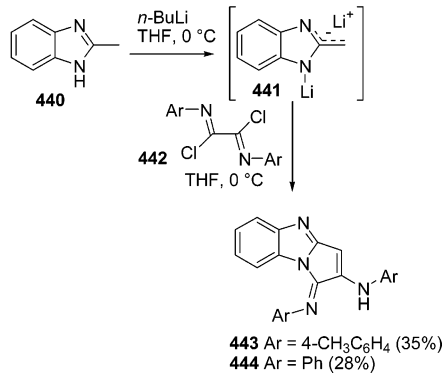
Using the same alkylation method, the synthesis of (−)-mesembrine (**439**) was accomplished.[124] Here the imidazoline **435** was sequentially stereoselectively alkylated with 4-bromo-1-butene (**436**) and the triflate derivative **437** (Scheme 79). After hydrolysis of the imidazoline **438** to the corresponding aldehyde, conversion of the terminal olefin to the methyl ketone, and intramolecular aldol reaction, **439** was formed by cleavage of the amino protecting group and subsequent cyclization.

Regioselective cyclization of the dilithiated 2-methylbenzimidazole **441** with the 1,2-dielectrophilic diimidoyl dichlorides **442** gave the 1-arylimino-1*H*-pyrrolo[1,2-*a*]benzimidazol-2-amines **443** and **444** (Scheme 80).[125] Similar benzimidazole- and pyridone-

Scheme 79

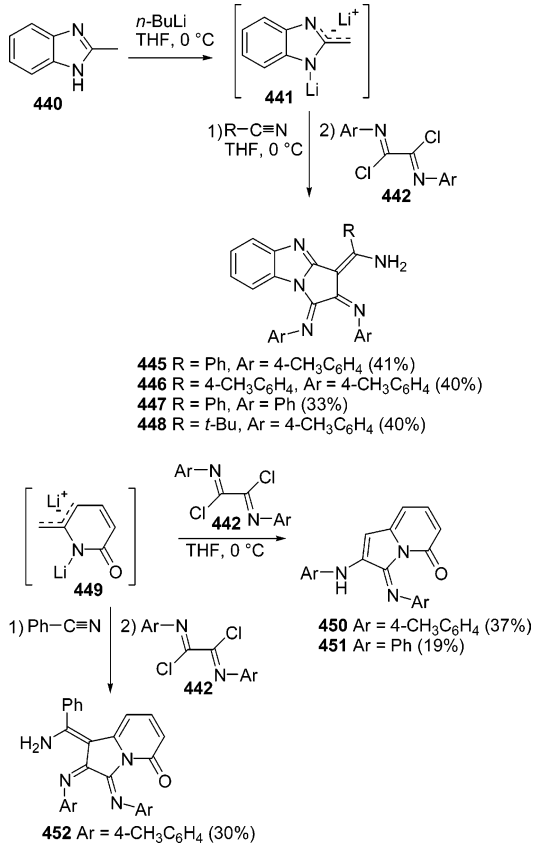


Scheme 80



derived radialene-shaped pyrrole derivatives **445**–**448** and **452** could be obtained by first reaction with nitriles and subsequent cyclization with oxalic acid bis(imidoyl)chlorides **442** (Scheme 81).[126]

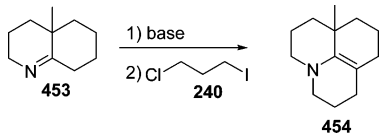
Scheme 81



2.9.2. Synthesis of Bicyclic and Polycyclic Compounds with an Annelated N-Containing Six-Membered Ring

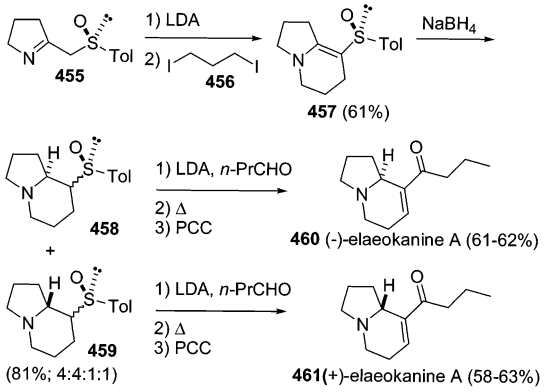
Similar to the reaction of Evans where the cyclic imines **241**, **243**, and **244** were formed by alkylation of imine **239** and **242** with 1-chloro-3-iodopropane (**240**) and cyclization under heating (vide supra, Scheme 47),[95] the alkylation of imine **453** with **240** and further ring closure yielded the tricyclic enamine **454** (Scheme 82).[127]

Scheme 82



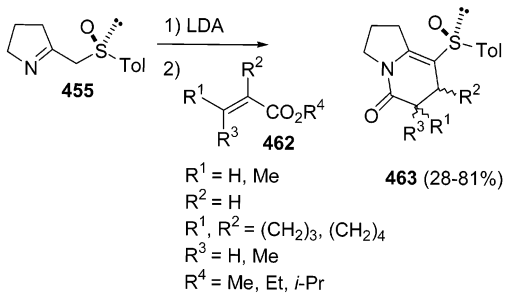
Lithiation of the chiral sulfinylketimine **455** and annulation with 1,3-diiodopropane (**456**) gave the β-enaminosulfoxide **457**, which could be further reduced with sodium borohydride to a mixture of sulfoxides **458** and **459** (Scheme 83). Butyrylation, dehydrosulfinylation, and oxidation yielded elaeokanines A **460** and **461**.[128]

Scheme 83



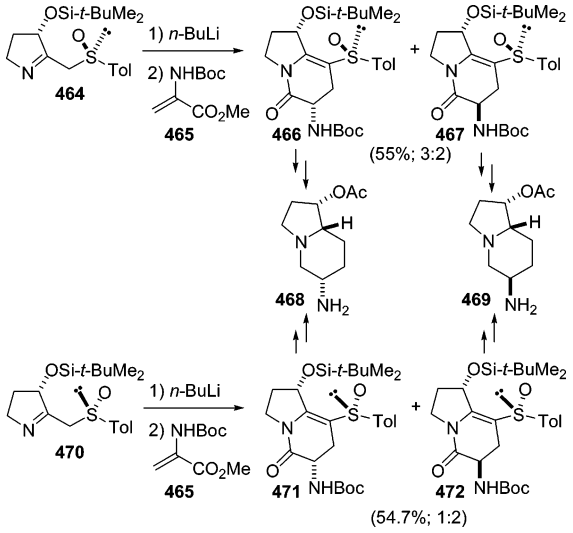
The conjugate addition of the same chiral α-sulfinylketimine anions, derived from **455**, to α,β-unsaturated esters **462** and ring closure led to indolizidinones **463** with moderate to excellent stereoselectivity (Scheme 84).[129] The enamine function of the latter could be reduced with sodium cyanoborohydride and further desulfurized with Raney nickel. This methodology was applied to the synthesis of several yohimbanoids.[130] When using the α′-oxygenated α-sulfinylketimines **464** and **470** for the

Scheme 84



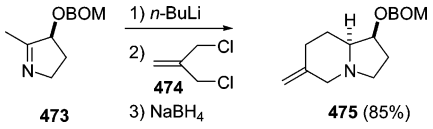
conjugate addition with α-amidoacrylic ester **465**, the aminoindolizidines (−)-slaframine (**468**) and (−)-6-epislaframine (**469**) were synthesized (Scheme 85).[131]

Scheme 85



The methodology developed by Evans for the bisalkylation of imines to introduce a piperidine ring (vide supra) was successfully applied for the synthesis of indolizidines.[132] Bisalkylation of 1-pyrroline **473** with 3-chloro-2-(chloromethyl)-1-propene (**474**) and reduction of the resulting iminium ion with sodium borohydride gave the indolizidine **475** (Scheme 86).

Scheme 86

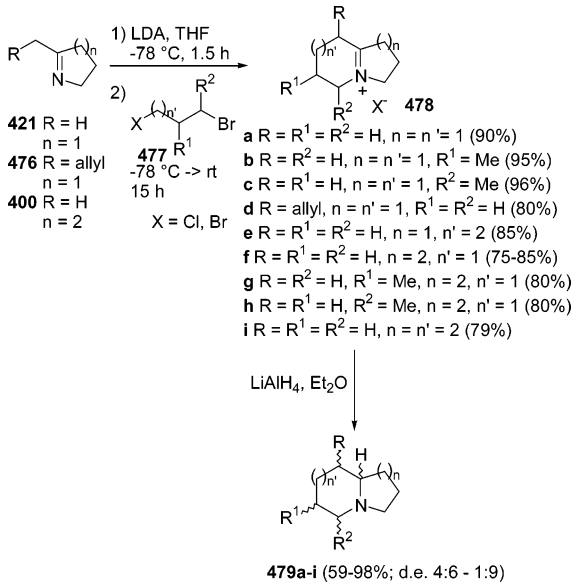


Analogously, the reduction of the intermediate iminium salts **478**, formed by alkylation of 1-pyrrolines **421** and **476** or **400** with 1,3- or 1,4-dihaloalkanes **477**, resulted in the synthesis of indolizidines **479a**−**d**, quinolizidines **479f**−**h**, and some higher homologues, such as 1-azabicyclo[5.4.0]undecane (**479i**) (Scheme 87).[133]

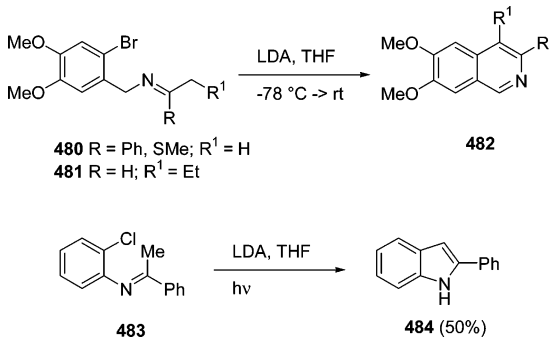
The synthesis of isoquinolines **482** could be achieved by the intramolecular reaction of the 1-azaallylic anion generated from (2-bromobenzyl)ketimines **480** and **481** (Scheme 88).[134] Cyclization of the corresponding *N*-(2-chlorophenyl)imine **483** to 2-phenylindole **484** needed irradiation however.[134]

Treatment of the alcohol **485**, after conversion to the corresponding triflate, with the metalloenamine **486**, derived from *N*-cyclohexylacetaldimine and LDA, followed by hydrolysis under mild acidic conditions gave the aldehyde **487** (Scheme 89). This aldehyde was condensed with (aminomethyl)tri-*n*-butylstannane to give the (2-azaallyl)stannane **488**. The (2-azaallyl)stannane **488** participated in intramolecular cycloadditions with the alkene and was further transformed, yielding the Amaryllidaceae alkaloids (−)-amabiline (**489**) and (−)-augustamine (**490**).[135]

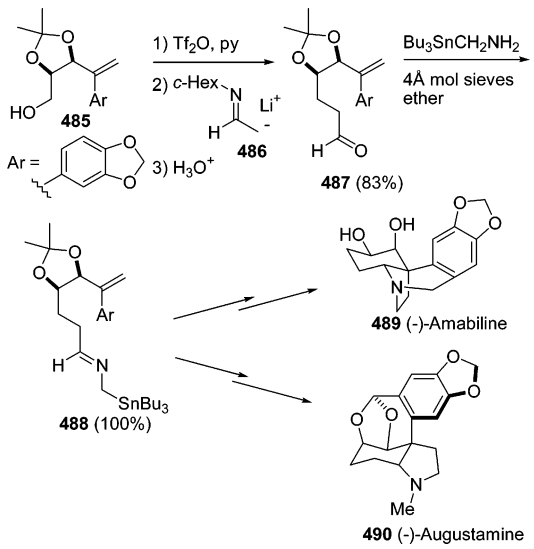
Scheme 87



Scheme 88



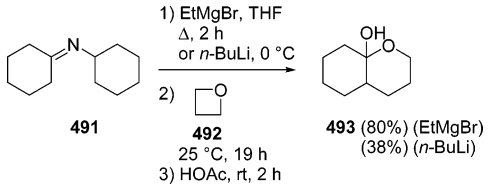
Scheme 89



2.9.3. Synthesis of O-Containing Bicyclic and Polycyclic Compounds

Treatment of oxetane **492** with the bromomagnesium salt of imine **491** derived from cyclohexanone, followed by acetic acid hydrolysis, gave the hemiacetal **493** in 80% yield (Scheme 90). When the lithium salt of imine **491** was used, the yield dropped to 38%.[136] The reactions of the bromomagnesium and

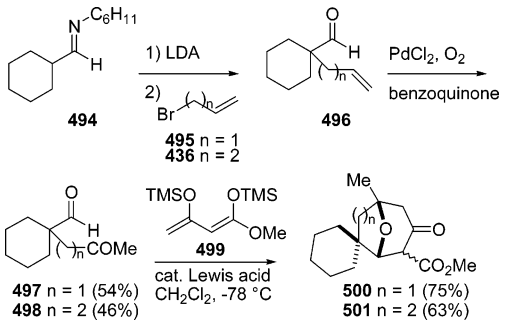
Scheme 90



lithium salts of imine **491** with propylene oxide however produced the corresponding open-chain keto alcohols.

Highly functionalized bicyclic ethers **500** and **501** are accessible by the annulation of 1,4- and 1,5-keto aldehydes **497** and **498** with the conjugated bis-(trimethylsilyl) enol ether **499**, derived from methyl acetoacetate (Scheme 91).[137] The keto aldehydes can

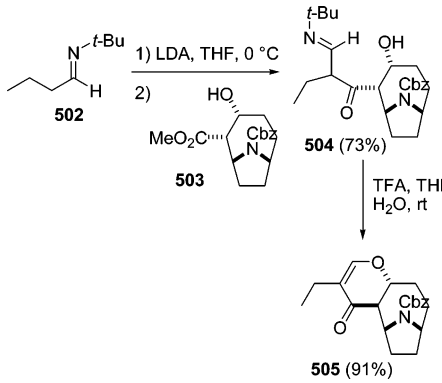
Scheme 91



be prepared by alkylation of cyclohexylimine **494** with allyl bromide (**495**) or 4-bromo-1-butene (**436**), followed by Wacker oxidation, utilizing oxygen in the presence of palladium(II) chloride and benzoquinone.

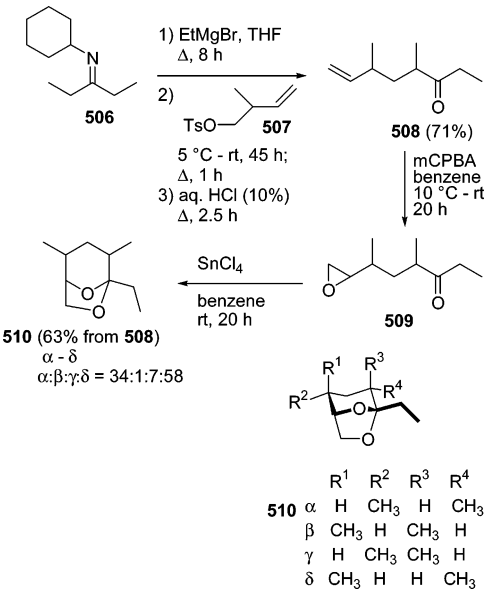
Condensation of β-hydroxy ester **503** with the lithium anion of *N*-*tert*-butylbutyraldimine (**502**) afforded the keto imine **504** (Scheme 92). Acid treatment resulted in cyclization and concomitant epimerization to the Cbz-protected pinnamine **505**.[138]

Scheme 92



Alkylation of the magnesium bromide salt of ketimine **506** with the tosylate **507** in THF afforded, after acid hydrolysis, the keto olefin **508** (Scheme 93).[139] The latter is the key intermediate in the synthesis of α-multistriatin (**510**), a component of the aggregation pheromone of the European elm bark beetle, *Scolytus multistriatus*. Epoxidation of 4,6-dimethyl-7-octen-3-one (**508**) with *m*-chloroperoxybenzoic acid, followed by intramolecular acetalization

Scheme 93

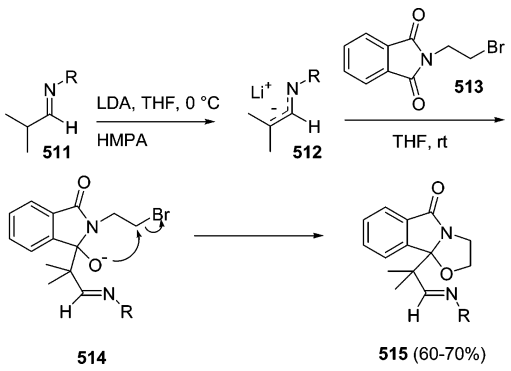


with $SnCl_4$, gave acetals **510** in good yield, with 34% of the biologically active 1α isomer **510**.[139]

2.9.4. Synthesis of N,O-Containing Bicyclic and Polycyclic Compounds

Instead of leading to the expected substitution reaction, the addition of *N*-(2-bromoethyl)phthalimide (**513**) to the 1-azaallylic carbanion **512** resulted in the formation of tricyclic heterocycles **515** (Scheme 94).[140] These 9b-functionalized 2,3-dihydro-[9b*H*]-

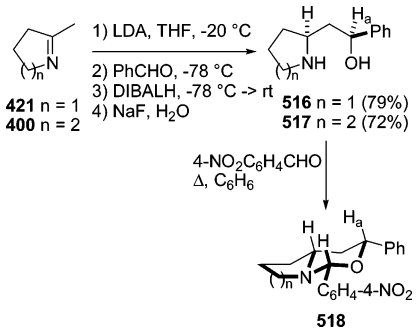
Scheme 94



oxazolo[2,3-*a*]isoindoline-5-ones **515** were formed by addition of the anion **512** across the imide carbonyl function and further ring closure. The phthalimide function proved to be an inappropriate *N*-protecting group for the synthesis of masked ω-aminoaldimines from the substitution reaction of the 1-azaallylic carbanions **512** with **513**.

Exocyclic metalation of imines **421** and **400** with LDA, followed by aldolization with benzaldehyde and reduction with DIBALH, gave the amino alcohols **516** and **517** as one diastereomer (Scheme 95). These amino alcohols **516** and **517** could be further transformed to the oxazines **518** by reaction with 4-nitrobenzaldehyde.[141] Similarly, reaction of the dianion of 2-methylbenzimidazole **441** with benzophenone and subsequent treatment with dielectrophilic carboxylic

Scheme 95

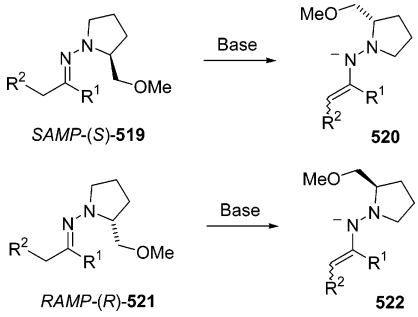


acid dichlorides resulted in formation of medium-sized lactones.[142,143]

3. Hydrazone Anions

During the past few decades 1-azaallylic anions derived from hydrazones have been extensively studied by NMR,[144−147] X-ray,[148−150] and theoretical calculations,[151,152] disclosing their ability to act as synthetic equivalents of enolate ions. They proved to have a greater efficiency of anion formation, lack of side reaction products, stability for hydrolysis or oxygenation in the absence of O_2, CO_2, and H_2O, and higher reactivity toward electrophiles such as halides, 2*H*-azirines, and carbonyl compounds (vide infra). Thus, hydrazone anions represent appealing reagents for asymmetric synthesis. In addition, when a chiral auxiliary is located at the nitrogen substituent(s), the procedures are amenable for enantioselective syntheses. A lot of examples are known in the literature; in particular anions derived from SAMP- and RAMP-hydrazones **519** and **521** have been extensively studied and recently covered by a review (Scheme 96).[4,153,154]

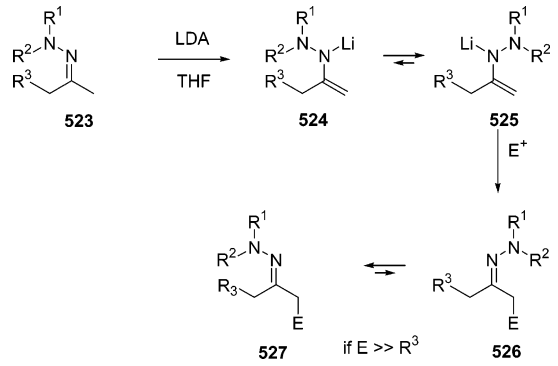
Scheme 96



3.1. Structural Data

Deprotonation of keto hydrazones was reported to proceed with equimolar amounts of sodium hydride, sodium or potassium amides ($NaNH_2$, KNH_2) in liquid ammonia, lithium or potassium dialkylamides (LDA, $LiNEt_2$, KDA), and *n*-BuLi or *t*-BuLi in THF (or Et_2O).[28,144] Although it is univocally reported that the less substituted *syn*-C−N anion **525** is the more stabilized (Scheme 97), it is still not clear how it is formed. First evidence on the regioselectivity of the deprotonation *anti* to the nitrogen lone pair[144] did not match further confirmations with *N*,*N*-dimethylhydrazones derived from acetone, suggesting that steric effects, as well as electronic factors, could be

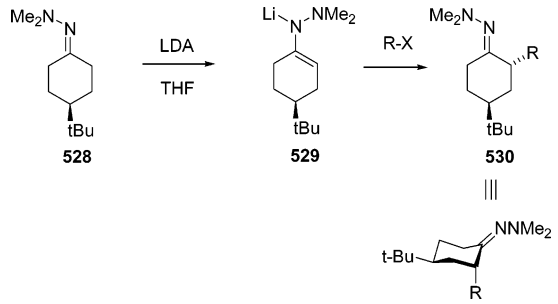
Scheme 97



involved in the regioselectivity of these reactions. 1-Azaallylic anions **525** upon treatment with electrophiles (alkyl halides, carbonyl compounds, ...) produce the regioselective (*Z*)-C−N hydrazone **526** that reequilibrates to the more stabilized *E* products **527** (according to the steric hindrance of the electrophiles used).[144,147,152,155]

The use of *N*,*N*-dimethylhydrazone **528** derived from 4-*tert*-butylcyclohexanone led to selective axially monoalkylated products at the α-carbon atom [145,148,156] (Scheme 98), a clear advantage as compared to

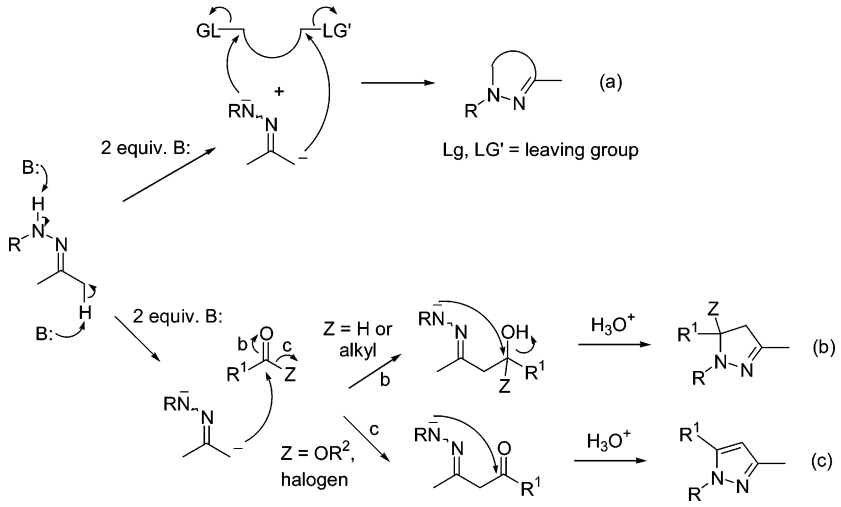
Scheme 98



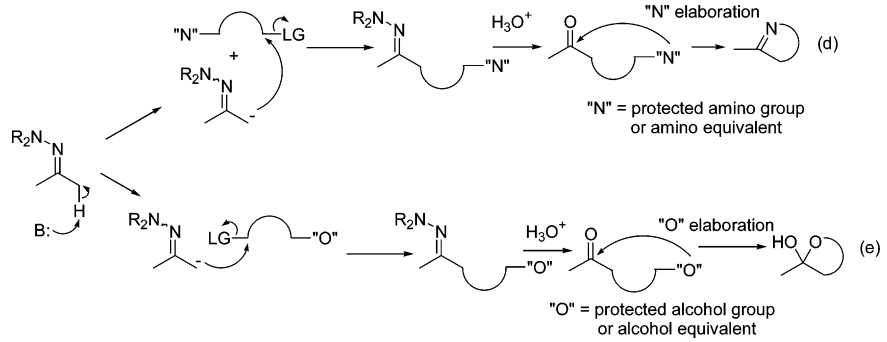
analogous enolates, which exhibit mediocre selectivity toward axial alkylation.[157−159] Moreover, an electronegative substituent (SR, OR, ...) at C-2 drove the deprotonation toward the more substituted carbon atom, without affecting the axial alkylation preference.[156] When an ester group was present at the α-position of the hydrazone moiety, not only was the methine deprotonated but the alkylation resulted in low axial selectivity. Further studies showed how the substituent(s) on the cyclohexanone imine could influence the stereochemistry, the axial position still remaining more favored.[148,149]

X-ray and theoretical studies on hydrazone lithioanions were done to try to explain the often >98% axial selectivity. Earlier hypotheses reported chelation[147,156] and orbital symmetry to explain the strong preference for the substituent on the imine nitrogen atom to orient *Z* to the carbanionic carbon.[160,161] These suggestions were revitalized a few years later, giving a significant contribution of the *syn* stabilization to the lithium chelation effect.[149] Theoretical evidence described the *syn*-C−N isomer as the favored one up to 4.5 kcal/mol.[10] The thermodynamic preference for the *syn* isomer arises from electron-repulsion consideration of the free electron pair of the sp^2 nitrogen and the anion at C-3.[10,162] It was

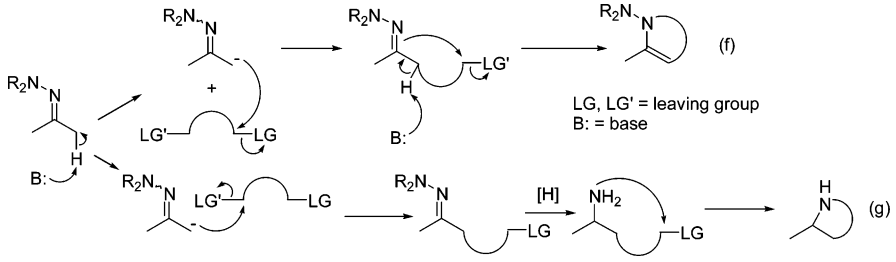
Scheme 99



Scheme 100



Scheme 101



discovered that the *syn* orientation arises from stereoelectronic preferences and coordination face selectivity. Although first evidence led to the conclusions that aggregation effects drive the stereoselectivity, further experimental analysis demonstrated that the stereoselectivity of hydrazone alkylation does not derive from an anion aggregation effect but rather from stereoselective alkylation of bissolvated monomeric lithium derivatives.[151]

3.2. Reactivity of Hydrazone Anions

1-Azaallylic anions generated from hydrazones underwent a series of reactions, similarly to anions derived from imines, to generate *N*- and *O*-heterocycles. In addition, *N*-monosubstituted hydrazones were treated with 2 equiv of bases, affording bidental nucleophiles that were trapped with ω,ω'-dielectrophiles (see reaction a in Scheme 99) or carbonyl compounds (see reactions b and c) to give diazaheterocycles.

In one case doubly deprotonated *N*,*N*-unsubstituted hydrazone anions reacted at nitrogen by addition at the nitrile moiety of acetonitrile and subsequently ring closed to triazaheterocyclic compounds in the presence of a base. Similar to imine anions, *N*,*N*-disubstituted hydrazone anions reacted with functionalized electrophiles bearing a nucleophilic moiety (see reactions d and e in Scheme 100). The latter included an amino function or amino equivalent, i.e., azides, easily reduced to amines (see reaction d). After hydrolysis, *N*-heterocycles were generated upon condensation of the amine toward the keto functionality. Moreover, a protected alcohol function or alcohol equivalent was introduced via deprotonation of *N*,*N*-disubstituted hydrazones and reaction with electrophiles functionalized with a protected alcohol function or alcohol equivalent. Further cyclization by addition across the hydrolyzed hydrazone function by the alcohol resulted in *O*-heterocycles (see reaction e).

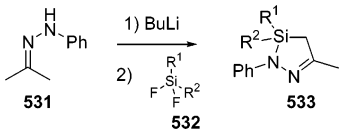
N,*N*-Disubstituted hydrazone reacted with bis-electrophiles, affording functionalized hydrazones. Intramolecular substitution was then achieved in the presence of a base (see reaction f in Scheme 101). Instead, *N*-heterocycles were formed when functionalized hydrazones were reduced at the hydrazone moiety to the amine and further cyclized (see reaction g).

3.3. Synthesis of Five- and Six-Membered Heterocyclic Compounds

3.3.1. Synthesis of Siladiazacyclopentenes and Triazolines

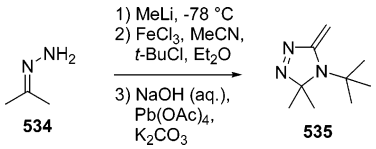
The 1-azaallylic dianion, generated from hydrazone **531** with 2 equiv of butyllithium at −78 °C, was trapped with difluorodialkylsilanes **532** to synthesize siladiazacyclopentenes **533** (Scheme 102).[163−165]

Scheme 102



Lithium 1-azaallylic anion of the *N*,*N*-unsubstituted hydrazone of acetone **534** added across acetonitrile in the presence of *tert*-butyl chloride to yield an amidrazone, which was then cyclized to triazoline **535** (Scheme 103).[166]

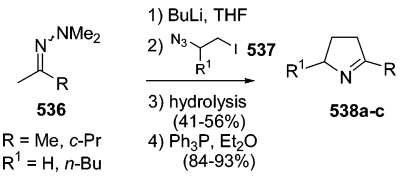
Scheme 103



3.3.2. Synthesis of Pyrroles, Pyrrolines, and Pyrrol-2-ones

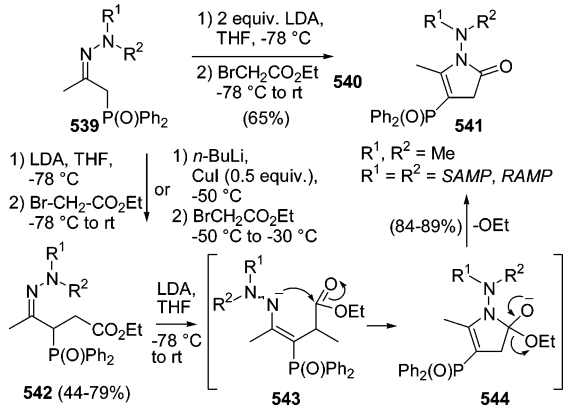
Numerous condensation and alkylation−ring closure reactions of acetone hydrazones leading to heterocycles have been reported. Alkylation of the 1-azaallylic anions of hydrazone **536** with β-iodoazides **537** followed by hydrolysis and treatment with triphenylphosphine afforded 1-pyrrolines **538** (Scheme 104).[167]

Scheme 104



α-Phosphorylated hydrazones were regioselectively deprotonated at the functionalized α-position and alkylated with activated halides **540**, bearing an alkoxycarbonyl moiety. Moreover, treating the resulting phosphinylhydrazones **542** with LDA, followed by aqueous workup, gave 1-aminopyrrol-2-ones **541** in 84−89% yield. Likewise, 1-aminopyrrol-2-ones **541** were synthesized in one pot from hydrazones **539**, performing the deprotonation with 2 equiv of LDA

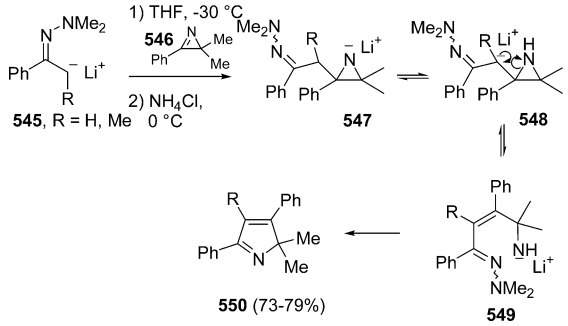
Scheme 105



in the presence of ethyl bromoacetate, resulting in 65% yield (Scheme 105). Attempts to extend the methodology to the analogous phosphonates were unsuccessful, as only the starting reagents were recovered.[168]

Furthermore, hydrazone anions, as well as oxime dianions, were evaluated for the synthesis of 2*H*-pyrroles and isoxazolines (vide infra) when reacted with 2*H*-azirines. *N*,*N*-Dimethylhydrazone anions **545** added across 2*H*-azirines **546** with the formation of 2*H*-pyrroles **550**, including aziridine adducts **547** and **548**, and allylamines **549** as intermediates (Scheme 106).[169]

Scheme 106

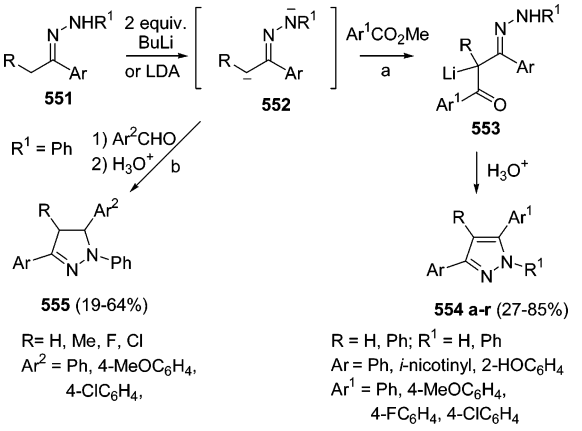


Beam and co-workers have extensively investigated the synthesis of pyrazole derivatives. Their major challenge included reactions of dilithiated hydrazone and oxime anions with esters and related electrophiles, and their ring closure to pyrazole and isoxazole derivatives via Claisen-type condensation−cyclization reactions.[170,171] In this matter, one-pot acylation reactions of *N*-phenylhydrazone dianions **552** and subsequent acid-catalyzed ring closure furnished pyrazoles **554** (Scheme 107, route a).[172−175] Following the same condensation−cyclization process, starting from *N*-unsubstituted hydrazone, 1*H*-pyrazoles were synthesized.[176]

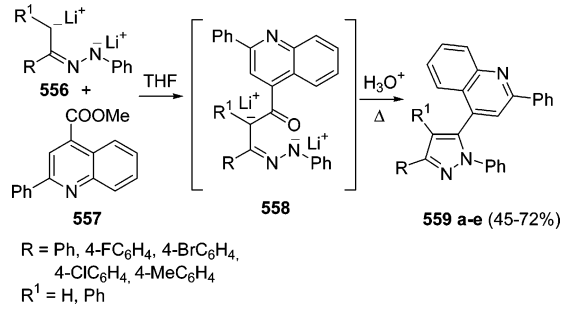
In the same way, condensation of 1-azaallylic anions **552** with aldehydes and subsequent treatment with acid gave 2-pyrazolines **555** (Scheme 107, route b).[177]

The previous reported strategy was further applied for the preparation of 2-phenyl-4-(1*H*-pyrazol-5-yl)-quinolines **559** (Scheme 108).[178] The same synthetic procedure could not be extended to dilithiated oximes and alkoxycarbonylhydrazone anions, because only

Scheme 107



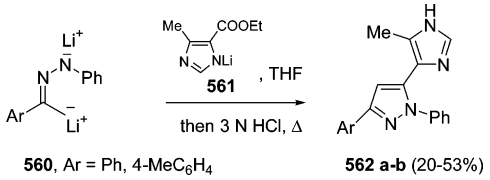
Scheme 108



C-acylation occurred without subsequent cyclization to the isoxazole analogues.[170]

When the electrophile is represented by ethyl 4-methyl-5-imidazolecarboxylate **561**, imidazolylpyrazoles **562** were produced (Scheme 109).[179] In analogy, imidazolylisoxazoles were synthesized from dilithiated oximes (vide infra).

Scheme 109

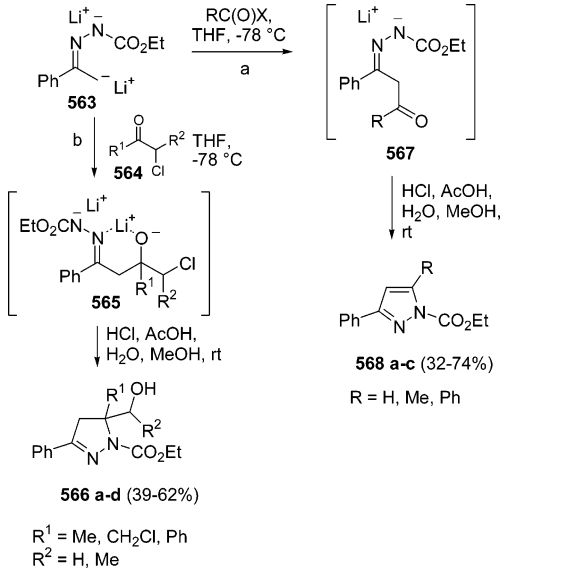


Hydrazones, bearing an alkoxycarbonyl moiety at the terminal nitrogen, can be doubly deprotonated and then monoacylated at carbon with a variety of carbonyl compounds, including esters, acyl chlorides, and amides, to give *N*-alkoxycarbonylpyrazoles **568** (Scheme 110, route a).[180,181] Alternatively, 1-azaallylic **563** anions react with α-halo ketones **564**, such as 1-chloro-2-propanone, 3-chloro-2-butanone, and 1,3-dichloro-2-propanone, giving *N*-alkoxycarbonyl-2-pyrazoline derivatives **566** (Scheme 110, route b).[181,182]

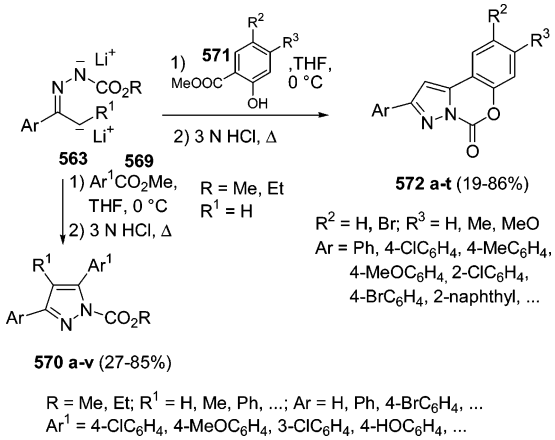
In a similar way, dilithiated *N*-alkoxycarbonylhydrazones **563** reacted with methyl benzoates **569** and methyl salicylates **571** to afford pyrazoles **570a**−**v** and benzopyranopyrazoles **572a**−**t**, respectively (Scheme 111).[175,183,184]

Moreover, as described for *N*-phenylhydrazones, dilithiated *N*-benzoylhydrazones **573**, metalated in the presence of an excess of LDA, were condensed with methyl benzoates. The resulting benzoylated

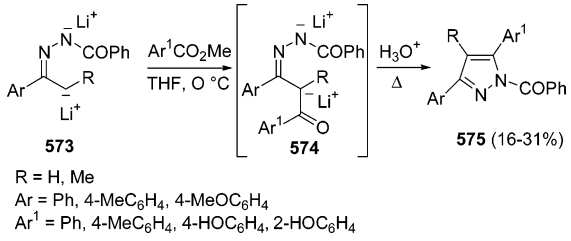
Scheme 110



Scheme 111



Scheme 112

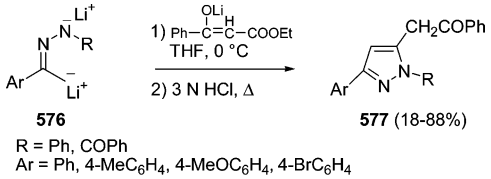


intermediates **574** were cyclized in acid medium to *N*-benzoylpyrazoles **575** (Scheme 112).[179]

N-Benzoylhydrazone and *N*-phenylhydrazone derivatives **576** are suitable for the synthesis of 5-phenacylpyrazoles **577** via a condensation with lithiated ethyl benzoyl acetate (Scheme 113).[179]

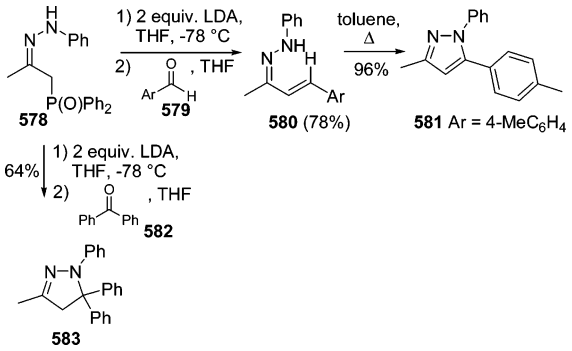
Deprotonation of *N*-phenyl-α-phosphinylhydrazone **578** with 2 equiv of lithium base gave a Horner−

Scheme 113



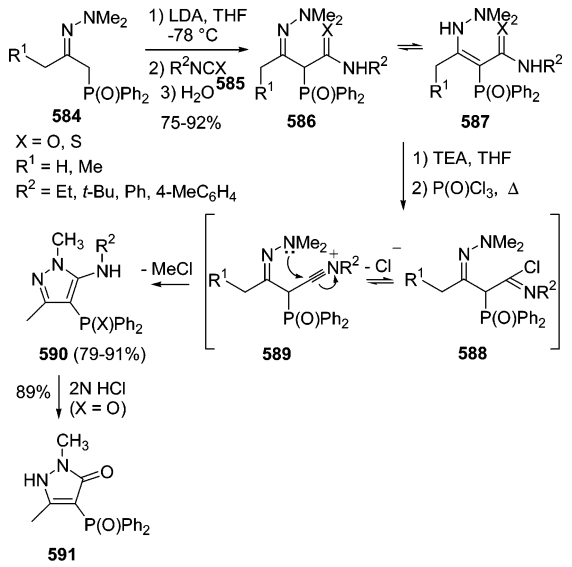
Wadsworth−Emmons-type reaction upon addition of benzaldehyde (**579**) and benzophenone (**582**). Furthermore, pyrazole **581** was produced by intramolecular Michael addition induced by heating at 100 °C in toluene (Scheme 114).[185] Addition of **582** to the lithiated hydrazone afforded dihydropyrazole **583**, while the corresponding 1-azadiene intermediate was not isolated.[185]

Scheme 114



In a similar way, anions derived from α-phosphorylated *N*,*N*-dimethylhydrazone **584** were trapped with isocyanates **585** (X = O) and hydrolyzed to obtain phosphine oxides **586**, in equilibrium with its enamine form **587**. Such a mixture was cyclized to pyrazoles **590** (X = O), in the presence of phosphorus oxychloride and triethylamine (Scheme 115). Acid-induced amino cleavage with 2 N hydrochloric acid led to the corresponding pyrazolin-5-ones **591** in 89% yield.

Scheme 115

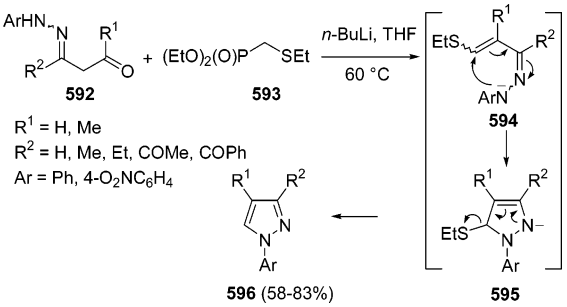


When isothiocyanates **585** (X = S) were used instead, pyrazolylphosphine sulfides **590** (X = S) were isolated, disclosing the tendency of a spontaneous oxygen−sulfur exchange (Scheme 115).[186]

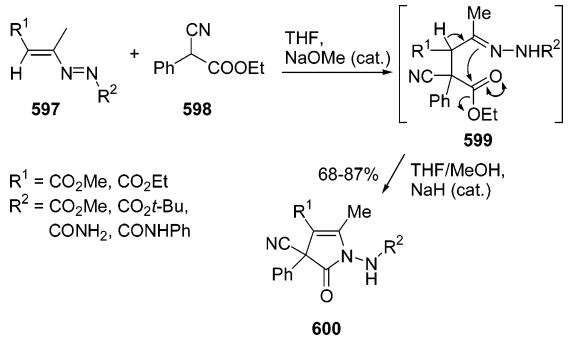
Pyrazoles **590** (X = O) were also obtained in a one-pot reaction upon stirring for 2 h at −78 °C, involving the addition of isocyanate to the lithiated *N*,*N*-dimethylated α-phosphinylhydrazone and phosphorus oxychloride at −78 °C.

In two cases, in situ generated 1-azaallylic anions underwent internal rearrangement to *N*-arylpyrazoles **596** and 1*H*-pyrrol-2-ones **600**, respectively (Schemes 116 and 117).[187,188] Thus, one-pot reaction

Scheme 116



Scheme 117

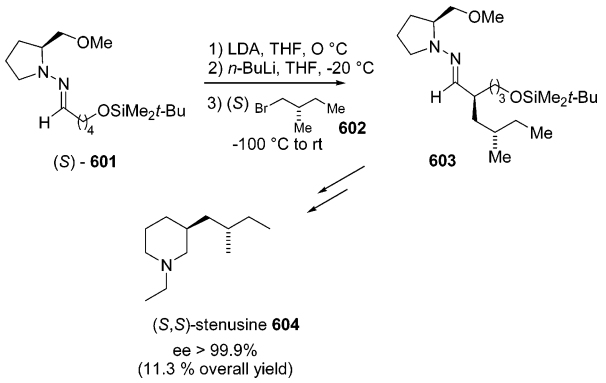


of arylhydrazones **592** and the carbanion of diethyl (ethylthiomethyl)phosphonate (**593**) included the formation of azaenolate intermediate **594** that suffered rearrangement to 3,4-disubstituted pyrazoles **595** (Scheme 116).[188] Moreover, condensation of α-cyano ester **598** with conjugated azoalkenes **597** in the presence of a catalytic amount of sodium methoxide led to adduct **599**, which was smoothly cyclized to 1-amino-3-cyano-1*H*-pyrrol-2(3*H*)-ones **600** by sodium hydride addition (Scheme 117).[187]

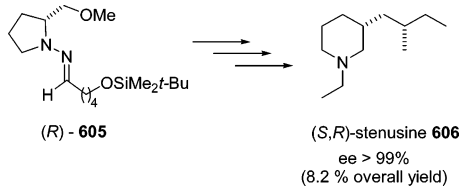
The enantioselective total synthesis of the two major stereoisomers of natural stenusine, the spreading agent of the beetle *S. comma*, has been developed from the SAMP and the RAMP derivatives (*S*)-**601** and (*R*)-**605**, respectively.[189] The key step involved the alkylation of the 1-azaallylic anions derived from the SAMP/RAMP-hydrazones with (*S*)-1-bromo-2-methylbutane (**602**). By several steps, including cleavage of the N−N bond by lithium in ammonia at −33 °C, Boc protection of the amine, *O*-mesylation, and finally deprotection−ring closure, the appropriate stenusine enantiomer was obtained (Schemes 118 and 119). The same synthetic strategy was applied for the SAMP- and the RAMP-hydrazones **601** and **605**, affording (+)-(*S*,*S*)- and (−)-(*S*,*R*)-stenusine (**604** and **606**) with >99% ee and 11.3% and 8.2% overall yields, respectively.[189]

The SAMP/RAMP synthetic strategy was applied for the synthesis of 2-substituted piperidin-3-ols **610**. This skeleton is represented in numerous natural and unnatural bioactive compounds, such as κ-opioid receptor agonists, GABA receptor binders, and the antimalarial (+)-febrifugine. Treating the SAMP/RAMP-hydrazone **607** with LDA in THF at −78 °C

Scheme 118

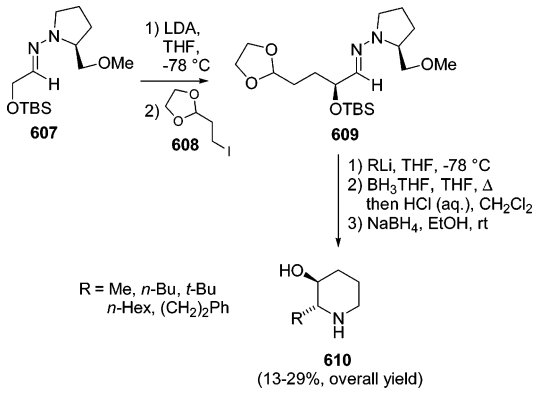


Scheme 119



resulted in the corresponding lithiated hydrazone that was trapped with iodoacetal **608**. Addition of different lithiated nucleophiles to the intermediate **609** gave an unstable hydrazine which, upon subsequent removal of the chiral auxiliary by BH_3·THF in refluxing THF, acid-catalyzed silyl ether cleavage, and reduction of the resulting endocyclic imine, led to 2-substituted piperidin-3-ols **610** in 13−29% overall yield (Scheme 120).[190]

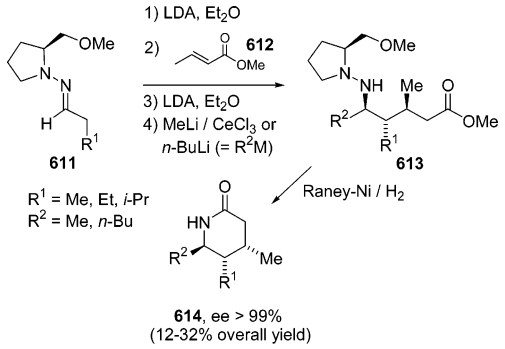
Scheme 120



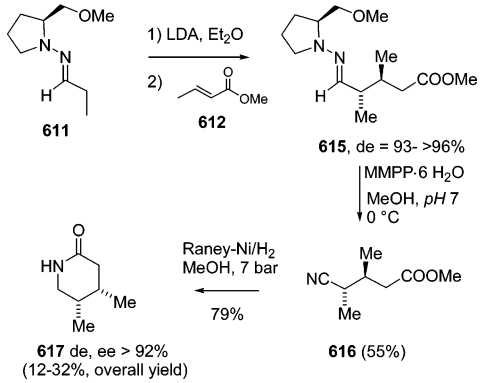
Moreover, the lithiated SAMP-hydrazone of **611** underwent diastereo- and enantioselective nucleophilic Michael addition across methyl crotonate (**612**). The resulting adduct was enolized with LDA in THF and reacted with organometallic compounds, e.g., alkyllithiums with or without added cerium(III) chloride, to give ester **613**. Subsequent hydrogenolysis and spontaneous cyclization during hydrogenolysis over Raney nickel resulted in 4,5,6-trisubstituted piperidin-2-ones **614** in more then 99% ee (Scheme 121).[191]

The use of magnesium monoperoxyphthalate hexahydrate (MMPP) led to the reduction of the SAMP-hydrazone **615** to δ-alkoxycarbonylnitrile derivative **616**, generated as previously reported through **612**. Then, reduction with Raney nickel in methanol

Scheme 121



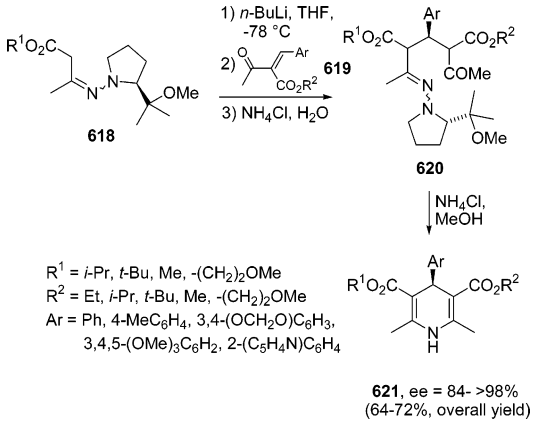
Scheme 122



afforded *cis*-4,5-dimethylated piperidine-2-ones **617** (Scheme 122).[192]

An efficient synthesis of chiral 1,4-dihydropyridines **621** via an asymmetric Hantzsch-type reaction of metalated chiral alkylacetoacetate hydrazones was disclosed (Scheme 123).[193]

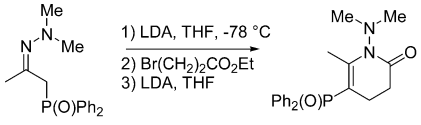
Scheme 123



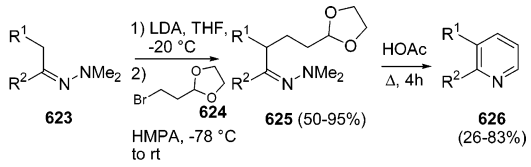
Phosphinylhydrazones **539** led to 5-phosphinylated 1-amino-3,4-dihydropyridin-2-ones **622** in 88% yield via an alkylation−deprotonation−ring closure sequence, as previously described for pyrrol-2-ones **541**. When performed in a one-pot reaction, dihydropyridine **622** was obtained in 67% yield (Scheme 124).[168]

N,*N*-Dimethylhydrazones **623** were regioselectively deprotonated by LDA in THF at −20 °C, and subsequently alkylated at −78 °C with 2-(2-bromoethyl)-1,3-dioxolane (**624**) in HMPA. The resulting hydrazone acetal derivatives **625** were then ring closed with acetic acid to give pyridines **626** in moderate to good yields (Scheme 125).[194]

Scheme 124

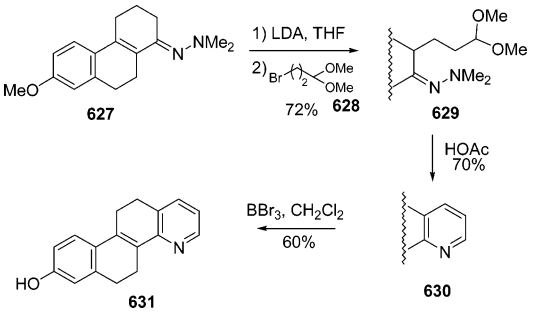


Scheme 125



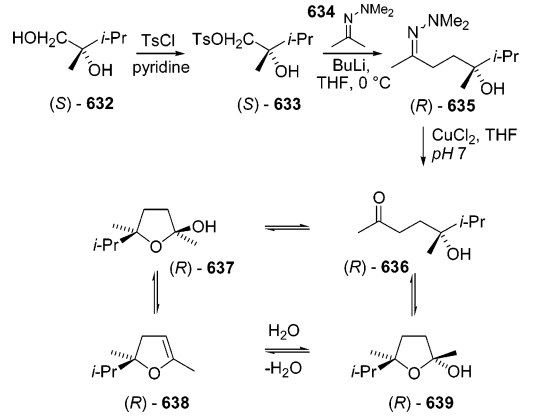
An interesting application of the latter procedure concerned the synthesis of 1-aza-9-hydroxy-5,6,11,12-tetrahydrochrysene (**631**).[195] Tetrahydrochrysenes represent a class of donor−acceptor substances used as fluorescent ligands for estrogen receptors. The tetracyclic heterocompound **631** was prepared via lithiation of hydrazone **627**, followed by substitution with the dimethyl acetal of 3-bromopropanal **628**, acid treatment, and cleavage of the methyl ether with boron(III) bromide (Scheme 126).[195]

Scheme 126



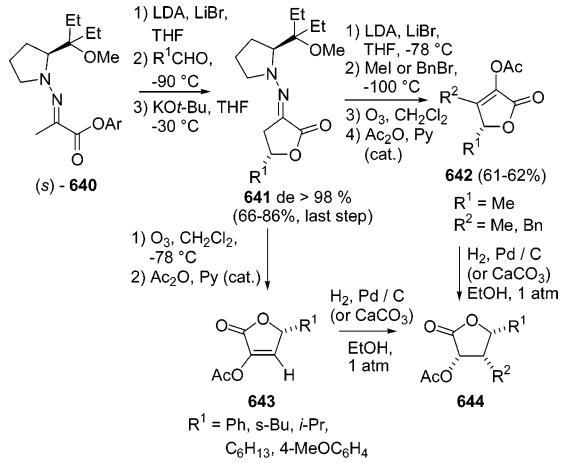
A straightforward enantioselective synthesis of (*R*)-2,3-dihydro-2,5-dimethyl-2-isopropylfuran (**638**) is described through hydrolysis of the hydrazone moiety of alcohol (*R*)-**635**, by copper(II) chloride and subsequent ring closure. Hydrazone **635** was easily accessible via alkylation of the *N*,*N*-dimethylhydrazone of acetone **634** with (*S*)-1-(tosyloxy)-2,3-dimethyl-2-butanol (**633**) (Scheme 127).[196] The isopropyldihydrofuran **638** in the presence of water at room temperature exists in equilibrium with its chain-opened form **636** and the tetrahydrofurans **637** and **639**. Dihydrofuran **638** is the sex-specific pheromone of females of the beetle *Hylecoetus dermestoides* L.

Scheme 127



The latter alkylation−cyclization protocol was applied for the enantioselective synthesis of 3,4-disubstituted 2-acetoxybutyrolactones.[197] Aldol adducts were generated upon reaction of 1-azaallylic anions of SAEP [(*S*)-1-amino-2-(1-ethyl-1-methoxypropyl)-pyrrolidine] hydrazone **640** and aldehydes in 82−94% yield and 78% to >98% de, followed by lactonization with KO-*t*-Bu in THF at −30 °C (Scheme 128).

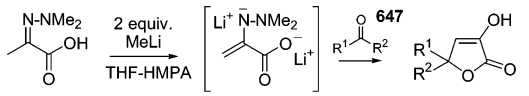
Scheme 128



Further, alkylation with methyl iodide or benzyl bromide afforded 3,4-disubstituted hydrazonelactones in 51−66% yield and 97−98% de. After cleavage of the hydrazone moiety by ozonolysis, the unstable α-keto lactones were immediately acetylated to butenolides **642**. The butenolides **643** were obtained from ozonolysis and acylation of SAEP-hydrazones **641**. Hydrogenation of **642** and **643** with palladium over carbon (or $CaCO_3$) in ethanol afforded 2,4- and 2,3,4-substituted butyrolactones **644** in 57−87% yields and ee > 89%.[197]

The useful methodology for the generation of the 1-azaallylic anion derived form α-hydrazono esters was applied to pyruvic acid dimethylhydrazone (**645**). Two equivalents of methyllithium was needed to generate the strongly ambident anion **646**, which condensed with a series of aldehydes and ketones to form γ,γ-disubstituted 2-hydroxybutenolides **648** upon acid workup (Scheme 129).[198]

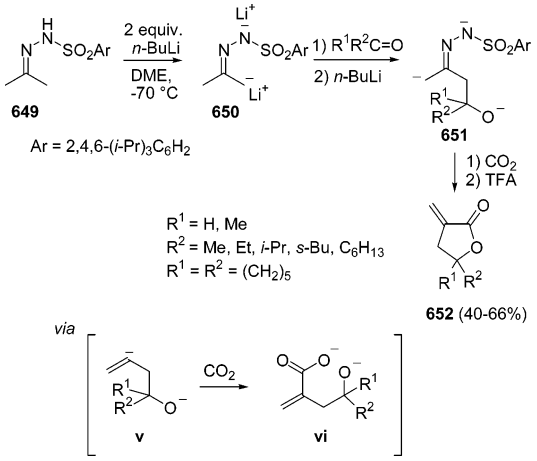
Scheme 129



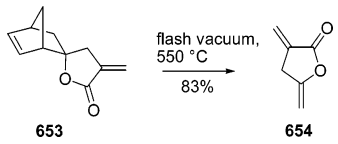
The same synthetic strategy could be extended to *N*-sulfonylhydrazones derived from acetone. Treatment of *N*-sulfonylhydrazone **649** with 2 equiv of *n*-butyllithium at −70 °C gave the dianion **650**, which, under Shapiro conditions, led to the formation

of trianion **651**.[199] Increasing the temperature to 3 °C resulted in vinyl carbanion **v**. The latter was trapped with carbon dioxide to give carboxylate **vi**, and quenched with trifluoroacetic acid to cyclize to α-methylene-γ-lactones **652** in 40−73% yield (Scheme 130).[200] When the carbonyl electrophile was represented by [2.2.1]hept-2-en-5-one, the spirocyclic lactone **653** was obtained in 61% yield. Upon flash vacuum pyrolysis at 550 °C, a retro-Diels−Alder reaction was induced to afford 3,5-dimethylenelactone **654** in 83% yield (Scheme 131).[201]

Scheme 130

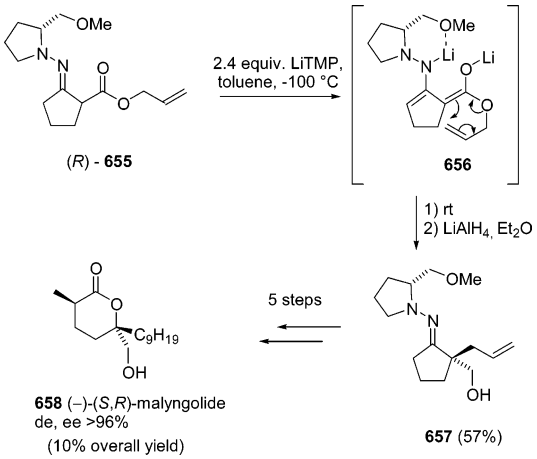


Scheme 131



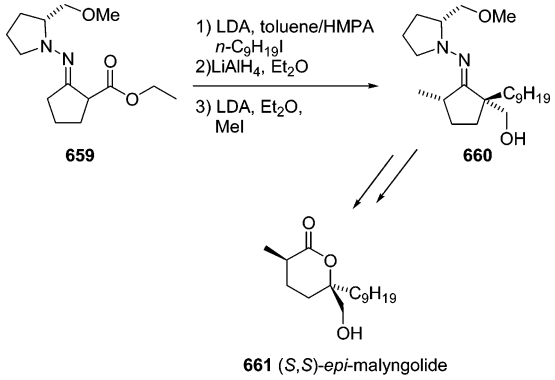
1-Azaallylic anions were applied in the synthesis of (−)-malyngolide and (+)-*epi*-malyngolide, two naturally occurring compounds of the marine algae *Lynbya majuscula*, which display antibiotic activity.[202] The key step in the synthesis of (−)-(*S*,*R*)-malyngolide was the [3,3]sigmatropic rearrangement of allyloxycarbonylcyclopentanone RAMP-hydrazone (*R*)-**655** after treatment with an excess of lithium tetramethylpiperidide (Scheme 132). Further elaboration in five steps led to the natural product **658** with 96% ee and 10% overall yield.[203]

Scheme 132



The synthesis of the analogous (+)-(*S*,*S*)-*epi*-malyngolide (**661**) started from a bis-α,α′-dialkylation reaction of the RAMP-hydrazone **659**, derived from 2-ethoxycarbonylcyclopentanone. Upon oxidative cleavage of the chiral auxiliary with ozone in pentane at −78 °C, and Baeyer−Villiger oxidation, (+)-(*S*,*S*)-*epi*-malyngolide was formed in six steps and 23% overall yield (Scheme 133).[203]

Scheme 133



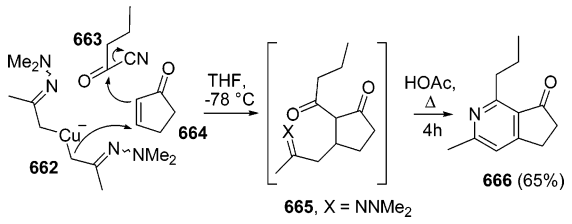
3.4. Synthesis of Bicyclic and Spiro Heterocyclic Compounds

Besides the numerous syntheses for the generation of regular heterocyclic systems (pyrroles, pyrazoles, piperidines, ...), anions derived from hydrazones represent useful building blocks for the construction of natural and unnatural biologically active compounds, such as unsaturated macrolides,[204] the *in*,*out*-tricyclo[7.4.1.0]tetradecan-14-one (the base ring of ingenol),[205] (+)-paspalicine and (+)-paspalinine,[206] pectenotoxin-4,[207] epothilone E,[208] ferensimycin B,[209] (+)-frontalin, the aggregation pheromone of *Dendroctonus* beetles,[210] (±)-pumiliotoxin C,[211] 2,3,4-trisubstituted γ-lactones,[212] ionophore A-23187,[213] the antibiotic X-206,[214] and the oxazole side chain of leucascandrolide A.[215] The syntheses of such compounds arose from the Corey−Enders protocol,[155] or included it as a key-step reaction, followed by multistep sequences to match the required heterocycles.

3.4.1. Synthesis of Cyclopenta[c]pyridin-7-ones, Tetrahydroquinolines, and Quinolines

An elegant one-pot synthesis of 3-methyl-1-propyl-5,6-dihydro-7*H*-cyclopenta[c]pyridin-7-one (**666**) was discovered via 1,4-addition of the cuprate **662**, derived from the anion of acetone *N*,*N*-dimethylhydrazone, to cyclopentenone (**664**) at −78 °C in THF, followed by acylation of the resulting enolate with butyryl cyanide **663** and subsequent acid-catalyzed cyclization, induced by refluxing the hydrazone adduct **665** in acetic acid for 4 h (Scheme 134).[216] In a similar way, hydrazone anions derived from 2-methylcyclohexanone, acetone, ... in combination with α,β-unsaturated systems, including 2-cyclopentenone, 2-cyclohexenone, 5,5-dimethyl-2-cyclohexenone, and

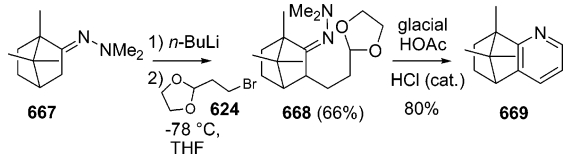
Scheme 134



carboxynitriles, were utilized in the synthesis of pyridine derivatives in low to good overall yield (14−82%).[216] The latter procedures are the precursor of the multicomponent reactions (MCRs) of the new generation.[217]

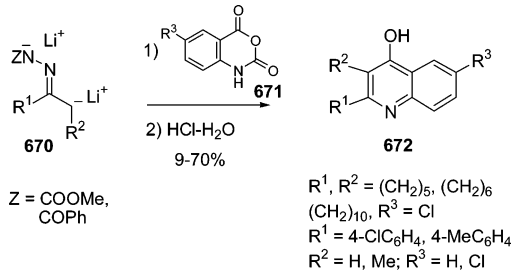
The dimethylhydrazone deprotonation−alkylation sequence was shown to be a valuable tool in the synthesis of tetrahydroquinoline **669** derived from (+)-camphor, whereas thermolysis of camphoroxime *O*-allyl ether or condensation−ring closure of (+)-3-(3-oxobutyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one with hydroxylamine failed, giving poor yields or retroreaction, respectively. In this matter, camphor *N*,*N*-dimethylhydrazone (**667**) was deprotonated with butyllithium at −78 °C in THF and alkylated with **624**, as previously described by the same authors in the synthesis of pyridine derivatives (Scheme 125). Moreover, refluxing the resulting acetal **668** in acetic acid or in carbitol afforded tetrahydroquinoline **669** in 80% yield (Scheme 135).[218]

Scheme 135



Quinolines **672** were prepared via addition of *N*-alkoxycarbonyl and *N*-benzoylhydrazone dianions **670**, starting with two molar equivalents of LDA, to isatoic anhydrides **671** followed by acid hydrolysis in 9−70% yields (Scheme 136).[219]

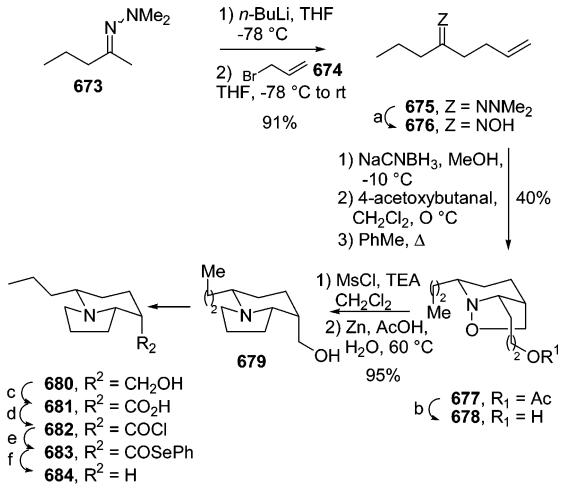
Scheme 136



3.4.2. Synthesis of Bicyclic Compounds with an Annelated N-Containing Six-Membered Ring

The 5,8-disubstituted indolizidine 167B (**684**) (R^2 = H), which presents structural similarities to the cardiotonic pumiliotoxins, has been synthesized via direct lithiation of *N*,*N*-dimethylhydrazone **673** and subsequent regioselective alkylation with allyl bromide. Conversion of the hydrazone **675** (X = $NNMe_2$) to the corresponding oxime **676** (X = NOH) and reduction with sodium cyanoborohydride gave rise to an unstable *N*-alkenylhydroxylamine. Upon condensation with 4-acetoxybutanal the sole (*Z*)-nitrone was formed, which underwent intramolecular dipolar cycloaddition to isoxazolidine **677** in refluxing toluene. Alkaline hydrolysis of the acetate, mesylation followed by spontaneous cyclization, and reductive N−O bond cleavage (Zn/HOAc) gave the 5,8-disubstituted indolizidine **679**. Further, oxidation with Jones reagent, acylation, and decarboxylation via the seleno ester yielded indolizidine **684** (R^2 = H; Scheme 137).[220,221] The same strategy applied to

Scheme 137

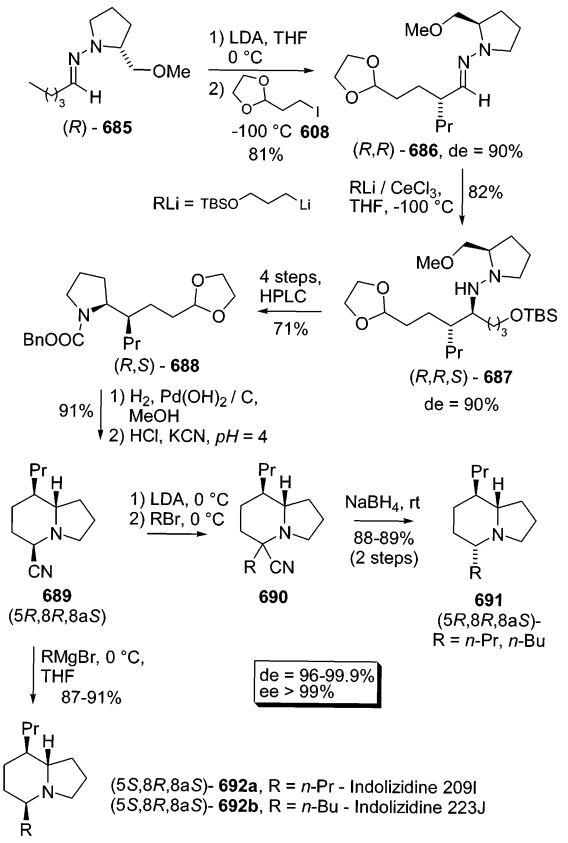


a = NH_2OH HCl, NaOAc, EtOH, rt (97%); b = K_2CO_3 (cat.), MeOH, rt (84%); c = Jones reagent, acetone, rt (67%); d = $(COCl)_2$, DMF (cat.), CH_2Cl_2, rt; e = PhSeH, py, THF, PhH, rt (78%, two steps); f = *n*-Bu_3SnH, AIBN (cat.), PhH, Δ (62%)

oximes led to indolizidines 235B and 235B′, respectively. The latter heterocycles are important pharmaceuticals, with partial agonist activity for the nicotinic acetylcholine receptor.[222]

The enantioselective synthesis of 5,8-disubstituted indolizidines (−)-209I and (−)-223J (**692a,b**), isolated from the skins of dendrobatid and metelline frogs, started from the asymmetric alkylation of pentanal RAMP-hydrazone to give acetal **686** in 81% yield and 90% de. Addition of α-functionalized organocerium reagent across the carbon−nitrogen double bound furnished hydrazine **687** in an asymmetric manner. The latter was converted to *N*-benzyloxycarbonylpyrrolidine **688** via a multistep sequence, involving cleavage of the N−N bond, desilylation, and further manipulation to afford the cyclized pyrrolidines **688** in 71% yield. Thus, hydrogenolysis followed by acid hydrolysis in the presence of potassium cyanide (Husson's protocol) led to the azabicycle **689**. The latter could be easily converted to the enantiomer **691** and to the corresponding epimers at C-5 (**692**), via two different strategies. One included treatment with Grignard reagents to give directly compounds **692**. On the other hand, a deprotonation−alkylation step followed by reduction with sodium borohydride smoothly afforded alkaloid indolizidines **691** in high de and ee (Scheme 138).[223]

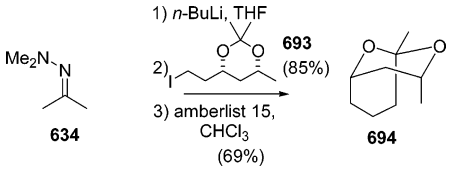
Scheme 138



3.4.3. Synthesis of Bicyclic Compounds with an Annelated O-Containing Five- and Six-Membered Ring

The *N*,*N*-dimethylhydrazone derived from acetone **634**, upon lithiation and reaction with iodoacetal **693**, although reversly indicated by the authors, afforded the enantiomerically pure (−)-[1(*R*),3(*R*),5(*S*)]-1,3-dimethyl-2,9-dioxabicyclo[3.3.1]nonane (**694**).[224] The latter is the host-specific substance of the beetle *Trypodendron lineatum* Oliver, isolated from the extracts of the bark of trees infected by this beetle (Scheme 139).[224]

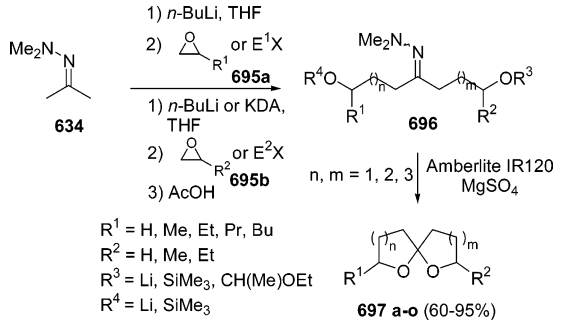
Scheme 139



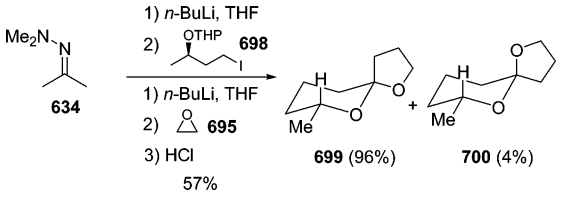
The one-pot synthesis of insect spiroacetal pheromones **697** started from the α,α′-bisalkylation process of lithiated acetone dimethylhydrazone. Cleavage and spirocyclization were executed in acid medium to afford the desired 1,6-dioxaspiro[4.4]nonane derivatives **697** (Scheme 140).[225] In a similar way, 1,6-dioxaspiro[4.5]decanes, 1,6-dioxaspiro[4.6]undecane, 1,7-dioxaspiro[5.5]undecanes, and 1,7-dioxaspiro[5.6]-dodecane were synthesized.[225]

Following the same synthetic strategy described by Enders and co-workers, the synthesis of (±)-7-methyl-1,6-dioxaspiro[4.5]decane (**699**) was performed, the natural product being isolated from the pentane extracts of the rectal glandular secretions of three

Scheme 140



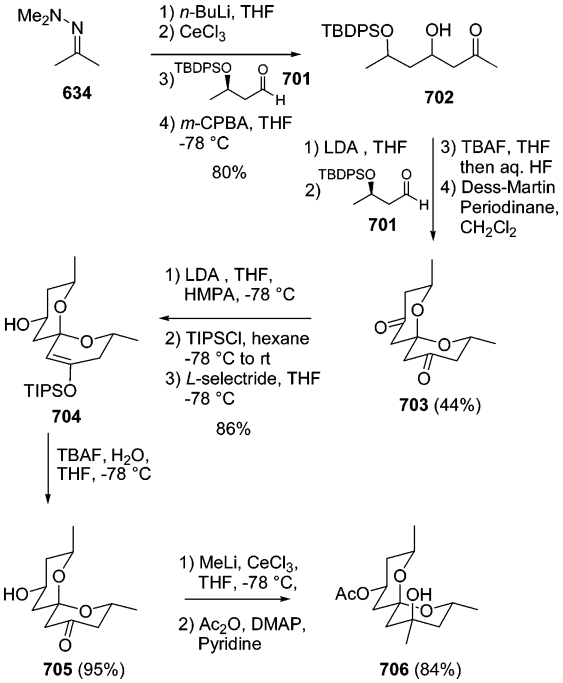
Scheme 141



unrelated species of *Bactrocera*. The use of chiral iodide **698** in the synthesis resulted in the formation of (5*R*,7*R*)-**699** (Scheme 141).[226,227]

Due to the presence of a spiroketal fragment in the structure of altohyrtin A, a marine-derived macrocyclic lactone with cancer growth inhibitor activity, a synthetic strategy to form this dispiroacetal moiety has been developed. The pattern started from the addition of the lithiated hydrazone **634** to the silylated aldehyde **701**, in the presence of cerium(III) chloride as transmetalation agent. Cleavage of the hydrazone functionality afforded the β-hydroxyketone **702** in two steps in 80% yield. Treatment of **702** with LDA in THF at −78 °C, followed by reaction with aldehyde **701**, resulted in aldol reaction. Deprotection of the crude aldol with tetrabutylammonium fluoride (TBAF) gave an intermediate dihydroxylated acetal that was immediately converted to the diketone **703**

Scheme 142



(Scheme 142). Formation of monosilylated enol ether, reduction of the ketone with L-selectride, silyl cleavage with TBAF·H_2O, addition of methyllithium across the carbonyl function ($CeCl_3$ directed), and, finally, acetylation of the hydroxyl moiety formed the desired model compound **706**.[228]

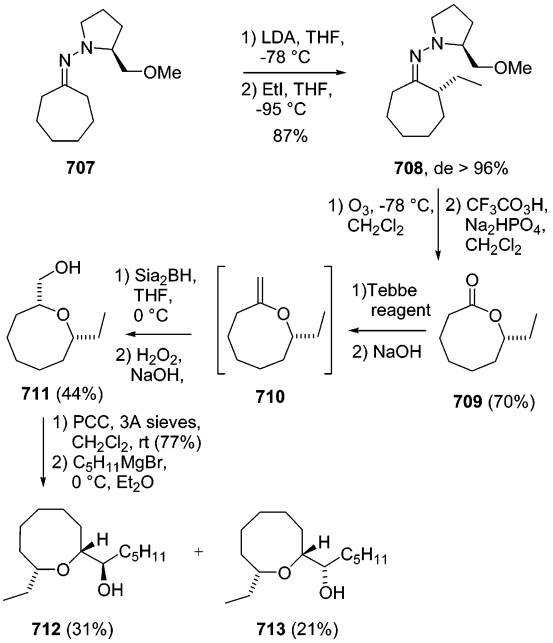
Bisalkylation of the anion of acetone dimethylhydrazone with epoxides resulted in the α,α′-bisfunctionalized hydrazone in a two-step reaction. The hydrolysis was effected upon treatment with Amberlite IR-120 (plus) ion-exchange resin, and subsequent ring closure gave 2-(2-hydroxyethyl)-7-methyl-1,6-dioxaspiro[4.4]nonane (exogonol), which was converted via pyridinium chlorochromate and silver(II) oxide oxidations to the corresponding exonoic acid, a constituent of the resin of the Brazilian tree *Ipomea operculata*.[229]

3.5. Synthesis of Higher Membered Heterocycles

3.5.1. Synthesis of Cyclic Ethers

The SAMP strategy was successfully applied to the synthesis of the eight-membered cyclic ether **712**, the marine natural product laurencin, isolated from red algae of *Laurencia* species. Lithiated SAMP-hydrazone of cycloheptanone was alkylated with ethyl iodide at −95 °C in THF, followed by ozonolysis and Baeyer−Villiger oxidation to give lactone **709**. Upon Tebbe methylenation, the ene intermediate **710** reacted with diisoamylborane, affording the *cis*-alcohol **711** as the sole diastereomer, after oxidation with hydrogen peroxide. Furthermore, oxidation with PCC in CH_2Cl_2 and treatment with pentylmagnesium bromide at 0 °C gave **712** together with the alcohol **713** (Scheme 143). To increase the amount of the target compound, the diastereomeric mixture of the alcohols **712** and **713** was oxidized and selectively reduced with L-selectride to afford exclusively laurencin.[230]

Scheme 143



4. Oxime Anions

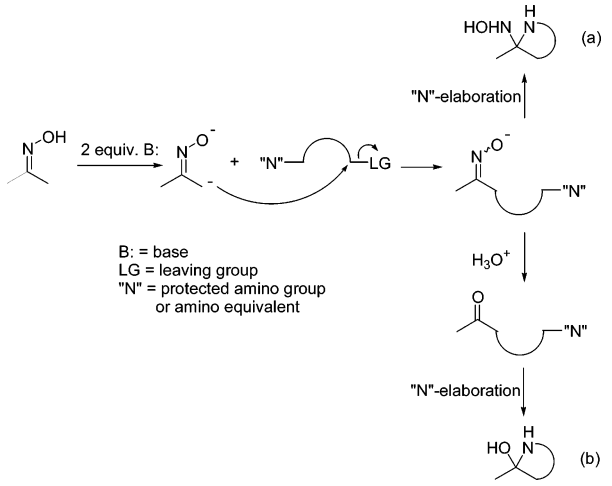
4.1. Structural Data

As well as the other 1-azaallylic anions, anions and dianions derived from oximes have shown *syn* preferences upon deprotonation with strong bases. In particular the regiochemical outcome of reactions using dilithium oxime dianions is explained via the chelating effect, exerted by lithium on the oxygen atom.[231] Studies on oxime anions bearing as counterion different metals (cerium, lithium, magnesium, ...) demonstrated that the stability of such anions is strongly dependent upon the counterion (Ce > Li ≡ Mg) and the temperature, explained in the formation of metal alkoxides. Thus, metals which complex with oxygen, such as lithium or magnesium, cause an increase of oxime anion decomposition. As a result, cerium, which coordinates less with the oxygen or the nitrogen atom, gave the more stabilized anions.[232] The same work brought experimental evidence on the pK_a of some oximes. As expected, the values are higher than those of the corresponding imines.[232]

4.2. Reactivity of 1-Azaallylic Anions Derived from Oximes

Similar to the anions derived from imines, 1-azaallylic anions derived from oximes are used for the introduction of a nucleophilic function in the structure of the oxime. The introduced nucleophilic function can be a protected amino group or amino equivalent which can add across the imino function or the corresponding carbonyl function after hydrolysis, resulting in *N*-heterocyclic compounds (see reactions a and b in Scheme 144).

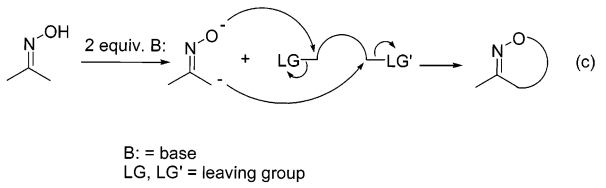
Scheme 144



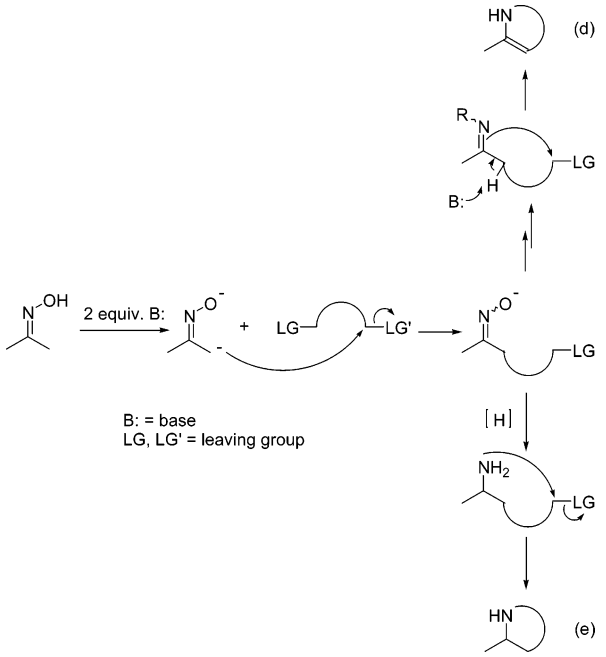
The 1,4-dianions derived from oximes can undergo *C*- and *O*-alkylation with dielectrophilic compounds, resulting in heterocycles containing both nitrogen and oxygen (see reaction c in Scheme 145).

Alkylation of the oxime dianion with a dielectrophilic reagent also leads to intermediates which can form *N*-heterocycles through transformation of the oxime function to the corresponding nucleophilic enamine and further ring closure (see reaction d in Scheme 146). The oxime function can also be reduced

Scheme 145



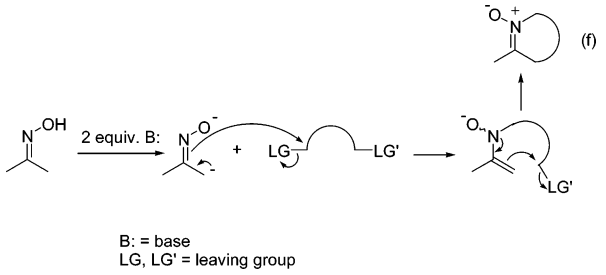
Scheme 146



to the corresponding amino group and then ring close (see reaction e).

Heterocyclic *N*-oxides are formed when the oxime 1,4-dianions are *N*- and *C*-alkylated with dielectrophilic compounds (see reaction f in Scheme 147).

Scheme 147

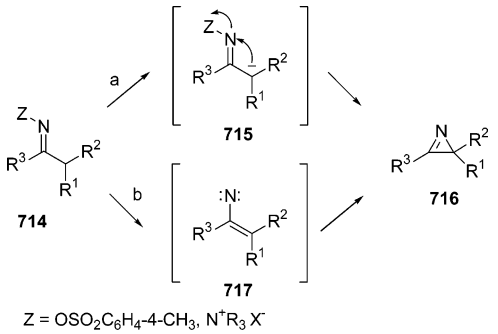


4.3. Synthesis of Three-Membered Heterocyclic Compounds

4.3.1. Synthesis of 2H-Azirines

The Neber-type rearrangement[233,234] was investigated through the synthesis of 2*H*-azirines[235] via the deprotonation of *O*-activated oximes. The Neber reaction consists of the treatment of oxime *p*-toluenesulfonates **714** (later extended also to trimethylhydrazonium halides) with bases and their rearrangement to α-amino ketones via 2*H*-azirines **716**. The generation of the azirines **716** was explained either via an intramolecular nucleophilic displacement (route a, Scheme 148) or through the electro-

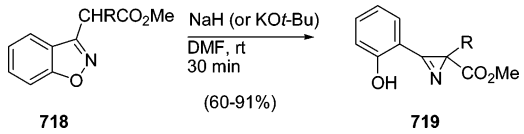
Scheme 148



cyclization of vinylnitrene **717** induced by the basic conditions (route b), and it is favored by the presence of electron-withdrawing groups at the α-position to *N*-functionalized imines (vide infra).[236]

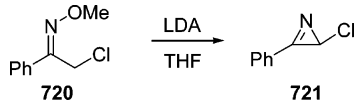
Isobutyrophenone trimethylhydrazonium iodide in the presence of sodium isopropoxide in 2-propanol gave 2,2-dimethyl-3-phenylazirine with less than 1 equiv of base at room temperature in 85% yield.[237] When heating and an excess of base were applied, 2,2-dimethyl-3-phenyl-3-isopropylaziridine was obtained.[237] Application of the Neber rearrangement gave access to 3-amino-2*H*-azirines **716** (R^1 = H; R^2 = ArNHCO or $ArSO_2$; R^3 = NH_2; Scheme 148) when amidoxime *O*-tosylates **714** (R^1 = H; R^2 = ArNHCO or $ArSO_2$; R^3 = NH_2; Z = $OSO_2C_6H_4$-4-CH_3) were treated with sodium methoxide in methanol in 74−88%.[238] In a similar way, the Neber rearrangement of benzisoxazoles **718** resulted in azirines **719** in 60−91% yield (Scheme 149).[239,240] Recently, the Neber-

Scheme 149



type cyclization of α-chloroacetophenone *O*-methyloxime **720** with LDA in THF provided 2-chloroazirine **721** (Scheme 150).[241] Finally, 2-(1*H*-1,2,3-benzo-

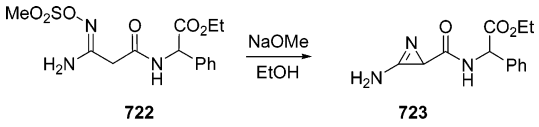
Scheme 150



triazol-1-yl)-1-ethanoneoximes were converted to 2-(benzotriazol-1-yl)-2*H*-azirines with tosyl chloride and aqueous KOH in a 3:1 mixture of diethyl ether and chloroform at 0 °C, in the presence of a catalytic amount of tetra-*n*-butylammonium hydrogen sulfate.[242]

The first enantioselective synthesis of 2*H*-azirines via the Neber rearrangement started from amidoxime *O*-mesylate **722** with sodium methoxide in ethanol to afford 3-amino-2*H*-azirine **723** in good yield and ee (Scheme 151).[243] Later, *O*-tosylated oximes of *β*-keto esters were converted into optically active azirine esters using chiral bases such as cinchona alkaloids (quinidine, dihydroquinidine).[244] In a similar way, phosphorylated alkyl- and aryl-substituted azirines have been obtained from *β*-

Scheme 151



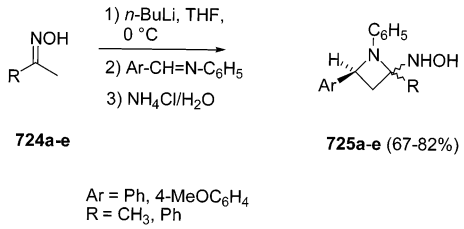
ketoxime diphenylphosphine oxides[245] and β-ketoxime diethylphosphonates[246] (in 94−96% yield and 24−82% ee, and 85−95% yield and 2−24% ee, respectively), using quinine, quinidine, hydroquinidine, and (−)-sparteine as bases. The latter strategies were extended to solid-phase synthesis using polymer-supported amines derived from diethylamine, morpholine, and (*S*)-(+)- and (*R*)-(−)-2-(methoxymethyl)-pyrrolidine.[247,248]

4.4. Synthesis of Four-Membered Heterocyclic Compounds

4.4.1. Synthesis of Azetidines

Readily available acetophenone oximes **724** afforded ring closure to 2-hydroxylamino 1,2,4-trisubstituted azetidines **725** in 55−82%, upon treatment with 2 equiv of butyllithium in THF at 0 °C, followed by addition of benzylidenanilines (Scheme 152).[249] No evidence about the stereochemical outcome was reported. The mechanism involved the formation of the 1-azaallylic dianions, followed by nucleophilic addition of the carbanion to the imines, and ring closure. The intermediate adducts could not be isolated.[249]

Scheme 152

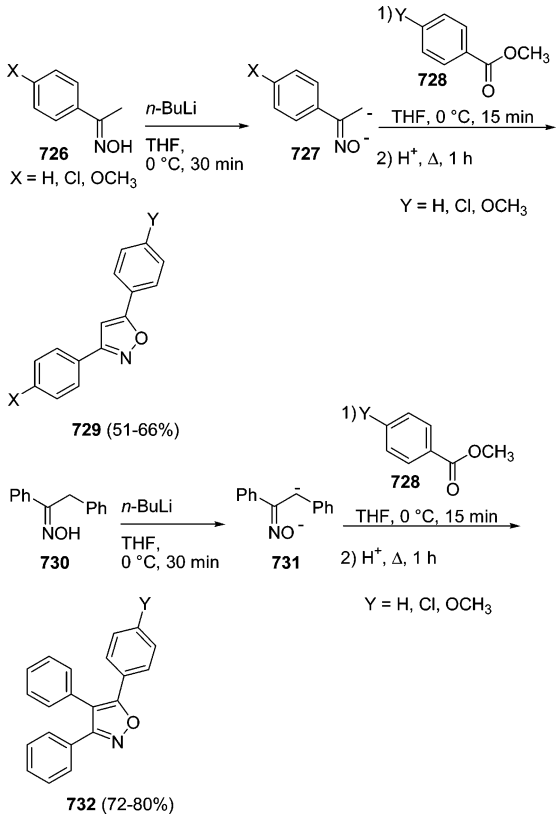


4.5. Synthesis of Five- and Six-Membered Heterocyclic Compounds

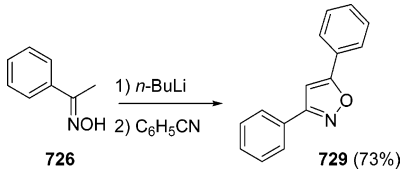
4.5.1. Synthesis of Isoxazoles, Isoxazolinones, and Isoxazolines

Several oximes, such as *para*-substituted acetophenone oximes **726** and deoxybenzoin oxime **730**, were converted to their dilithio salts **727** and **731** with two molar equivalents of *n*-butyllithium (Scheme 153). Aroylation of the dianions **727** and **731** with methyl benzoate or methyl *para*-substituted benzoates **728** followed by acid cyclization yielded the corresponding 3,5-diarylisoxazoles **729** and 3,4,5-triarylisoxazoles **732**, respectively.[250,170] When dilithiooximes were condensed with ethyl benzoyl acetate and methyl salicylate, the corresponding 5-phenylacylisoxazoles and 5-hydroxyphenylisoxazoles were prepared.[171] Similar reaction of the oxime dianion derived from **726** with nitriles also led to isoxazole **729** (Scheme 154).[173] Instead of esters[179,251−254] and nitriles, also amides and amide derivatives could be used for the synthesis of isoxazoles **735**.[255,256] The acylation of dilithiocyclohexanone oxime **733** with excess *N*,*N*-dimethylformamide, followed by acid cyclization, gave the desired isoxazole **735** in 87% yield (Scheme 155).[255] *C*(α),*O*-Dilithiooximes were also reacted with diesters to give the corresponding bisisoxazoles upon acid cyclization.[257]

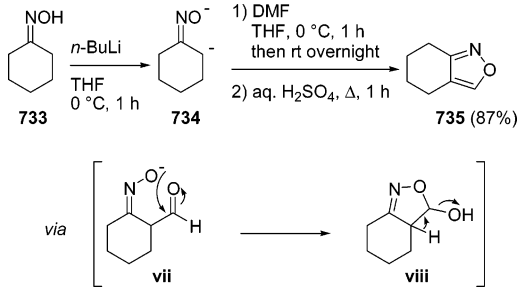
Scheme 153



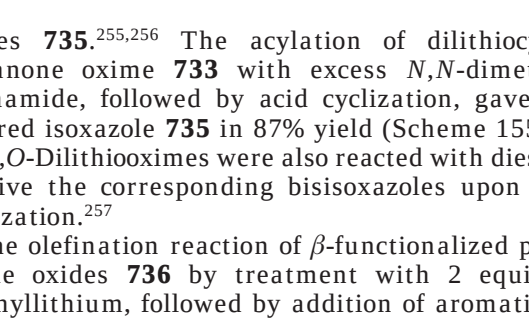
Scheme 154



Scheme 155



Scheme 156

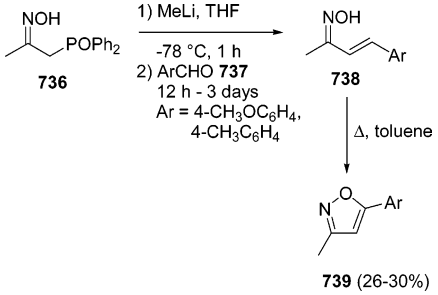


Several oximes, such as *para*-substituted acetophenone oximes **726** and deoxybenzoin oxime **730**, were converted to their dilithio salts **727** and **731** with two molar equivalents of *n*-butyllithium (Scheme 153). Aroylation of the dianions **727** and **731** with methyl benzoate or methyl *para*-substituted benzoates **728** followed by acid cyclization yielded the corresponding 3,5-diarylisoxazoles **729** and 3,4,5-triarylisoxazoles **732**, respectively.[250,170] When dilithiooximes were condensed with ethyl benzoyl acetate and methyl salicylate, the corresponding 5-phenylacylisoxazoles and 5-hydroxyphenylisoxazoles were prepared.[171] Similar reaction of the oxime dianion derived from **726** with nitriles also led to isoxazole **729** (Scheme 154).[173] Instead of esters[179,251−254] and nitriles, also amides and amide derivatives could be used for the synthesis of isoxazoles **735**.[255,256] The acylation of dilithiocyclohexanone oxime **733** with excess *N*,*N*-dimethylformamide, followed by acid cyclization, gave the desired isoxazole **735** in 87% yield (Scheme 155).[255] *C*(α),*O*-Dilithiooximes were also reacted with diesters to give the corresponding bisisoxazoles upon acid cyclization.[257]

The olefination reaction of β-functionalized phosphine oxides **736** by treatment with 2 equiv of methyllithium, followed by addition of aromatic aldehydes **737**, led to α,β-unsaturated oximes **738**, which cyclized in toluene via intramolecular Michael addition, giving isoxazoles **739** (Scheme 156).[258]

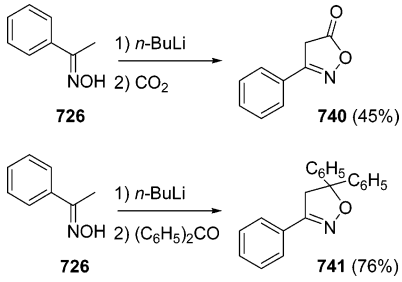
The use of carbon dioxide as electrophile for the reaction with 1,4-dimetalated oximes derived from

Scheme 156



726 afforded the corresponding 2-isoxazolin-5-ones **740**,[259] while aldehydes and ketones yielded isoxazolines such as **741** (Scheme 157).[260] 5-Aminoalkylated isoxazolines were formed by reaction of the dianions of oximes with 2*H*-azirines.[169]

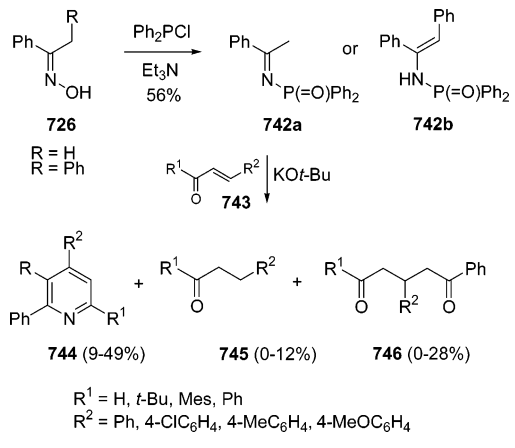
Scheme 157



4.5.2. Synthesis of Pyridines

Another elegant way for the generation of phenyl-substituted pyridines started from oximes **726**, which were masked as *N*-(phosphinyl)imines **742**. After treatment of **742** with potassium *tert*-butoxide in benzene at room temperature, *N*-phosphinyl-1-aza-allylic anions were formed, which were added across α,β-unsaturated carbonyl compounds **743**, affording phenyl-substituted pyridines **744** via Michael addition, followed by intramolecular aza-Horner−Wittig reaction (Scheme 158). The reaction also produced ketones **745** and 1,5-diones **746** as side products.[261]

Scheme 158

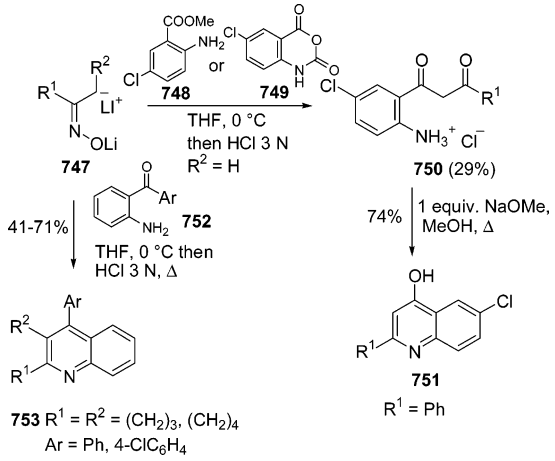


4.6. Synthesis of Bicyclic and Polycyclic Compounds

4.6.1. Synthesis of Quinolines, Ring-Fused Pyridines, and Indolizidines

Oxime dianions **747** underwent condensation−cyclization reactions with 2-aminobenzophenones **752** and methyl anthranilate **748** or 5-chloroisatoic anhydride (**749**) to yield substituted quinolines **753** and **751,** respectively.[262,263] In the case of 6-chloro-4-hydroxy-2-phenylquinoline (**751**) the reaction was performed in two steps, involving the condensation of oxime **747** with **749**, followed by treatment with diluted acid, giving the resulting hydrochloride which was refluxed in methanol in the presence of 1 equiv of sodium methoxide (Scheme 159).[219] The overall

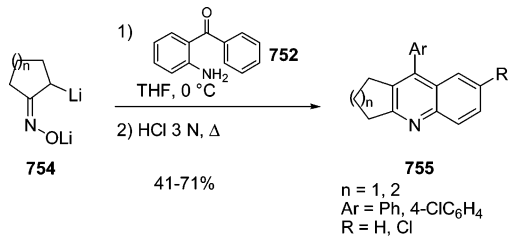
Scheme 159



yield of the two-step procedure was lower than that of the corresponding one-pot synthesis of *n*-benzoylhydrazone of 4-methylacetophenone and 5-chloroisatoic anhydride (Scheme 136), i.e., 21% vs 28% overall yield, respectively.[219]

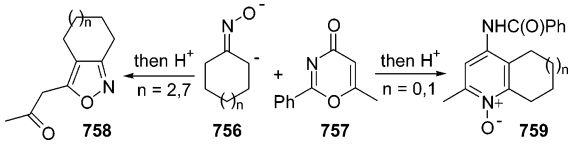
In a similar way, cyclopentanone and cyclohexanone oxime dianions **754** were condensed with 2-aminobenzophenone (**752**) to give the corresponding lithiated intermediates that were then neutralized, hydrolyzed, and cyclized to quinoline derivatives **755** (Scheme 160).[219]

Scheme 160



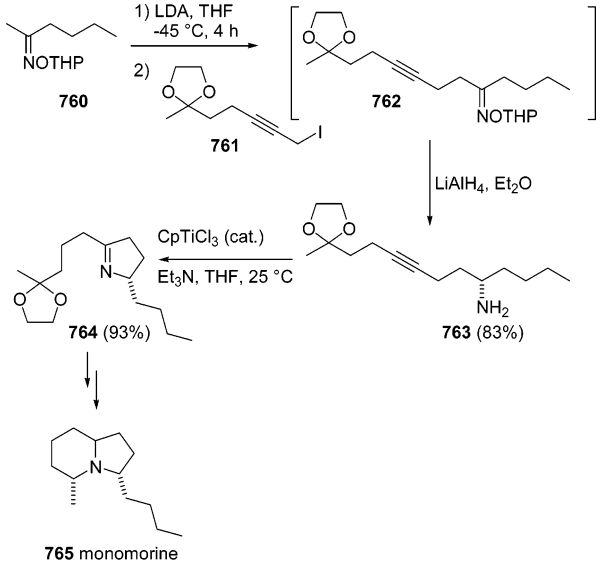
Ring-fused pyridine *N*-oxides **759** were prepared after treatment of 6-methyl-2-phenyl-4*H*-1,3-oxazin-4-one (**757**) with oxime dianions **756** derived from cyclopentanone oxime and cyclohexanone oxime, whereas reaction of the dianions **756** of cycloheptanone oxime and cyclododecanone oxime with oxazin-4-one **757** afforded the corresponding isoxazoles **758** (Scheme 161).[264]

Scheme 161



Lithiation of the *O*-(tetrahydropyranyl)oxime **760** followed by alkylation with the propargyl iodide **761** afforded the thermally labile oxime **762**, which was reduced with lithium aluminum hydride to give the key aminoalkyne **763** (Scheme 162).[265] This amino-

Scheme 162



alkyne **763** was subjected to an imidotitanium [2+2] cycloaddition, giving rise to the 1-pyrroline **764**. Further transformation led to (±)-monomorine (**765**). Similar aminoalkynes underwent imidotitanium alkyne [2+2] cycloaddition−azatitanetine acylation in the presence of acyl cyanides, leading to functionalized pyrrolidine derivatives.[266]

5. Miscellaneous (Oxazolines, 2-Methylpyridines, 2-Methylquinolines, 2-Methylbenzothiazolines)

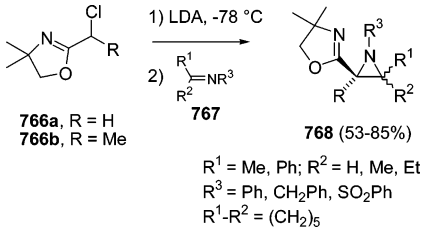
Recently some 2-(haloalkyl)heterocycles, which can give rise to related 1-azaallylic anions (vide supra), have been disclosed as suitable reagents for Darzens-type reactions with carbonyl compounds and imines for the synthesis of oxiranes[267−270] and aziridines,[271−273] with nitrones to give alkenylheterocycles[274,275] (not related to this review), and with electron-poor alkenyl heterocycles to synthesize highly heterosubstituted cyclopropane derivatives (not related to this review).[276,277] In the absence of an electrophile some of these activated heterocycles can undergo dimerization or trimerization according to the structure of the anions.[276−278] However, some classes of heterocycles such as 2-oxazolines bearing a substituent at the 2-position, containing at least one hydrogen atom at α, have been used to generate 1-azaallylic anions, useful for the synthesis of heterocycles. Accordingly, these 2-oxazolines are covered in this review as well. To a very minor extent, such anions derived from pyridines, quinolines, and benzothiazoles will be mentioned here.

5.1. 2-Methyloxazoline Anions

5.1.1. Synthesis of Aziridines

The synthesis of aziridines **768** resulted from the treatment of 2-chloromethyl-4,4-dimethyl-2-oxazoline (**766a**) and 2-(1-chloroethyl)-4,4-dimethyl-2-oxazoline (**766b**) with LDA in THF at −78 °C, followed by addition of the imines **767** (Scheme 163).[272,273] The

Scheme 163

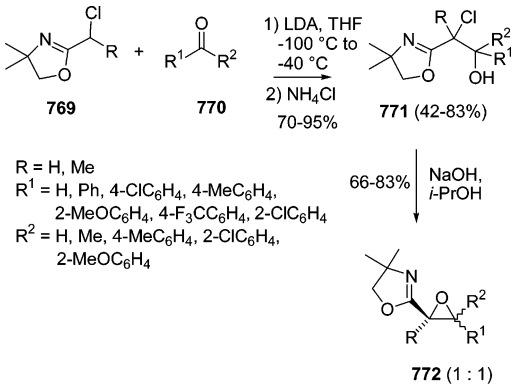


mechanism proceeds according to a Darzens-type reaction. The use of aromatic imines **767** led to the *trans* diastereomer as the major or the unique isomer (i.e., **768**; de = 100%; R = Me; R^1 = H; R^2 = Ph; R^3 = CH_2Ph).

5.1.2. Synthesis of Oxiranes

Addition of LDA in THF to a solution of 2-chloromethyloxazoline **769** and aldehydes **770** resulted in chlorohydrins **771**. The latter were treated with NaOH in *i*-PrOH to produce the corresponding oxiranes **772** in a 1:1 mixture of *cis*/*trans* isomers (Scheme 164).[267,268,273]

Scheme 164

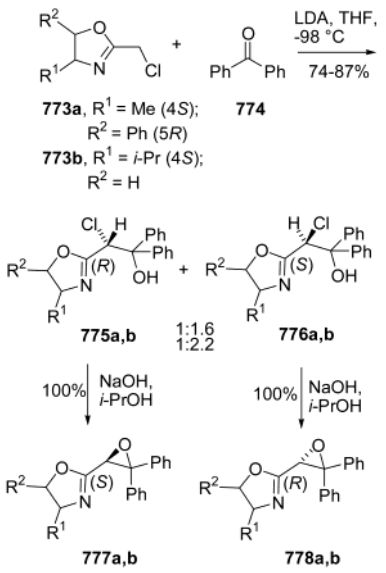


When a chiral substituent is present in the oxazoline ring, the latter procedure is suitable for the formation of optically active oxiranes.[279] For instance, lithiated 1-chloromethyl-2-oxazolines **773a,b** furnished diastereomeric mixtures of chlorohydrins **775** and **776** upon reaction with benzophenone. These mixtures could be separated and ring closed to the corresponding chiral oxiranes **777** and **778** by treatment with NaOH in *i*-PrOH (Scheme 165).[269] In a similar way, a THF solution of oxazoline **773c** and ketones **779** (benzophenone, 4,4′-dichlorobenzophenone, cyclohexanone, cyclododecanone, 2-adamantanone) was added to LDA in THF at −98 °C, giving inseparable mixtures of chlorohydrins that were converted to mixtures of diastereomeric epoxides **780** (Scheme 166).[269]

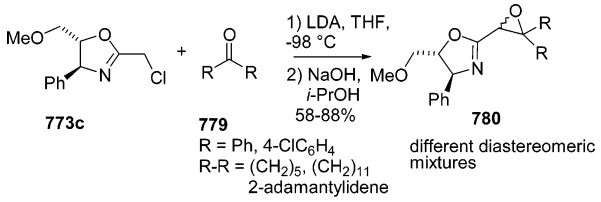
5.1.3. Synthesis of γ-Butyrolactones

Lithiated oxazolines, generated from oxazolines **781** with LDA in THF at −78 °C in the presence of TMEDA, were reacted with epoxides **782**, resulting in the hydroxypropyloxazolines **783**. Hydrolysis of the

Scheme 165

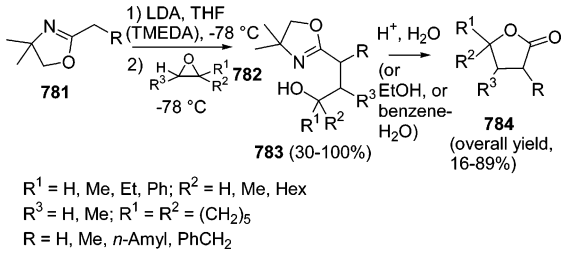


Scheme 166



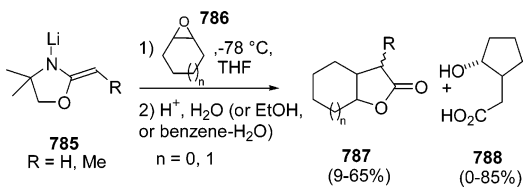
latter produced a variety of γ-butyrolactones functionalized at the α-, β-, or γ-position in high overall yields (Scheme 167).[280] Poor yields or no ring-opened

Scheme 167



products were observed when 1,2-disubstituted epoxides were used, with the exception of cyclohexene and cyclopentene oxides (Scheme 168). The hydrolysis steps were carried out in three different procedures, namely, refluxing in 3 N hydrochloric acid, by long heating in a solution of concentrated sulfuric acid in 95% ethanol, or reflux of toluenesulfonic acid in a benzene−water mixture for 18 h.[280] The reactions of the oxazoline anions **785** with cyclohexene oxides **786** ($n = 1$) afforded lactone **787**. The γ-hydroxy acid **788** appeared as the major compound when cyclo-

Scheme 168

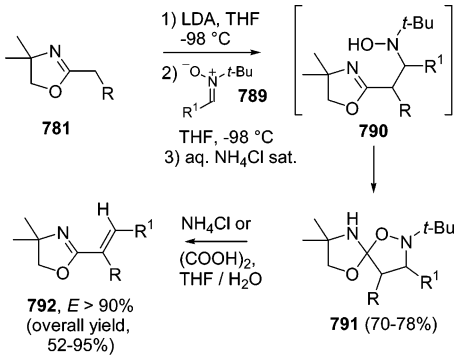


pentene oxide **786** ($n = 0$) was used as electrophile (Scheme 168).

5.1.4. Synthesis of Spiro Heterocyclic Compounds

An elegant synthesis of spirocyclic isoxazolidines started from the lithiation of 2,4,4-trimethyl-4,5-dihydro-1,3-oxazoles **781** with nitrone derivatives **789** (Scheme 169). Most of the spiro compounds were not

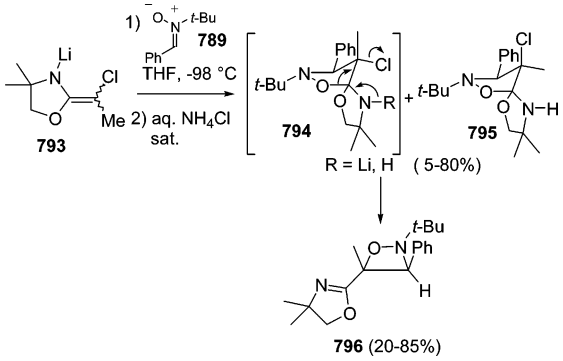
Scheme 169



isolated, as they were converted to 2-(*E*)-alkenyl-4,5-dihydro-1,3-oxazoles **792** upon longer reaction times (18 h), with the elimination of *tert*-butylhydroxylamine. The spiro heterocycle **791** (R = H; R^1 = Ph) and the hydroxylamine derivatives **790** (R = H; R^1 = Ph) occurred as an equilibrium mixture in solution in deuterated chloroform.[281]

As previously described, lithiated 2-(1-chloroethyl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole **793** reacted with nitrone **789**, furnishing the spirocyclic compounds **794** and **795**, together with the oxazolinyloxazetidine **796** in different relative amounts according to the reaction times (Scheme 170). Quenching the reaction upon 5 s afforded compounds **794**, **795**, and **796** in a 74:6:20 ratio, while quenching after 1 h of reaction gave 85% **796** and <5% compounds **794** and **795**.[281]

Scheme 170

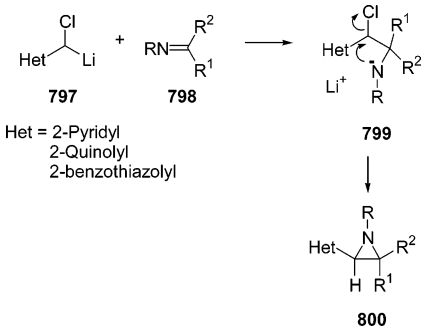


5.2. Heteroarylchloromethyl Anions

Lithiation of chloromethylheteroaryl compounds, such as 2-chloromethylpyridine, 2-chloromethylquinoline, and 2-chloromethylbenzothiazole, with LDA in THF at −78 °C affords heteroarylchloromethyl anions **797**, which subsequently react with imines **798** to lead to heteroarylaziridines **800** in a

stereoselective way via Darzens-type reaction (Scheme 171).[271] When aldimines **798** were used (Scheme 171; R = Ph, SO_2Ph; R_1 = Ph; R_2 = H) the *trans*-isomer was the only one observed.[271]

Scheme 171



797 798 799 800

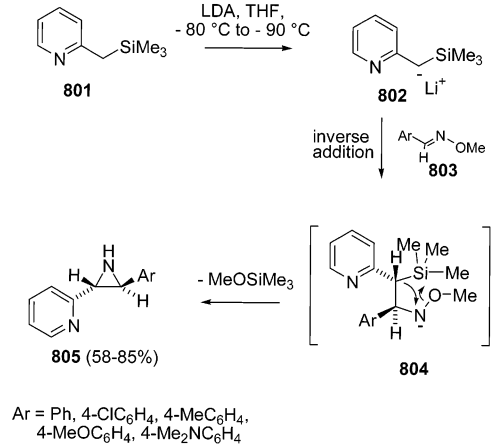
5.3. 2-Methylpyridine Anions

Although there is a great similarity of 2-methylpyridine (2-picolyl) anions to 1-azaallylic anions, as recently shown via computational studies,[37] only some leading references will be highlighted further and no discussion with complete coverage will be provided for the use of this type of building block.

5.3.1. Synthesis of Aziridines

2-(Trimethylsilylmethyl)pyridine (**801**) underwent deprotonation with LDA to generate the corresponding 1-azaallylic anion, which reacted with oxime ethers **803** to afford the adducts **804**, which gave the corresponding *trans*-2-aryl-3-(2-pyridyl)aziridines **805**. High yields of aziridines were recorded only when a THF solution of anion **802** was added to a THF solution of compounds **803** between −80 and −90 °C (Scheme 172).[282]

Scheme 172

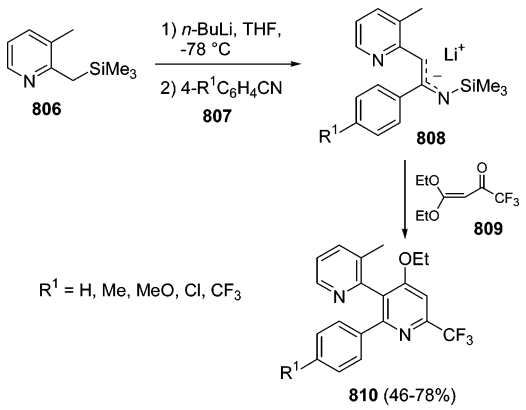


801 802 803 804 805 (58-85%)

5.3.2. Synthesis of Pyridines

N-Trimethylsilyl-1-azaallylic anions **808**, easily formed from the corresponding aromatic nitriles **807** and the α-silyl carbanion derived from 3-methyl-2-(trimethylsilylmethyl)pyridine (**806**), are ambident nucleophiles, readily available for the synthesis of *N*-heterocyclic compounds.[283−285,106] In this matter, *N*-trimethylsilyl-1-azaallylic anions **808** were converted to heavily functionalized pyridine derivatives

Scheme 173



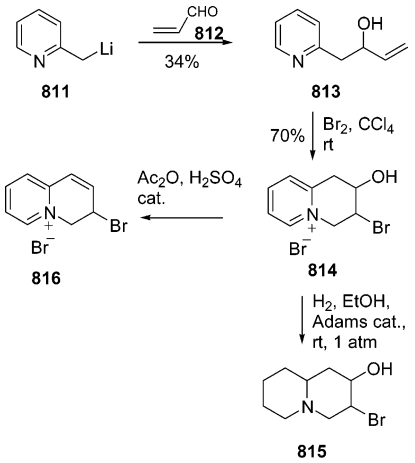
806 807 808 809 **810** (46-78%)

810 via Michael addition−ring closure with trifluoroacetylketene diethyl acetal **809** (Scheme 173).[106]

5.3.3. Synthesis of Quinolizinium Salts

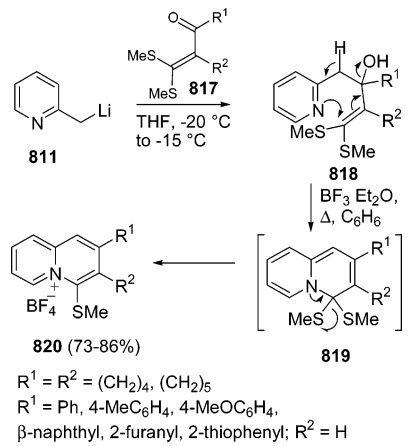
Condensation of 2-picolyllithium (**811**) with acrolein (**812**) gave rise to the pyridinyl alcohol **813**, which spontaneously cyclized to 1,2,3,4-tetrahydroquinolizinium bromide **814** upon bromination with bromine in carbon tetrachloride (Scheme 174).[286] The resulting tetrahydroquinolizinium salt **814** afforded the dehydration product 3-bromo-3,4-dihydroquinolizinium bromide (**816**) in acetic anhydride with acid catalysis, and 3-bromooctahydro-2*H*-quinolizin-2-ol

Scheme 174



811 812 813 814 815 816

Scheme 175



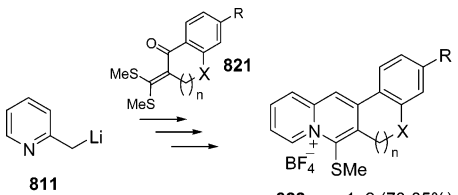
811 817 818 819 **820** (73-86%)

(**815**) upon hydrogenation with Adams catalyst in ethanol.[286]

In a similar way, when **811** was reacted with β,β-dimethylthio α,β-unsaturated ketones **817**, adducts **818** were cyclized to quinolizinium tetrafluoroborate **820** in the presence of boron(III) fluoride etherate in refluxing benzene in 73−86% overall yields (Scheme 175).[287]

Analogously tetracyclic derivatives **822** were generated from anion **811** and enones **821** (Scheme 176).[287]

Scheme 176



6. Acknowledgments

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