SYNTHETIC APPROACHES TO CONIINE AND OTHER 2-ALKYL PIPERIDINES[†]

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Abstract. *The first synthesis of coniine, a neurotoxic piperidine alkaloid found in poison hemlock (*Conium maculatum *L.), was performed back in 1886 by Ladenburg. Since that time, numerous different approaches to the synthesis of this and related alkaloids (2-alkylpiperidines) have been developed. Nowadays, the enantioselective/specific synthesis of coniine is taken as a paradigm of the usefulness of new chiral synthetic methodologies. This review aims to summarize and systematize recent progress in the synthesis of coniine and related compounds.*

Key words: *synthetic approaches, coniine, 2-alkylpiperidines*

1. INTRODUCTION

Alkaloids containing 2-substituted piperidine core are produced by several different plant taxa [1]. Many of these compounds are attributed with pronounced biological/pharmacological activity. For example, coniine and γ-coniceine are the main toxic principles of one of the most poisonous members of the plant kingdom, *Conium maculatum* L. (poisonous hemlock) [2,3]; some 2-alkylpiperidines inhibit neuromuscular, ganglionic, central neuronal nicotinic acetylcholine receptors, HIV-protease, etc. [4,5].

High biological activity of this group of compounds definitely made them interesting from medicinal, pharmacological, toxicological, biological and (bio)chemical points of view. However, many piperidine alkaloids are often available in only trace amounts from natural sources [5]. Thus, the only reasonable way to acquire suitable quantities of the naturally (plant) occurring 2-alkylpiperidines (or their analogues/derivatives) for activity- or studies oriented toward structural elucidation is via their synthesis. Thus, it is not surprising that starting from Ladenburg's synthesis of coniine back in 1886 (Scheme 1) [6]– this is believed to be the very first synthesis of an alkaloid [1]–a number of synthetic ap-

proaches to 2-alkylpiperidines have been developed [7]. In this review, we have tried to summarize and systematize these different approaches, starting from the "Ladenburg's time" to the latest, sophisticated stereocontrolled syntheses.

We thought it to be convenient to divide the text on the basis of the process (reaction) leading to the formation of the piperidine ring, either starting from an appropriate acyclic precursor or from some other available six membered nitrogen heterocycle. We adopted this approach from an excellent review on the stereocontrolled synthesis of piperidone- and piperidine-type heterocycles [8]. We have tried to systematize quite a large volume of available literature data on the topic in a way as to provide the reader a variety of different options and did not attempt to give comprehensive overview of the subject. In other words, we have not tried to give an exhaustive survey of all papers ever published on the synthesis of this type of compounds, but to critically address different synthetic routes, with special attention paid to their diversity and efficiency.
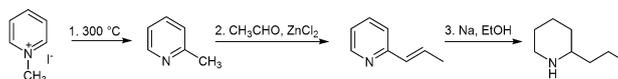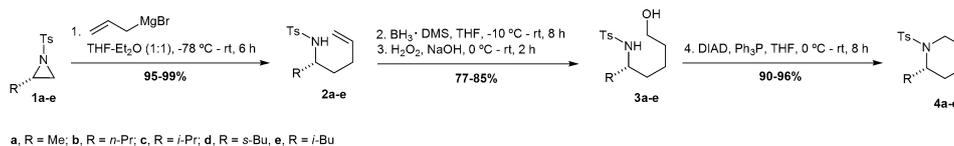

Scheme 1

2. Synthesis of Coniine and Other 2-Alkyl Substituted Piperidines

2.1. Intramolecular N-C bond formation

2.1.1. Nucleophilic substitutions

Intramolecular S_N2 displacement of a halide or activated alcohol by a nitrogen nucleophile is a well-established method for the formation of piperidine rings. The application of this methodology in the synthesis of 2-alkylpiperidines is based on obtaining an appropriate precursor with 1,5-relationship of the nitrogen nucleophile and the leaving group. In the last 20 years there were several reports published dealing with different stereocontrolled approaches to 1,5-aminoalcohols which are suitable substrates for an efficient intramolecular S_N2 reaction known as Mitsunobu reaction. Syntheses of coniine and coniine-like alkaloids based on an asymmetric Mitsunobu reaction were performed starting from naturally occurring L-α-amino acids [6], by using (S)-l-amino-2-methoxymethylindoline (SAMI) hydrazones as chiral auxiliaries in additions of organolithiums [9], by employing chiral catalysts in Sharpless asymmetric dihydroxylation [10] or chiral quinap ligands in copper-catalyzed one-pot three-component condensation reactions of terminal alkynes, aldehydes and secondary amines [11] and etc. Singh and Bisai developed an efficient and a generally flexible approach to chiral 2-substituted *N*-tosylpiperidines starting from chiral α-substituted-*N*-tosylaziridines **1a-e** (Scheme 2) which could easily be synthesized from naturally occurring L-α-amino acids. In this synthesis the regioselective cleavage of *N*-tosylaziridines **1a-e** by allylmagnesium bromide was achieved in almost quantitative yield. Thus, the obtained alkenes **2a-e** were subjected to hydroboration using BH₃·DMS (borane dimethylsulfide complex), followed by an oxidative cleavage of the borane adduct to provide 1,5-*N*-tosyl amino alcohols **3a-e**. These were further cyclized using triphenylphosphine and diisopropyl azodicarboxylate (DIAD) *via* Mitsunobu condensation. In this way, *N*-tosyl-(S)-coniine **4b** was acquired in the overall yield of 70%.

Scheme 2

2.1.2. Imine, enamine or 2-piperidone reduction; reductive amination

Intramolecular cyclization of 1,5-aminocarbonyl (or related) compounds is an often used strategy in the synthesis of the title alkaloids. Initially obtained imines, iminium ions, enamines or 2-piperidones are subsequently reduced to give the target 2-alkylpiperidines. Modification of such an approach even enables directing the stereochemistry of C-2 center. A brilliant strategy for the enantioselective synthesis of (*S*)-coniine **9**, in a very concise fashion, was achieved by using enantiopure (*S*)-1-(1-phenylethyl)-2-methylene-aziridine **5** as the chiral starting material [12]. The aziridine was first converted to a metalloenamine, which was then alkylated by a 1,3-difunctionalized electrophile ($ICH_2CH_2CH_2I$). *In situ* cyclisation of the resultant imine **6** and the reduction of the obtained iminium cation **7** led directly to the piperidine **8.** Thus, the sequential formation of two C–C bonds, one C–N bond and a C–H bond was formally achieved in a single-step (one pot transformation) (Scheme 3). The high level of stereochemical control seen in favor of the (2*S*)-diastereomer **8** can be rationalized by assuming that the iminium cation **7** adopts a conformation in which the allylic 1,3-strain is minimized by projecting the hydrogen atom of the benzylic carbon towards the propyl group, with a subsequent hydride addition from the least hindered *re*-face.
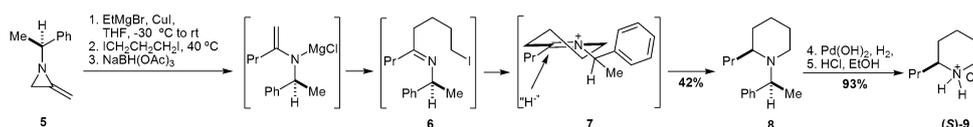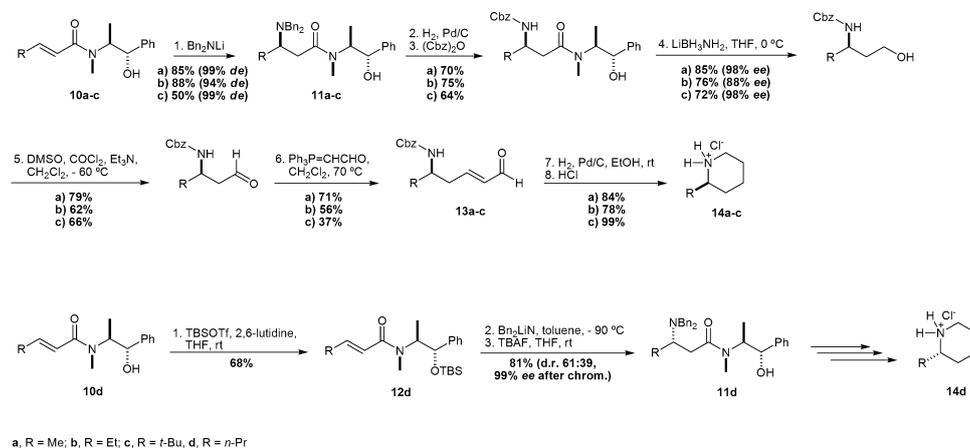

Scheme 3

Hartley et al. (2006) showed that alkylidenetitanium reagents smoothed the progress of the reagent-controlled high throughput asymmetric synthesis of 2-alkylpiperidines and rapid access to multiple cyclic imines using solid-phase synthesis [13]. The usefulness of a method based on the diastereoselective addition of pent-4-enylmagnesium bromide to a chiral oxime ether of butyraldehyde in the presence of boron trifluoride etherate was illustrated by the synthesis of (*S*)-coniine **9** [14].

Intramolecular cyclization of 1,5-aminoesters leads to 2-piperidone skeletons, which could be easily converted to 2-alkylpiperidines by $LiAlH_4$ reduction. A highly efficient stereoselective synthesis of (*S*)-coniine **9** carried out by Davies and coworkers nicely demonstrates the utility of this methodology in the synthesis of 2-alkylpiperidines [15]. This procedure applies the combination of diastereoselective conjugate addition of lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide to a α,β-unsaturated Weinreb amide and DIBAL-H[1]/Wadsworth–Emmons sequence for the synthesis of the 2-piperidone skeleton.

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[1] Diisobutylaluminum hydride

Another quite simple and very efficient protocol for the preparation of highly enanti-oenriched 2-alkylpiperidines has been recently set up [16]. The protocol allows the preparation of both possible stereoisomers (configurations at C-2) from the very same starting material. The key step of this synthesis relies on a diastereodivergent intermolecular aza-Michael reaction of the readily available and cheap derivatives of (+)-(S,S)-pseudoephedrine as chiral auxiliaries. Usage of unmodified chiral auxiliaries (**10a-c**) leads to the formation of **11a-c**. But, if the chiral auxiliary is modified, e.g. if -OH group from (+)-(S,S)-pseudoephedrine converted to a bulky trialkylsilyl ether moiety (**12d**), an aza-Michael adduct **11d** would be formed. In comparison to **11a-c**, **11d** would have the opposite configuration at the newly created stereogenic center (stereodivergent protocol for the asymmetric synthesis of β-aminocarbonyl compounds). Obviously, the aza-Michael reaction was only utilized to set the appropriate stereochemistry; the desired piperidinic structures **14a-d** were formed from δ-amino aldehydes **13a-d** via a cascade process, involving hydrogenation of the C-C double bond, followed by removal of the N-Cbz[2] protecting group and a final intramolecular reductive amination step (Scheme 4).


a, R = Me; **b**, R = Et; **c**, R = t-Bu, **d**, R = n-Pr

Scheme 4

2.1.3. Aza-Michael addition

Conjugate addition of amines or their synthetic equivalents to α,β-unsaturated compounds represents a readily employed method for C-N bond formation. The resulting β-aminocarbonyl adducts are structural fragments found in many natural products or pharmaceutical agents. Despite the importance of this methodology, a catalyzed enantioselective aza-Michael reaction remains elusive and can thus be considered as a challenging task. Just a few years ago, Fustero and coworkers described a highly enantioselective organocatalytic intramolecular aza-Michael reaction of carbamates bearing a remote α,β-unsaturated aldehyde moiety (Michael acceptor) [17]. The starting carbamate derivative **16** was assembled through a cross metathesis reaction of the corresponding unsaturated carbamate **15** with acrolein. The reaction was catalyzed by a second-generation Hoveyda-

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[2] Carboxybenzoyl

Grubbs catalyst (Scheme 5). The enantioselective intramolecular aza-Michael addition reaction itself was efficiently catalyzed by a prolinol derivative known as Jørgensen catalyst **17**. Finally, intermediate **18** was subjected to a Wittig reaction and subsequent hydrogenation and gave (*S*)-coniine **9**. The role of Jørgensen catalyst was to activate the *α,β*-unsaturated carbonyl compound through the "iminium ion mechanism", and, therefore, to facilitate intramolecular addition of the nucleophile to the *β*-carbon atom. The *si* face of the *E*-diene intermediate is shielded by the chiral group of the catalyst. Thus, the nitrogen nucleophile would approach from the *re* face. Nevertheless, if the CH$_2$-group *β* to the N-atom is replaced by O, S, or N-PG[3], CIP-priority of the substituents is reversed, and in these cases the N-nucleophile would attack from the *si* face [17] (although this is only a formal change of the side of attack).
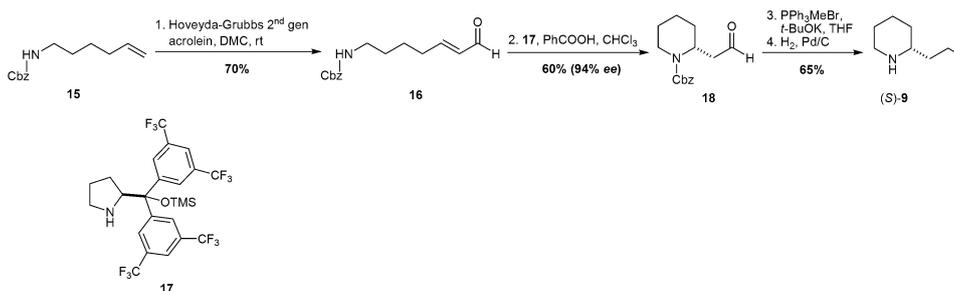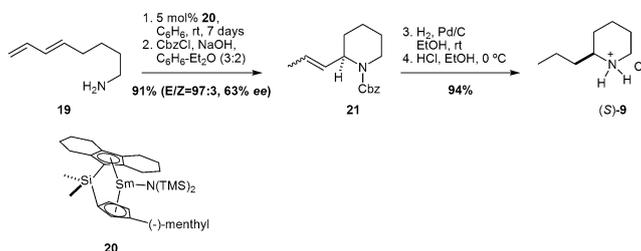

Scheme 5

2.1.4. Hydroamination-cyclisation

Catalytic N-H addition to C-C multiple bonds is av convenient approach to the synthesis of organonitrogen molecules. Organolanthanides were found to be highly efficient catalysts for inter- and intramolecular hydroamination/cyclization of aminoalkenes, aminoalkynes, and aminoallenes, reflecting the facile insertion of C-C unsaturation into lanthanide-ligand *σ* bonds. Nevertheless, an efficient cyclization of amine-tethered 1,2-disubstituted alkenes, which could be a very concise, elegant route to 2-substituted substituted piperidines, has remained elusive. This inherent limitation in 1,2-disubstituted alkene insertion is attributed to severe nonbonding steric repulsions and a possible charge separation imbalance in the relatively well-characterized transition state. The most prominent results in this area were achieved in the study of Marks and coworkers [18], who developed a route to five- and six membered rings through highly diastereoselective intramolecular hydroamination/cyclization of primary and secondary amines tethered to conjugated dienes. The reaction is catalyzed by organolanthanide complexes such as **20** (Scheme 6). This transformation is highly regioselective: 2-substituted pyrrolidines and piperidines (for instance compound **21**) are formed *via* 5-*exo* and 6-*exo* cyclizations, respectively, with no evidence of the alternative 6- or 7-*endo* products. Moreover, in contrast to aminoallene hydroaminations in which the *Z* double bond isomer is generally obtained as a major product, good-to-high *E* double bond selectivity is observed with these aminodienes. This strategy enabled high-yield, two-step conversion of the prochiral ami-

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[3] Protecting group

nodiene substrate **19** to (*S*)-coniine hydrochloride (**9**). Although currently available chiral organolanthanide catalysts do not allow complete enantioselection in the key hydroamination/cyclization step, this example demonstrates the potential synthetic utility of this approach to 2-alkylpiperidines.

Scheme 6

2.1.5. Syn-azapalladation

Pd^{II}-catalyzed C-N bond formation reactions have been documented well in the literature and proceed under mild conditions with high functional group tolerance and high stereoselectivities. Recently, Uenichi *et al.* have reported an efficient and general method for the syntheses of 2- and 2,6-substituted piperidines using a Pd^{II}-catalyzed 1,3-chirality-transfer reaction of chiral allylic alcohols [4]. The syntheses of (*S*)- and (*R*)-coniine **9** were achieved in 3 steps from the optically pure allylic alcohols (*S*)- and (*R*)-**22**, respectively. 2-Alkylpiperidines (*S*)- and (*R*)-**23** were obtained with high stereoselectivities by cyclization of the appropriate *N*-protected aminoallylic alcohols (*S*)- and (*R*)-**22** in the presence of PdCl$_2$(CH$_3$CN)$_2$ which was found to be the best catalyst for this transformation (Scheme 7). A plausible reaction pathway involves a chiral-secondary-allylic-alcohol-directed formation of a Pd π-complex, followed by *syn*-azapalladation, and a subsequent *syn*-elimination of PdCl(OH).
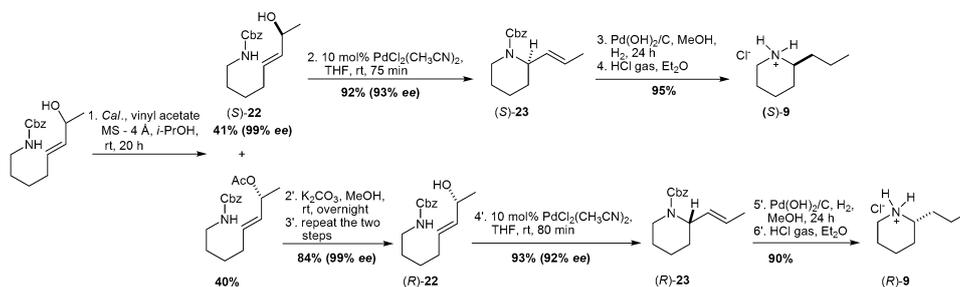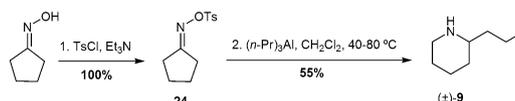

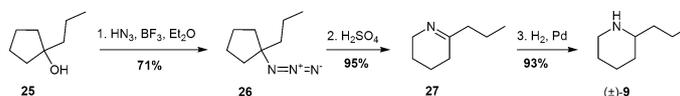**Scheme 7**

2.1.6. Ring expansions

The Beckmann rearrangement of oxime sulfonates with simultaneous nucleophilic trapping of the intermediary imino carbocation by organoaluminum reagents was described as a highly efficient two-step route to racemic coniine (±)-**9** [19]. In this synthesis (±)-**9** was

obtained as the major product only after switching the initial temperature from −78 to 40-80 °C. Such conditions favor (±)-**9** over cyclopentylamine (Scheme 8). Most probably, rapid dissociation of theb dimeric tri-*n*-propylaluminum at high temperature enhances its Lewis acidity (this favors the rearrangement of oxime sulfonate **24**), as well as the nucleophilicity of *n*-propyl groups from (*n*-Pr)$_3$Al toward intermediary formed imino carbocation. A similar N-insertion approach to the synthesis of 2-pentylpiperidine (conmaculatine, a related hemlock alkaloid) was recently undertaken to corroborate its structure [3].

Scheme 8

Another quite efficient ring-expansion-based approach to racemic coniine employed the azide rearrangement [20]: 1-azido-1-propylcyclopentane **26**, prepared by treatment of its 1-hydroxy analog **25** with HN$_3$/BF$_3$, underwent ring enlargement with H$_2$SO$_4$ and gave γ-coniceine **27**. Finally, γ-coniceine was subjected to hydrogenation to give (±)-**9** (Scheme 9).
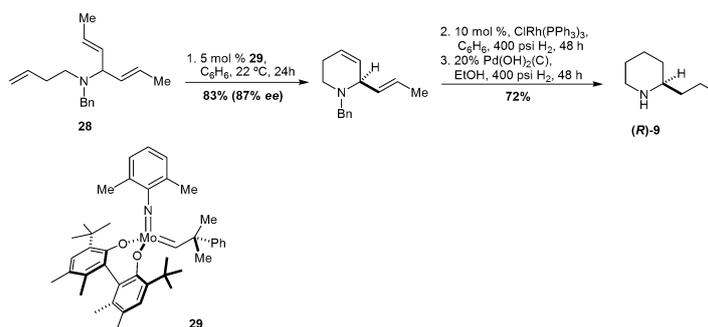

Scheme 9

2.2. C-C bond formation

2.2.1. Ring closing metathesis

The ring-closing olefin metathesis (RCM) reaction is another promising approach to the synthesis of nitrogen heterocycles. With the development of practical and reliable catalysts by Grubbs and others, RCM became a powerful synthetic method that has been successfully used for the synthesis of a vast variety of compounds, including nitrogen heterocycles. The development of chiral Mo-based catalysts (such as **29**)–these promote asymmetric ring closing metathesis (ARCM) reactions–provided access to optically enriched small and medium ring cyclic amines [21]. For example, (*R*)-coniine **9** was prepared with good enantioselectivity from the readily available achiral aminopolyene substrate **28** (Scheme 10) through a Mo-catalyzed desymmetrization followed by two simple reductive steps. Subtle variations in the structure of the chiral catalyst can lead to a significant alteration in reaction efficiency and/or enantioselectivity. Nevertheless, as possible internal chelation between the Lewis basic amine and the Lewis acidic Mo center may results in lack of reactivity, the described catalytic asymmetric method is restricted to substrates bearing the readily removable groups (such as Bn, Cbz, CF$_3$CO etc.) or to sterically hindered amines.
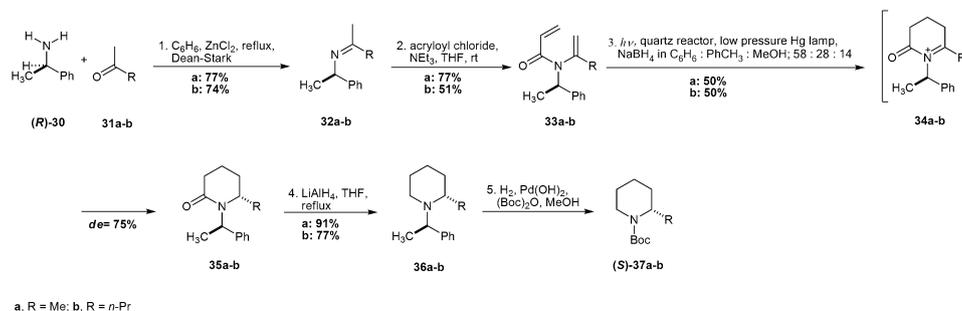
Scheme 10

The great advantage of metathesis-based syntheses of 2-alkylpiperidines is that most of them include the use of readily available starting molecules, a relatively small number of reaction steps and give final products of very high optical purity (>90%). The differences between these strategies are primarily in the manner and form in which nitrogen is introduced into the ring, as well as in the way of directing the stereochemistry of chiral centers. A common approach is that the chiral auxiliary group also serves as a source of nitrogen. α-Methyl benzylamine [22] and 1-amino-2-(methoxymethyl)pyrrolidine [23], which are commercially available in both enantiomeric forms, are usually used in this sense. The first is easily removed by catalytic hydrogenation, and the second by reductive cleavage of the N-N bond. Both readily react with aldehydes to form imines and hydrazones. The presence of a chiral center of appropriate configuration directs diastereoselective addition to the resulting C=N bond thus establishing the stereochemistry of the target structure. A similar approach to the previously described was developed by Moody and his associates [24] and is based on the diastereoselective addition to C=N bonds of easily available chiral O-(1-phenylbutyl) aldoximes. One more class of organic compounds that has played a crucial role as chiral auxiliaries in asymmetric syntheses is oxazolidin-2-ones. Coldham and coworkers have shown that organomagnesium species attack the carbonyl group and promote a ring-opening of oxazolidin-2-ones. The resulting tertiary amides are useful substrates for stereoselective transformations and might be subjected to a RCM reaction to give six-membered lactams (a formal synthesis of (−)-coniine **9** and (+)-stenusine) [25].

Besides this, the stereochemistry could also be controlled by employing chiral starting molecules. For example, hydrolysis of scalemic trichloroacetamides, followed by allylation or acylation with but-3-enoic acid, gave intermediates suitable for RCM; RCM led to the formation of unsaturated piperidine building blocks [26]. Another interesting way to control the stereochemistry in position 2 of the piperidine ring is based on tandem Mitsunobu/3,3-sigmatropic rearrangement of allylic azides: thanks to its exceptional steric bias, the chiral auxiliary system would favor formation of one of the possible isomers [27]. Subsequent ring-closing metathesis would lead toward the target heterocycle (e.g. coniine) and a recyclable form of the chiral auxiliary. The chiral aminodiene substrates for RCM could also be obtained by diastereoselective conjugate addition of lithium (S)-N-allyl-N-α-methylbenzylamide to a range of α,β-unsaturated esters [28] or starting from the commercially available amino acid L-norvaline [29].

2.2.2. Reductive photocyclization

A short, efficient and enantioselective synthesis of 2-alkylpiperidines was achieved in excellent enantiomeric excess by means of reductive photocyclization of dienamides prepared from (R)- or (S)-α-methylbenzylamine **30** as chiral auxiliaries; this allows access to both enantiomers of the desired piperidines [30]. The imines **32a-b** were obtained in excellent yield by condensation of (R)-α-methylbenzylamine **30** with acetone **31a** or pentan-2-one **31b**; further N-acylation gave dienamides **33a-b**, which are key intermediates in this synthesis (Scheme 11). The photocyclization of dienamides **33a-b** led to the intermediate acyliminium ions **34a-b,** which were reduced *in situ* by sodium borohydride to give piperidin-2-ones **35a-b**. The stereochemical outcome of this reaction could be explained by the nucleophilic addition of hydride to the intermediate iminium ions **34a-b** (these were not isolated from the reaction mixture); hydride attack took place from the less hindered side of its two diastereotopic faces. Lactams **35a-b** were then reduced with LiAlH$_4$ and thus obtained piperidines **36a-b** were first debenzylated and then converted *in situ* to their *tert*-butoxycarbamate derivatives (S)-**37a-b** (this was done in order to avoid the manipulation/contact with volatile and toxic alkaloids). The antipodal (R)-N-Boc-coniine **37b** was obtained by the same procedure using (S)-α-methylbenzylamine (S)-**30** as the chiral auxiliary. Cleavage of the carbamoyl group by treatment of small quantities of compounds (S)-**37a-b** and (R)-**37b** with trifluoroacetic acid and anisole led to (S)-pipecoline **14a**, (S)- and (R)-coniine **9** in 90% enantiomeric excess.

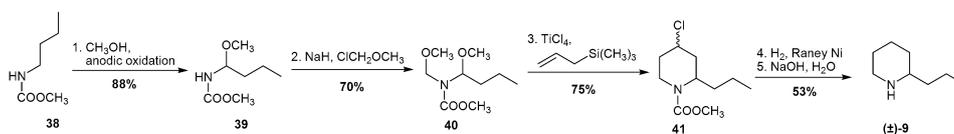**Scheme 11**

2.3. Intermolecular reactions

2.3.1. Formal [3+3] annelation

Ring formation through [m+n]-type annelation is a highly useful approach to the synthesis of cyclic compounds. A convenient method for the formation of piperidine skeletons is based on [3+3]-type annelation between allyltrimethylsilane and α,α′-dimethoxylated amide **40**; these could be easily prepared either by anodic α-monomethoxylation of N-monoalkylamide **38** followed by methoxyalkylation of the α-methoxylated product **39** or by anodic α,α′-dimethoxylation of N,N-dialkylamides [31]. (±)-Coniine **9** was prepared from the annelated product **41** by hydrogenation followed by alkaline hydrolysis (Scheme 12).

Scheme 12

2.3.2. Formal [4+2] cycloadition

Tandem Mannich-Michael and aza-Diels-Alder reactions, which could be classified as (formal) [4+2] cycloadditions, may lead to piperidine derivatives *via* 2,3-dihydro-4-pyridones. In this [4+2] cycloadditions, 1-alkoxy-3-siloxy-1,3-butadienes and its derivatives (also known as Danishefsky's dienes) are often used as activated dienes, whereas aldimines (in tandem Mannich-Michael reactions) and its stable equivalents acylhydrazones (in aza-Diels-Alder reactions) are used as dienophiles. Recently, the employment of *O*-derivatized amino sugars (e.g. 2,3,4-tri-*O*-pivaloyl-α-D-arabinopyranosylamine [32] and 2,3,4,6-tetra-*O*-pivaloyl-*β*-D-galactosylamine [33]) as chiral auxiliaries enabled successful enantioselective syntheses of piperidine alkaloids. This approach leaned on steric, stereoelectronic, and complexing properties of carbohydrates, which allowed diastereofacial differentiation of nucleophilic additions to the corresponding *N*-functionalized aldimines. Kranke and Kunz reported full experimental details for the application of D-arabinosylamine **42** in the stereoselective synthesis of 2-substituted *N*-arabinosyl dehydropiperidinones **45** and their subsequent regioselective and stereoselective modification in the preparation of variously substituted piperidines (Scheme 13). A domino Mannich-Michael reaction of 1-methoxy-3-(trimethylsiloxy)butadiene **44** (Danishefsky's diene) with *O*-pivaloylated arbinosylaldimines **43** furnished *N*-arabinosyl dehydropiperidinones **45** with high diastereoselectivity. The stereochemical course of the reaction, and hence the configuration of **45**, was controlled by the sterically demanding pivaloyl group at C-2 of the carbohydrate auxiliary, which effectively shielded the *si* side of aldimine **43**. Thus, the initial step in the domino Mannich-Michael reaction consisted of the nucleophilic addition of Danishefsky's diene **44** to the *re* side of glycosyl imine **43**. In this auxiliary-mediated synthesis of coniine, the double bond of *N*-arabinosyl-2-propyl-5,6-dehydropiperidin-4-one (**45**) was reduced with lithium tri*sec*-butylborohydride (L-Selectride®) and the intermediary enolate was subsequently trapped as triflate **46**. Hydrogenation of the enol triflate **46** afforded 2-propylpiperidine derivative **47**. The enantiomerically pure alkaloid (*S*)-**9** was released from the auxiliary by mild hydrolysis using dilute HCl in methanol.
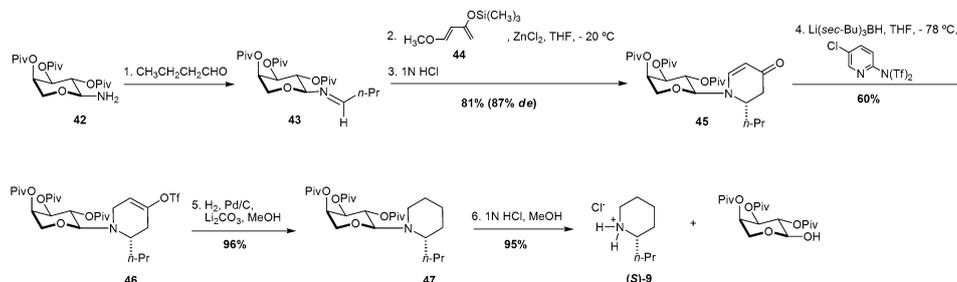
Scheme 13

The Diels-Alder reaction is probably one of the most significant reactions used to prepare six-membered rings. Given the rather ubiquitous appearance of the piperidine ring in natural products and pharmaceuticals, it is understandable that aza-equivalents of this venerable reaction are utilized as a way to synthesize this heterocycle. Recently, catalytic asymmetric versions of aza Diels-Alder reactions have been explored. Kobayashi and coworkers have developed a catalytic asymmetric aza Diels-Alder reaction of acylhydrazones **48** with Danishefsky's diene **49** using a chiral zirconium catalyst **50** [34]. Choice of solvents was an important factor for the reactivity, and better reactivity was obtained in mixed solvent systems containing aprotic polar solvents. Asymmetric formal synthesis of coniine **9** was conducted using this catalytic asymmetric reaction as a key step (Scheme 14). The aza Diels-Alder product **51** was hydrogenated in the presence of Pd/C to afford compound **52**. Its carbonyl group was then protected with 1,2-ethanedithiol (**53**), and the N–N bond was cleaved with SmI$_2$. After the Boc protection of the nitrogen atom, the dithioacetal moiety **54** was cleaved by Raney Ni to afford *N*-Boc-protected (*S*)-coniine **55** in good yield.
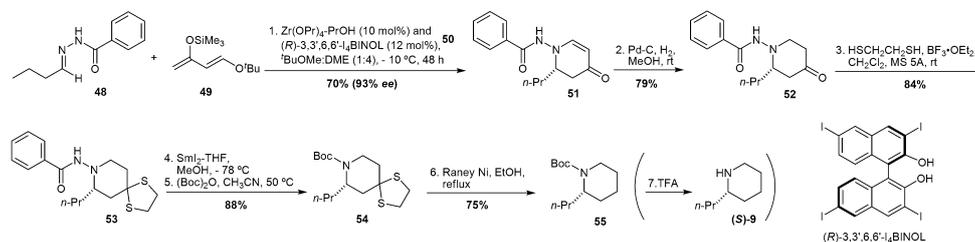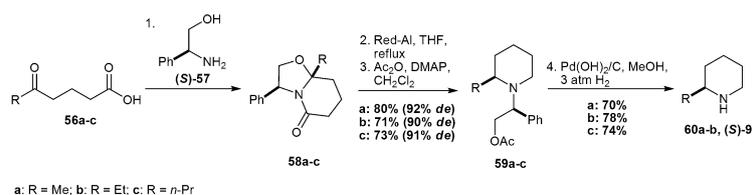

Scheme 14

2.3.3. Intermolecular condensation of terminally bifunctionalized molecules with nitrogen containing species

The intermolecular condensation of terminally bifunctionalized molecules with nitrogen containing species is a well-established method for the synthesis of 2-alkylpiperidines. In fact, some of the first asymmetric syntheses of 2-alkyl piperidines were based on condensation of bifunctionalized compounds with chiral nitrogen nucleophiles. Chiral nitrogen nucleophiles served both as sources of nitrogen and as chiral auxiliary groups. A wide range of 1,5-bifunctionalized compounds are suitable substrates for the mentioned reaction: 1,5-dihalogenides [35], δ-halogenketones [36-38], δ-ketoaldehydes [39], δ-ketoacids [40-42], glutaraldehyde [43-45] and cyclic acid anhydrides [46]. Mostly because they are easily removed by catalytic hydrogenation, the most commonly used chiral nitrogen nucleophiles are phenylglycinol isomers [38, 41, 42, 47] and other benzyl amines such as (*S*)-l-phenylethylamine or (*R*)-l-(l-naphthyl)ethylamine [39]. In addition, the possible usefulness of a variety of pyrrolidine chiral auxiliaries (their advantage is regeneration), such as isomers of l-amino-2-pyrrolidinemethanol, was also explored [46, 48]. Two different approaches could be recognized in this type of stereoselective syntheses. The first involves the setting of the stereochemistry on the piperidine ring during the condensation process; this requires usage of bifunctionalized compounds that contain suitably attached alkyl residues. The cyclodehydration of (*R*)- or (*S*)-β-amino alcohols (these could be derived from amino acids) with δ-ketoacid derivatives has been proven to be

highly useful in this sense. For example, the chiral bicyclic lactams **58a-c** derived from (*S*)-phenylglycinol **57** and δ-ketoacids **56a-c** were readily transformed to enantiomerically pure 2-alkylpiperidines **60a-c** and (*S*)-**9** (Scheme 15) [41]; this is a three-step process that involved consequent reduction and hydrogenolysis. The stereoselectivity of the lactamization process is attributed to a chair-like transition state in which the R-substituent occupied an equatorial position, with the approach of the carboxylate group to the more accessible face of the oxazolidine nitrogen atom. The reduction of diastereomerically pure **58a-c** proceeded with virtually complete retention of configuration at the angular position. This suggests that during the reduction step HAlR$_2$ might coordinate to the oxygen of the oxazolidine ring, weakening the C-O bond and promoting iminium ion formation. Subsequent delivery of hydride from the oxygen-aluminum hydride face provides the observed products.
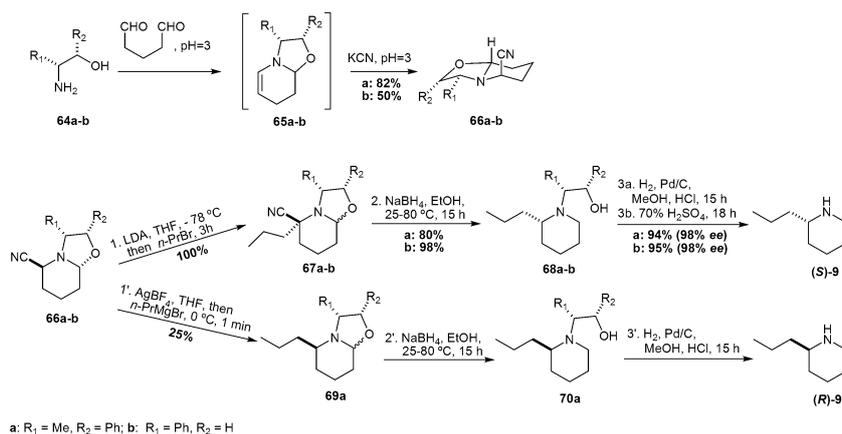

Scheme 15

The key step of an additional efficient synthesis of (*R*)-2-alkyl piperidines **14a-b** and **9** (Scheme 16) includes the stereoselective reductive ring opening of chiral bicyclic 1,3-oxazolidines **62a-c**; these were prepared by condensation of (*R*)-phenylglycinol **57** with the corresponding δ-chloroketones **61a-c** [38]. The reductive ring opening of the *N,O*-acetal moiety in bicyclic oxazolidines also took place with total retention of the configuration at the angular carbon atom; the stereochemical outcome in this opening is similar to those described for related bicyclic lactams. The reductive opening of oxazolopiperidin-2-ones and 1,3-oxazolidines may be accomplished by a vast number of other reductive agents [42].
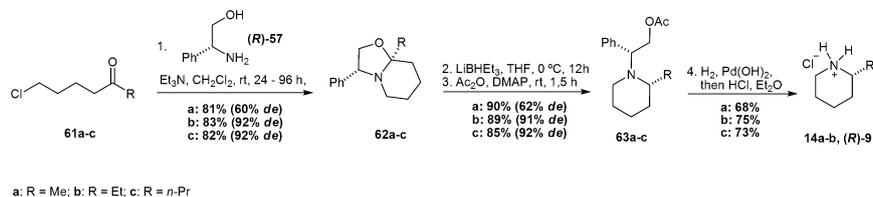
Scheme 16

A second approach is based on Robinson-Schopf-type condensation of glutaraldehyde with amino alcohols, e.g. the already mentioned phenylglycinol, in the presence of KCN (Scheme 16). The condensation product is a single, more stable isomer of 2-cyano-6-phenyloxazolopiperidine, which represents an activated chiral equivalent of 1,4-dihydropyridine synthon which shows nonequivalent reactivities at the positions 2 and 6. As required, chemo- and stereoselective reaction at either the C-2 (α-amino nitrile) or C-6 (α-

amino ether) centers of **66a-b** could be achieved by an appropriate choice of reaction conditions. This is illustrated by the enantiospecific synthesis of both (*R*) and (*S*) enantiomers of coniine **9** from these synthons [43] (Scheme 17). Alkylation of the anions of **66a-b** with propyl bromide gave compounds **67a-b** in nearly quantitative yields. Reaction of these products with NaBH$_4$ gave alcohols **68a-b**. The chiral auxiliary attached to the nitrogen of **68b** was cleaved under hydrogenolysis conditions giving (*S*)-**9**. More drastic conditions (70% H$_2$SO$_4$, 18 h) were used to cleave the chiral side chain of **68a**; nevertheless excellent chemical and optical yields (94%, 98% *ee*) of (*S*)-coniine **9** were obtained. The high stereoselectivity observed in the reactions of **66a-b** with a hydride ion implied a mechanism wherein the first step involves formation of an iminium ion by elimination of the cyano group. Completely stereoelectronically controlled approach of "H⁻" from the axial direction (upper face) of the appropriate iminium conformer generates the *S* absolute configuration. Reaction with PrMgBr was used to introduce the propyl side chain to C-2 of **66a**, giving the product with an opposite (*R*) configuration at the appropriate stereocenter. Nevertheless, for this transformation it was necessary to complex the cyano group with a silver ion, in order to ensure the reaction of the amino nitrile moiety only. The reductive opening of the oxazolidine ring **69a** to **70a** and cleavage of the chiral auxiliary by treatment with 70% H$_2$SO$_4$ gave (*R*)-coniine **9** in high overall yield. Simple modification of the one-pot reaction of (*R*)-phenylglycinol with glutaraldehyde and KCN by addition of ZnBr$_2$ (this enables equilibration) leads to higher yield and a reverse stereochemical outcome: (*S*)-coniine was obtained in 90% overall yield and 95% *ee* [44]. Katritzky and coworkers developed a very similar route to chiral 2-alkyl substituted piperidines *via* tricomponent condensation of glutaraldehyde with phenylglycinol and benztriazole. Advantages of this methodology in comparison to Husson's [43,44] include avoiding the use of KCN as starting material, and of AgBF$_4$ for removal of the cyano group, as well as higher yields and better stereoselectivity [45].
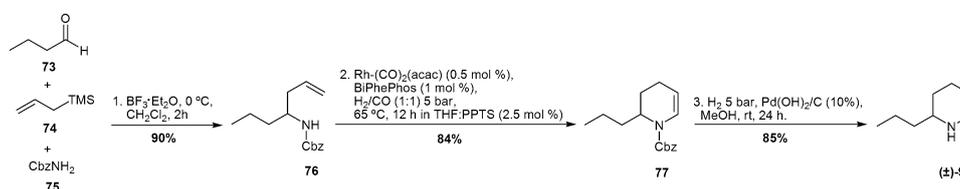

Scheme 17

2.3.4. Cyclohydrocarbonylation

Ruy and coworkers have recently developed a new method for the synthesis of 2-pi-peridinones based on the free-radical-mediated carbonylation and 6-*endo* cyclization of the resultant acyl radicals onto the imine and oxazoline nitrogen, and then examined its applicability in the synthesis of (*R*)-coniine **9** [49]. The treatment of oxazoline derivative **70**, which was prepared from 4-phenylselenobutyric acid and (*R*)-2-phenylglycinol, with carbon monoxide in the presence of tris(trimethylsilyl)silane **71** and 2,2'-azobisisobu-tyronitrile (AIBN) provided a bicyclic lactam **72** in 65% yield as 7:3 *cis:trans* mixture (Scheme 18). Since **72** was used as a key substrate in one of the previously reported synthesis of (*R*)-coniine **9** [47], the formal synthesis of (*R*)-coniine **9** was achieved.
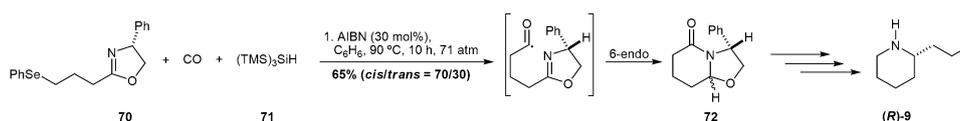
Scheme 18

The linear hydroformylation of allyl- and homoallyl- amines (cyclohydrocarbonyla-tion) is described as a general strategy for the syntheses of different alkaloids encom-passing the piperidine ring system. One convenient method for the preparation of homoallylamines is based on a multicomponent aza-Sakurai-Hosomi reaction. By em-ploying aza-Sakurai-Hosomi hydroformylation sequence, a three-step synthesis of (±)-coniine **9** in 64% overall yield was achieved [50]. In this synthesis (Scheme 18) allyltri-methylsilane **74** and benzylcarbamate **75** were selected as the nucleophilic partners and BF$_3$ as the Lewis acid (Scheme 19). With use of butyraldehyde **73**, the aza-Sakurai-Ho-somi reaction proceeded smoothly to give the desired protected homoallylamine **76**. Homoallylamine **76** was transformed by hydroformylation to the corresponding linear aldehyde which subsequently cyclized (in the presence of pyridinium *p*-toluenesulphonate (PPTS)) to a six-membered enamide **77**. The hydroformylation proceeded with a very good catalyst-based regiocontrol, as shown by the clean formation of enamide **77** in ex-cellent yield. Finally, enamide **77** was submitted to a catalytic hydrogenation employing Pearlman's catalyst; a clean tandem piperidine deprotection/double bond reduction took place to form (±)-**9**.
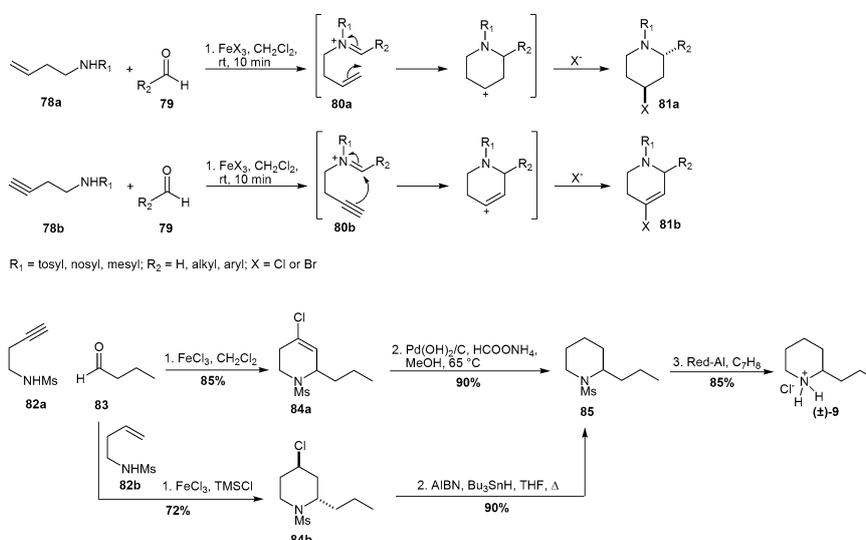

Scheme 19

2.3.5. Aza-Prins cyclization

The Prins cyclization is one of the most powerful methodologies for generating heter-ocycles through concomitant carbon–heteroatom and carbon–carbon bond formation, showing great potential in organic synthesis. The aza-Prins cyclization is the nitrogen

version of the reaction, which permits a rapid access to aza-cycles of natural and synthetic products, but it has received less attention than the oxygen version. Recently, the direct aza-Prins cyclization reaction between γ,δ-unsaturated *N*-sulfonylamines **78a-b** and aldehydes **79**, conducted in the presence of inexpensive, environmentally friendly, and stable iron(III) halides, produced six-membered aza-cycles **81a-b** in good-to-excellent yields; these could be easily further transformed to 2-alkylpiperidines [51]. This process was based on the generation of a γ-unsaturated iminium ion (**80a-b**), which was subsequently attacked by the unsaturated C–C bond that acted as a nucleophile. The racemic coniine **9** was synthetized by using the homopropargyl- and homoallyl-(mesyl)amine **82a-b** approaches (Scheme 20). Thus, tetrahydropyridine **84a** was obtained in 85% yield from an alkyne aza-Prins cyclization reaction using butanal **83** and $FeCl_3$ as the promoter. The chlorovinyl system in **84a** was hydrogenated by using $Pd(OH)_2/C$ as the catalyst and ammonium formate as the hydrogen source; this gave the *N*-mesylpiperidine **85**. Deprotection of the *N*-mesyl group with Red-Al in toluene led to ($\pm$)-coniine **9** hydrochloride. The Alkene-aza-Prins-cyclization using the catalytic system $FeCl_3/TMSCl$ led to the piperidine **84b** in 72% yield. The treatment of piperidine **84b** with Bu_3SnH and AIBN gave the *N*-mesylpiperidine **25**.

Scheme 20

2.4. Modifications of already available six membered nitrogen heterocycles

2.4.1. Catalytic hydrogenation of pyridine derivatives

Catalytic hydrogenation of pyridine derivatives, such as 2-alkyl [52] or 2-alkenylpyridines [53], is one of the oldest established methods for the synthesis of 2-alkylpiperidines. Owing to its general unrivalled efficiency and selectivity, catalytic asymmetric hydrogenation is a key approach to 2-alkenylpyridines both on the micro- (e.g. academic research) and macroscale (industry). Nevertheless, the asymmetric hydrogenation of aromatic or heteroaromatic substrates is still quite a challenging task. The recent advances in

this area offer an efficient and unprecedented auxiliary-based method for the asymmetric hydrogenation of substituted pyridines **88a-b** which enables the stereoselective formation of piperidines (*S*)-**14a** and (*S*)-**9**, respectively [54]. Substrates **88a-b** can be readily synthesized from oxazolidinone **87** and the appropriate 2-bromo- or chloropyridines **86a-b** by copper catalysis (Scheme 21). Hydrogenation of pyridines **88a-b** in acetic acid with Pd(OH)$_2$/C as the catalyst led to the formation of (*S*)-**14a** and (*S*)-**9** of excellent optical purities. Importantly, the reaction does not stop at aminals **90a-b**, but leads directly to piperidines (*S*)-**14a** and (*S*)-**9** and oxazolidinone **79**. Due to dipole-moment minimization, conformation represented in **88a-b** should be strongly preferred for unprotonated pyridines. Contrary to that, upon protonation, hydrogen bonding between the pyridinium and the oxazolidinone moieties would favor conformations **89a-b**, in which the auxiliary is oriented coplanar with the pyridine ring but rotated by 180°. Indeed, on hydrogenation the *i*Pr substituent shields one of the diastereotopic π-faces and selective hydrogen transfer to the opposite side leads to aminals **90a-b**. This transformation unites for the first time highly selective chirality transfer and nondestructive and traceless cleavage of the chiral auxiliary in one reaction. After the treatment of the crude reaction mixture with hydrochloric acid, separation and purification of the less soluble piperidine hydrochloride (*S*)-**14a** or (*S*)-**9** and the more soluble auxiliary **87** could be achieved efficiently by simple extraction with ether/hexanes mixtures allowing the recycling of the auxiliary.
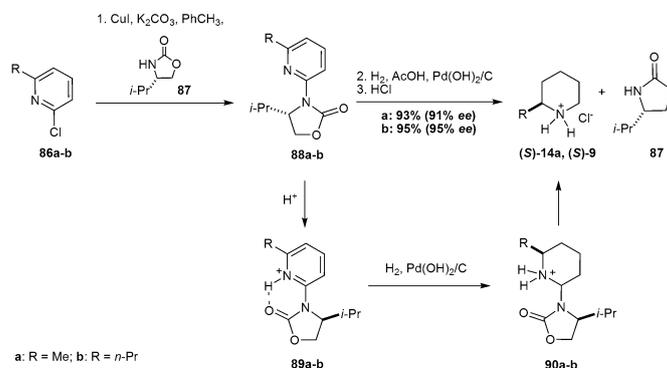
Scheme 21

2.4.2. Addition of nucleophiles to N-acylpyridinium salts

Another quite attractive and cost-effective approach consists of activating pyridine to generate an *N*-acylpyridinium salt. A subsequent nucleophilic attack by an organometallic reagent generates a substituted dihydropyridine which can then be further derivatized. A^{1,3} strain causes the C-2 substituent to occupy an axial position thereby influencing the stereochemical outcome of subsequent transformations [8]. The drawback of this approach is the lack of regiocontrol when an unsubstituted pyridinium salt is used. Typically, this approach leads to mixtures of 1,2- and 1,4-adducts that have to be separated. The problem regarding regio- and stereocontrol might be circumvented by inclusion of directing or appropriate blocking groups [55]. Charette and coworkers have reported a novel highly regio- and stereoselective approach to 2-substituted dihydropyridines from unsubstituted

N-pyridinium salts [56]. This approach relies on the stereoselective formation of the (*E*)-isomer of *N*-pyridinium imidate **92** from the corresponding amide, in which the nitrogen imidate lone pair is oriented in the proper position to direct the addition of an organometallic reagent at the position 2. It was found that amide bearing a bidentate chiral auxiliary derived from (*S*)-valinol produced excellent diastereoselectivity of nucleophilic addition. To demonstrate the synthetic potential of this methodology, an expedient synthesis of (*R*)-coniine starting from amide **91** was accomplished (Scheme 22). The addition of *cis*-1-propenylmagnesium bromide proceeded with a good yield of 1,2-dihydropyridine **93**. Hydrogenation of the three alkenes and hydrogenolysis of the benzyl ether led to **94**, which spontaneously cyclized under the reaction conditions to the oxazoline **95** and to (*R*)-coniine **9** (this was isolated as *N*-Boc derivative).
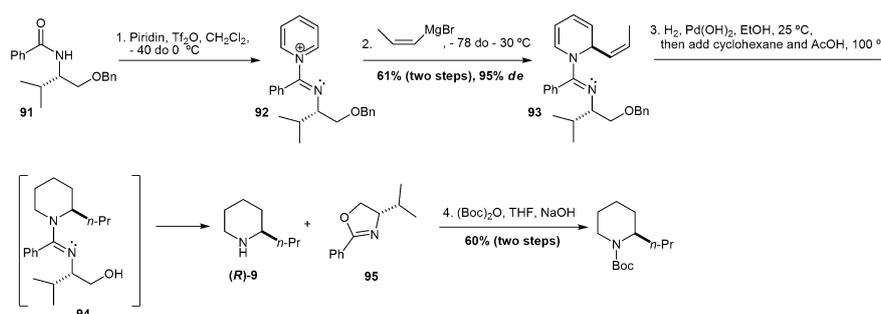
Scheme 22

Despite significant progress achieved in the area of asymmetric addition of nucleophiles to *N*-acylpyridinium salts, most studies focused on the use of chiral pyridine substrates. An exception is an example of a catalytic enantioselective addition of dialkylzinc reagents to *N*-acylpyridinium salts using copper/phosphoramidite catalysts (such as **97**) [57]. Employing this new methodology, a formal synthesis of (*R*)-coniine **9** was achieved in the good yield and with high enantioselectivity by addition of the non-commercially available *n*-Pr₂Zn to a pyridine derivative (Scheme 23): 2,3-dihydro-4-pyridone **98** was used as the key substrate for the two-step synthesis of (*R*)-coniine **9** [55].
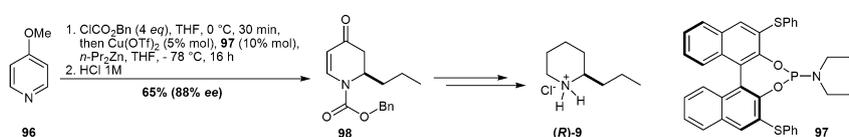
Scheme 23

Worth mentioning is a unique "hybrid approach synthesis" (combination of solution and solid-phase methodologies) of *N*-Boc-(*R*)-coniine, which uses tetraarylphosphonium salts for solubility-control [58]. Efficient stereodifferentiation of enantiotopic sites of 2-pyridone could be achieved by conjugate addition of Grignard and organocuprate reagents to the corresponding *O*-silylated *N*-(galactosyl)pyridinium salts, as well [59].

2.4.4. Electrophilic quench of N-Boc-2-lithiopiperidine

The formation of carbon-carbon bonds is a fundamental process in synthetic organic chemistry and often involves the direct interaction of nucleophilic intermediates with appropriate electrophilic partners. Organolithium compounds have emerged as very attractive nucleophilic intermediates, and their chemical behavior (reactivity) have been studied extensively. In 1989, Beak and coworkers showed that racemic 2-substituted piperidines can be conveniently prepared by deprotonation and electrophilic quenching of *N*-Boc-piperidine **99** using *s*-BuLi and *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (TMEDA) [60]. However, generally speaking, addition of organolithiums to allyl halides results in low yields (if any) of 2-allylated cyclic amine products; this problem could be overcome by transmetalation of organolithiums to, for example, organocopper species [61]. One more problem is that allylation typically gives mixtures of regioisomers (S$_N$2 and S$_N$2' products) but the regiochemistry could be controlled using allyl phosphates [62]. Asymmetric sequence transmetalation-electrophilic quench of *N*-Boc-2-lithiopyrrolidine and *N*-Boc-2-lithiopiperidine was further investigated and although very good results were obtained for *N*-Boc-pyrrolidine (for example enantioselective deprotonation with the chiral base *s*-BuLi/(-)-sparteine [63]), those conditions were less effective for *N*-Boc-piperidine [63]. The most successful results in this area were obtained by an alternative approach using dynamic resolutions of 2-lithiopiperidines. In dynamic-thermodynamic resolutions (DTRs), chiral ligands coordinate to the metal of a chiral organolithium, causing it to undergo carbanion inversion at a selected temperature and populate single stereoisomer through equilibration. After the mixture is cooled to "freeze" the equilibrium, quench with an appropriate electrophile gives enantioenriched products. Coldham and coworkers [64] recently reported that *N*-Boc-2-lithiopiperidine can be resolved by dynamic resolution under thermodynamic conditions, using several monolithiated diaminoalkoxide ligands (such as **99**). Subsequent transmetalation with zinc chloride, and then with copper cyanide (this have to be lithium chloride solubilized), followed by allylation, led to enantioenriched *N*-Boc-2-allylpiperidine **100** (*er* 78:22). Hydrogenation of the alkene and removal of the *N*-Boc group gave the alkaloid (*R*)-coniine **9** (Scheme 24).

1. *sec*-BuLi, TMEDA, Et$_2$O, - 78 °C, 3 h
2. **100**, - 30 °C, 1 h
3. ZnCl$_2$, THF, 30 min
4. CuCN·2LiCl, THF, - 78 °C, 30 min
5. allyl bromide
41% (*er* 78:22)

1. Pd(OH)$_2$, H$_2$, MeOH, rt, 24 h
2. TFA, CH$_2$Cl$_2$, rt, then NaOH
84% (for two steps)
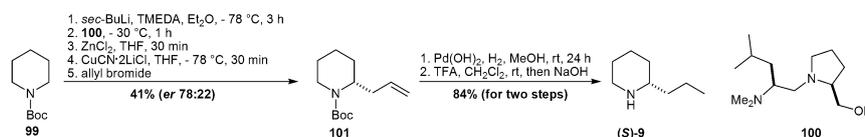
Scheme 24

Furthermore, Gawley and Beng investigated the enantioselectivity of dilithiodiaminoalkoxides **101a-b** in a stoichiometric DTR using the conditions very similar to Coldham's [65]. Under these conditions, in reaction with ligand **101-a**, allyl bromide afforded (*R*)-**100**; (*S*)-**100** was obtained when **101-a** was substituted for **101-b** (Scheme 25). Notably, diastereomeric ligands **101-a** and **101-b** afforded very high enantiomeric ratios and opposite configurations of **100**. Hydrogenation of (*S*)-**100** and deprotection gave (*S*)-coniine **9**.
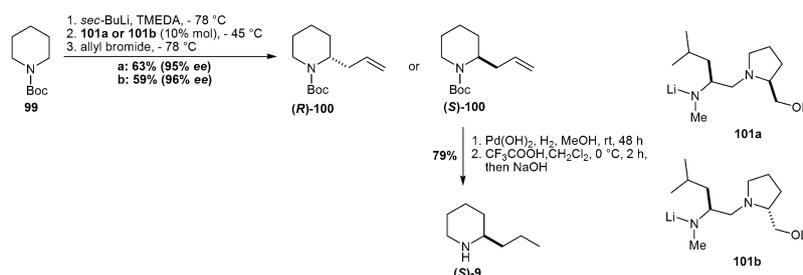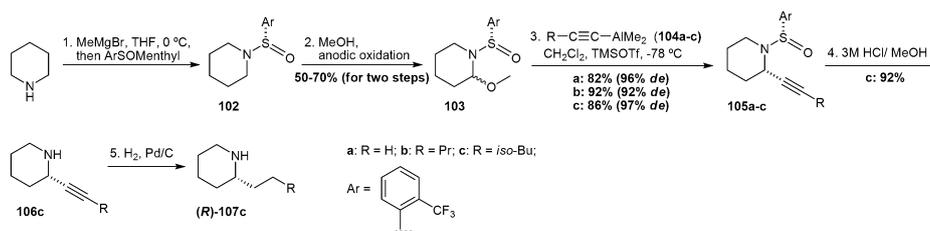
Scheme 25

One more quite interesting approach to 2-alkyl piperidines combines the quenching of *N*-Boc-2-lithio-3-methoxypiperidine with carbon dioxide and asymmetric hydrogenation of the double bond in the obtained *N*-Boc-1,4,5,6-tetrahydropyridine-2-carboxylic acid, followed by extension of the alkyl chain by a Wittig reaction [66].

2.4.5. Asymmetric α-alkynylation of piperidine

Asymmetric substitution α to the amine nitrogen is still a challenging synthetic problem, particularly in the cyclic series. The very unique solution to this problem is asymmetric α-alkynylation of piperidine in a four-step sequence: transformation to a chiral nonracemic *N*-sulfinylpiperidine **102**, anodic oxidation to *N*-sulfinyliminium ion equivalent **103**, alkynylation through addition of a mixed organoaluminum derivative (**104a-c**), and final acidic deprotection of the sulfoxide [67]. Hydrogenation of the triple bond in **105c** led to 2-alkylpiperidine **106c** (Scheme 26). It was found that diastereoselectivity of this reaction is dependent upon the structure of the aryl group attached to the sulfur atom.

Scheme 26

The methyl or trifluoromethyl groups should be at the *ortho* position to have a significant effect on the diastereoselectivity, whereas the better diastereoselectivity of the *o*-CF$_3$ group is probably due to the larger steric demand. It was also verified that the alkynyl group was introduced on the same face of the iminium of both *o*-tolyl- and *o*-trifluoromethylphenylsulfinyl derivatives. Another plus point for this method is that there is no addition onto the sulfur atom, and that in only a few cases trace amounts of enamine were detected.

2.4.6. From cyclic imines and iminium ions

A general methodology for the enantioselective allylation-boration of cyclic imines has been recently developed. The method was applied for the efficient total syntheses of several naturally occurring alkaloids [68]. For example, (*R*)-coniine **9** was obtained in one pot from imine **108** (Scheme 27). The asymmetric allylboration of cyclic imines was achieved using chiral disubstituted binaphthol (BINOL) modified allylboronates. All of the 3,3′-disubstituted systems examined gave reasonable to excellent selectivities, while the unsubstituted parent binaphthol exhibited essentially no stereoselectivity. The (lack of) stereoselectivity for this reaction might be explained using a six-membered chair transition-state model. There are two possible transitions states. The repulsion between one of the substituents on the BINOL and the methylene protons α to the imine nitrogen is the major destabilizing interaction in one of them. Among the chiral boronates tested, **109** gave the best enantioselectivity probably due to the largest steric demands of 3,5-trifluoromethylphenyl substituent. The desired amine was isolated by simple aqueous acid-base extraction, and the chiral ligands were recycled from the organic phases without detectable loss of enantiomeric purities. Thus, although stoichiometric amounts of reagents are employed, those reactions seem to be quite practical.
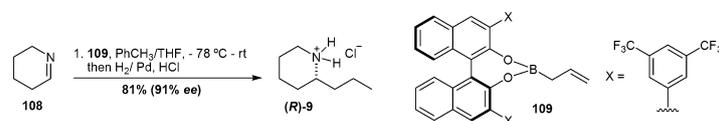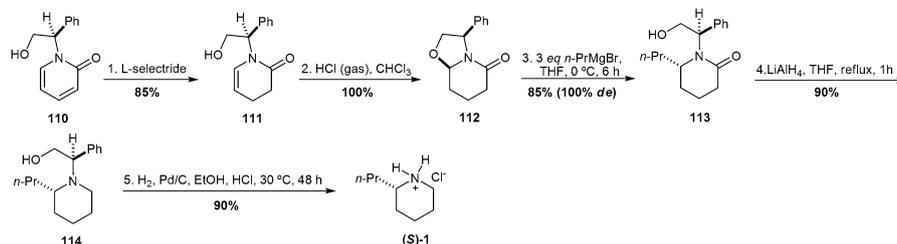

Scheme 27

The alkyl chain could also be introduced by reaction of imine with Grignard reagents [69] or by quenching the iminium ion (this might be generated by fragmentation of β-amino alcohol derivatives on treatment with (diacetoxyiodo)benzene and iodine) with allylTMS [70].

2.4.6. Alkylation of activated synthons

Easily available activated synthons such as oxadiazinones [71], *S*-alkylthioamidium salts [72], α-cyanourethanes [73], α-aminonitriles [74], oxazolopyridine-5-carbonitriles [75], 6-ethoxypiperidinones [76], chiral bicyclic lactams [77] and analogous thiolactams [78] are very useful starting materials for the synthesis of piperidine derivatives. Their usage allows regioselective, or even stereoselective, formation of a C-C bond at the position α to the N atom. Particularly valuable results in this area were achieved by Gnecco's group that carried out extensive research in the development of new, simple approaches to chiral bicyclic lactams, thiolactams and 2-alkylpiperidines. Gnecco's group has set up a very efficient method for the synthesis of the chiral bicyclic lactam **112** (Scheme 28): reduction of (1*R*)-(−)-1-(2-hydroxy-1-phenylethyl)-1*H*-pyridin-2-one **110** (this could be easily prepared by oxidation of the appropriate chiral pyridinium salt [79]) gave product **111**, which was converted to **112** by treatment with catalytic amounts of acid [78]. The three-step sequence from **112** afforded (*S*)-coniine hydrochloride **9** in good yield. The first step was the reaction of **112** with *n*-propylmagnesium chloride, followed by lithium

aluminium hydride reduction of **113** and hydrogenolysis of **114**. The outcome of this re-action sequence (the enantiomerically pure (*S*)-(+)-coniine **9**) indicates that the oxazolo opening of **112** by *n*-propylmagnesium chloride proceeds with complete inversion at C-(2a*R*) *via* an S$_N$2 mechanism.

Scheme 28

Stereoselective reactions of bicyclic thiolactam **115** with Grignard reagents **116a-b** generated 6-alkylpiperidin-2-thiones **117a-b** (Scheme 29); these also were further trans-formed to 2-alkylpiperidines [78]. A possible explanation of the high stereoselectivity of the ring opening could be sought in the coordination of the magnesium atom with the ox-azolidine oxygen that would further direct the attack of the appropriate alkyl group. The treatment of alkylation products **117a-b** with MeI gave 5-alkylhexahydro-oxazolo[3,2-a]pyridin-4-ylium iodides **120a-b**. This result could be explained by the nucleophilic at-tack of the hydroxyl group at the C-2 of the methylsulfanyl intermediates **118a-b** to give the sulfoniums **119a-b**, which by elimination of the methanethiol group furnished **118a-b**. Finally, LiAlH$_4$ reduction of **120b** and the removal of the 2-phenylethanol auxiliary from **121b** (this was done by catalytic hydrogenation) gave (*S*)-coniine **9**. The starting thio-lactam **115** was readily prepared from the corresponding lactams by substitution of C-5 carbonyl group with thiocarbonyl group [80].
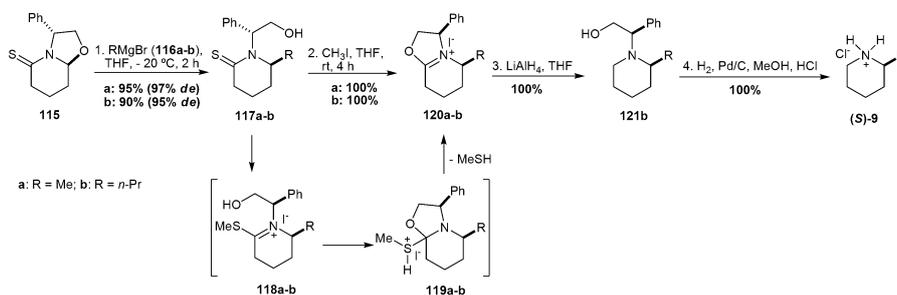
Scheme 29

Additional approaches to the synthesis of 2-alkylpiperidines, based on modification of already (commercially) available six membered nitrogen heterocycles, include extension of alkyl chain in 2-substituted piperidines by Wittig reaction [81], Grignard reaction [82] or by free radical alkylation of piperidine [83] and 2-methylpirydine [84].

3. CONCLUSIONS

The piperidine ring is a ubiquitous structural fragment found in many natural products and therapeutics. Even simple (naturally occurring) 2-alkylpiperidines exhibit an extensive range of (useful) biological activities, making them very interesting pharmaceutical molecules. No wonder then that the development of efficient procedures for the (stereocontrolled) preparation of this type of compounds become quite an important task and the goal of many different research groups oriented toward organic synthesis and medicinal chemistry. From the 19th century, when Ladenburg reported the very first synthesis of coniine, to nowadays a number of different strategies for the preparation of (enantiomerically pure) 2-alkylpiperidines have been developed. These strategies rely on different types of reactions: aza Diels-Alder reaction, Mannich-Michael reaction, intramolecular cyclizations, condensation reactions or modifications of already available six membered nitrogen heterocycles, ring closing metathesis and others. In recent years, atom-economy, tandem/cascade reactions or protecting group free strategies have been advocated as principal goals in contemporary organic synthesis and were also applied in the syntheses of 2-alkylpiperidines. The enantioselectivity has been induced mainly by starting with a chiral substrate or auxiliary containing substrate, by enzymatic resolution, using Sharpless asymmetric dihydroxylation, following a chiron approach, and by chiral catalysis. The variety of methods presented in this review and their broad applicability will, hopefully, provide an impetus for additional applications.

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STRATEGIJE U SINTEZI KONIINA I DRUGIH 2-ALKILPIPERIDINA

*Prvu sinteza koniina, neurotoksičnog piperidinskog alkaloida prisutnog u kukuti (*Conium maculatum *L.), izveo je Ladenburg još davne 1886. godine. Od tada je razvijen veliki broj različitih pristupa sintezi ovog i srodnih alkaloida (2-alkilpiperidini). Čak se u današnje vreme sinteza enantiomerno čistih optičkih antipoda koniina uzima kao standardna za potvrdu primenljivosti neke nove hiralne sintetske metodologije. Ovaj pregledni članak ima za cilj da sumira i sistematizuje napredak na polju sinteze koniina i srodnih jedinjenja.*

Ključne reči: *strategije u sintezi, koniin, 2-alkilpiperidini*