Russian Chemical Reviews **84** (7) 758 – 785 (2015) © 2015 Russian Academy of Sciences and Turpion Ltd

DOI 10.1070/RCR4478

Ruthenium-catalyzed intramolecular metathesis of dienes and its application in the synthesis of bridged and spiro azabicycles

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The review presents a historical excursion into catalytic alkene metathesis, covering the problems of history of the discovery of this process, as well as investigations on the properties, structure and reactivity of the most popular ruthenium catalysts for metathesis, mechanism of their action and decomposition. The main part covers studies devoted to the syntheses of bridged azabicyclic and 1-azaspirocyclic compounds comprising the intramolecular metathesis of dienes as the key step. The formation of a bicyclic skeleton of a series of natural bridged (cocaine, ferruginine, calystegines, and anatoxin-a) and spiro (pinnaic acids, halichlorine, hystrionicotoxin, and cephalotaxine) azabicycles, as well as their analogues and compounds with larger rings is demonstrated. The methods for the synthesis of diene precursors and the conditions for final assembling of the bicyclic compounds are considered in detail. The generalization of the literature data allows one to efficiently carry out the mentioned process taking into account the most important features.
The bibliography includes 129 references.

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I. Introduction

Almost a quarter of a century has passed since the discovery and structure assignment of the first catalysts for alkene metathesis.† During this period, a considerable progress has been achieved in understanding of principles and mechanisms of this reaction, and efficient catalysts have been created. Moreover, from the field of mere organometallic chemistry, metathesis has shifted to a new level, having become one of the most powerful tools in organic chemistry for construction of various cyclic systems (intramolecular metathesis). However, for successful application of metathesis in the synthesis of bi- and polycyclic natural molecules, it is necessary to develop equally efficient methods for synthesis of the starting dienes, which is a great challenge. The current review deals with the syntheses of bridged and spiro azabicyclic systems the core of which is constructed using intramolecular metathesis as a key step. Since azabicyclic moieties form the basis of many biologically active molecules, their synthesis is of particular interest for creation of new medicines for the treatment of neoplastic and viral diseases, Alzheimer's disease and so on.

Investigations on the mechanism of alkene metathesis, the employed catalytic systems and numerous examples of

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Received 29 June 2014
Uspekhi Khimii **84** (7) 758 – 785 (2015); translated by D A Aleksanyan

† In the scientific literature, the compounds with the double carbon – carbon bond are often called 'olefins'. In the present review, we use the term 'alkenes' according to the latest IUPAC recommendations for nomenclature of organic compounds.

their application are reflected in many reviews and books (see, for example, Refs 1–4). Meanwhile, the synthesis of bridged azabicyclic compounds *via* metathesis reactions have evolved since 2002,[5] and nowadays only two reviews[6,7] on this topic are available (published in 2004 and 2010). The latest review is most comprehensive, but it does not cover all the available studies and does not analyze in detail the methods for the construction of diene precursors. The same is true for 1-azaspirocyclic molecules; a review on their preparation appeared in 2006.[8] There are also reviews on total syntheses of natural compounds bearing an azaspiro system as a part of their structures.[9–13] We have considered the construction of these molecules *via* metathesis reactions and analyzed the efficiency of synthetic methods for the starting dienes. Therefore, all relevant information on the application of intramolecular metathesis in the synthesis of azabicyclic compounds is presented.

II. History of the discovery of alkene metathesis

Historically, the catalytic alkene metathesis[14–19] was observed for the first time by researchers from DuPont company (USA). In 1954, they discovered the transformation of norbornene into poly(divinylcyclopentane) over the mixed $LiAl(C_7H_{15}\text{-}n)_4–TiCl_4$[20,21] catalyst, and in 1956, they performed the polymerization of propylene over the promoted molybdenum catalyst (Al_2O_3-supported molybdenum oxide pretreated with H_2 and $LiAlH_4$), which gave but-2-ene and ethylene as gaseous by-products.[22] In both cases, the major reaction products were previously unknown polymers containing repeating alkene units. Subsequently, several studies appeared utilizing improved Mo and W catalysts for polymerization of cycloalkenes and disproportionation of linear alkenes.[23–25] In 1967, Calderon *et al.*,[26–28] who used a catalytic system based on WCl_6, $EtAlCl_2$ and EtOH, established that both these reactions are virtually a single process. It was shown that one and the same catalytic system allows for performing both ring-opening polymerization[26] and disproportionation of acyclic alkenes.[27,28] Therefore, 1967 is considered to be 'the date of birth' of the term 'alkene metathesis', which was introduced for the first time by Calderon[29] to describe the process of disproportionation (transalkylidenation) of unsaturated hydrocarbons.

III. Mechanisms, types and catalysts of alkene metathesis

To explain the process of metathesis, several hypotheses have been proposed that, nevertheless, could not fully describe the observed regularities, which is discussed in detail in a review.[30] In 1971, Herisson and Chauvin[31] suggested a new mechanism for this transformation according to which a key role of the catalytically active species was assigned to a metal carbene complex. In a series of sequential equilibrium steps including the formation of quasi-cyclobutane intermediates, this complex induced either disproportionation or poly- and telomerization of alkenes. In 1972, Russian researchers Dolgoplosk, Makovetsky, Tinyakova *et al.*,[32,33] who studied the polymerization of cycloalkenes, also underlined the key role of transition metal (M) carbene complexes in the catalytic process. This hypothesis accounted for most of the qualitative and quantitative regularities of the mentioned process and was

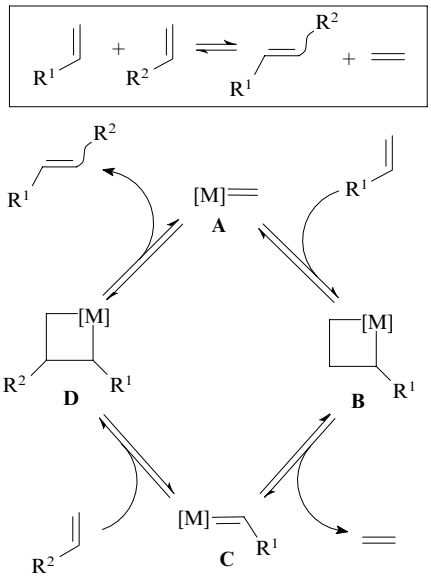


Figure 1. General pattern of alkene metathesis mechanism.[31]

commonly recognized.[34] Investigations on the mechanism of metathesis are still in progress, which is mainly related to the appearance of new catalysts. However, the scheme of transformations suggested by Chauvin (Fig. 1) is a basis for any alkene metathesis.

Using terminal alkenes as the examples, the process of metathesis was shown in which a catalytically active metal carbene species **A** reacts with alkene to give metallacyclobutane **B**, which decomposes with release of ethylene. Being a gaseous product, the latter is removed from the reaction medium, thus shifting the equilibrium towards the formation of metal carbene species **C**, and further the process is repeated with the participation of another alkene molecule, affording metallacycle **D**. The catalytic cycle is completed

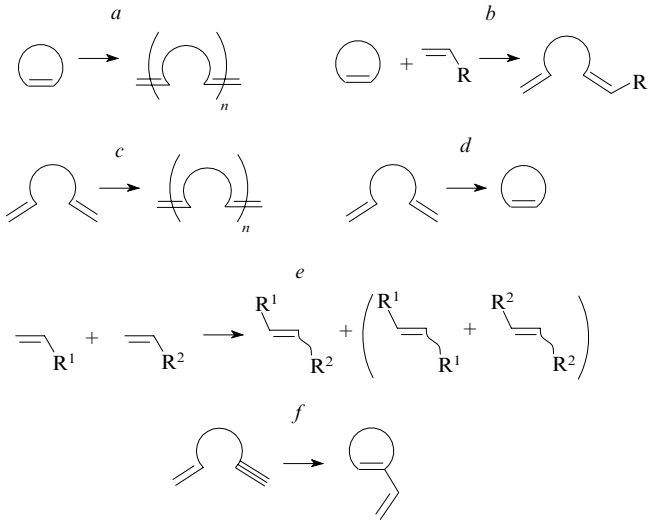


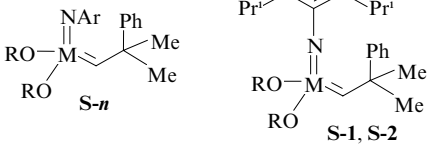
Figure 2. Types of alkene metathesis reactions: (*a*) ring-opening metathesis polymerization (ROMP), (*b*) ring-opening metathesis (ROM), (*c*) acyclic diene metathesis polymerization (ADMET), (*d*) ring-closing metathesis (RCM), (*e*) cross-metathesis (CM), (*f*) enyne metathesis.

by the formation of a new alkene (metathesis product) and recovery of the catalytic species **A**.

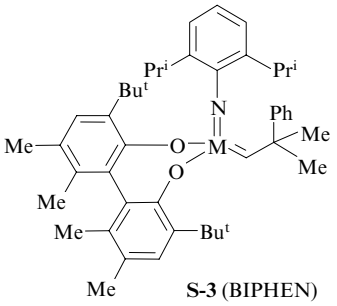
Currently, several types of metathesis reactions are distinguished; their names and abbreviations are given in Fig. 2. All the schemes with regard to the above-mentioned mechanism clearly reflect the essence of the process.

It should be emphasized that intensive development of metathesis processes became possible only owing to the synthesis of individual metal complex (metal carbene) catalysts. Among the main catalytic systems, of particular attention are tungsten, molybdenum and ruthenium derivatives.[1,2] Commercial catalysts **S-*n*** (*e.g.*, **S-1**–**S-3**) developed by Schrock and Hoveyda[35] based on tungsten and molybdenum are still among the most active and can be used even in the case of sterically hindered substrates. Furthermore, the chiral analogues of complex **S-3** [based on (*R*)- and (*S*)-BIPHEN] were devised for enantioselective modification of intramolecular metathesis.[36]

Structures S-1–S-3



R = Bu^t (**S-1**), C(CF$_3$)$_2$Me (**S-2**)



M = W, Mo

However, these catalysts have also significant drawbacks such as high sensitivity to moisture, atmospheric oxygen and solvent impurities, low thermal stability, incompatibility with many functional groups (especially hydroxyl and carbonyl groups) and high cost. The catalysts based on ruthenium developed under the supervision of Grubbs[15,37,38] are almost free from these drawbacks, although they possess lower activity. The comparison of compatibility of the catalysts based on some metals with functional groups of organic compounds is presented in Table 1.

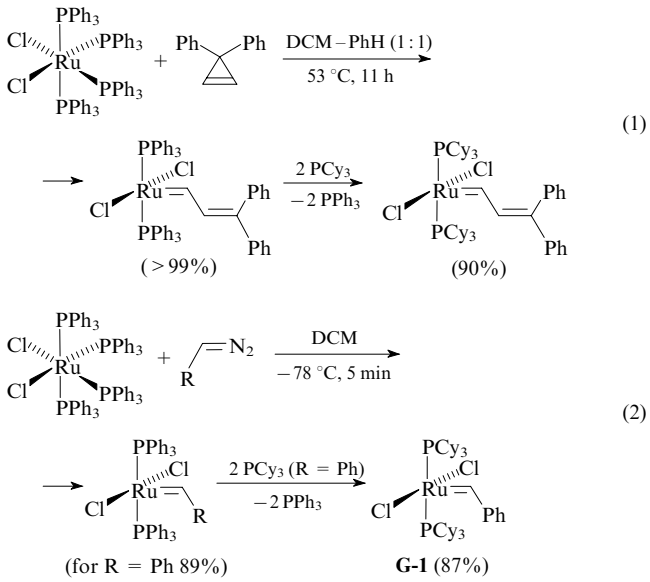
It is obvious that the catalysts based on ruthenium are preferred for synthetic purposes. One could say that just owing to Grubbs catalysts, over the last decade the metathesis reaction has become so popular that hardly any work related to the synthesis of aliphatic hetero- or carbocyclic compounds can do without it (strained small rings are exception). A strong impetus for the rapid development of investigations on the Ru catalysts was provided by introduction of the procedure for the synthesis of benzylidene complexes using 3,3-diphenylcyclopropene [Scheme 1, reaction (1)].[38]

Table 1. Comparative stability of metathesis catalysts based on metals (W, Mo and Ru) with respect to organic compounds.[38]

Tungsten	Molybdenum	Ruthenium	**Stronger interaction**
Acids	acids	**alkenes**	↑
Alcohols, water	alcohols, water	acids	
Aldehydes	aldehydes	alcohols, water	
Ketones	**alkenes**	aldehydes	
Alkenes	ketones	ketones	
Ethers, amides	ethers, amides	ethers, amides	

The first isolated and characterized alkylidene catalyst for metathesis containing PPh_3 as a ligand was described by Grubbs and co-workers[39] in 1992 [the first step of reaction (1) in Scheme 1]. At that time it seemed improbable that this catalyst could be active in the ROMP process even in the presence of alcohols and water.

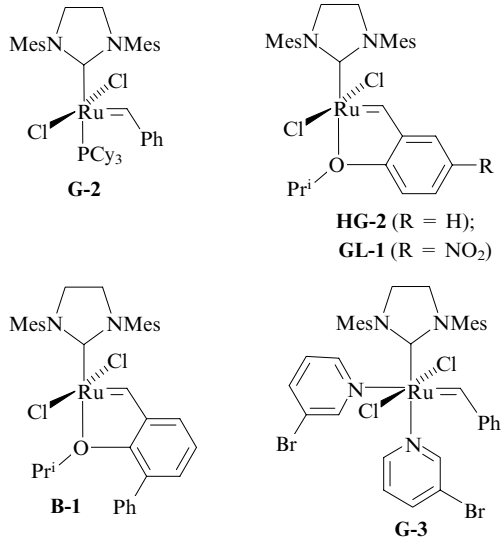
Scheme 1



R = Ph, Me, Et; DCM is dichloromethane, Cy is cyclohexyl

Further studies showed that the introduction of the more bulky donor ligand PCy_3 instead of PPh_3 substantially improves the catalyst activity.[40] The next catalyst which gained wide application in synthesis was so-called first-generation Grubbs catalyst (**G-1**). This catalyst and a series of its analogues were prepared in 1995 by a simpler procedure involving alkyl- and aryldiazoalkanes [reaction (2) in Scheme 1].[41] Catalyst **G-1** is suitable for the metathesis reaction with dienes bearing different functional groups. However, its activity appeared to be an order of magnitude lower than that of Schrock's molybdenum catalyst, and its stability in reaction was moderate. The following stage was the development of the second-generation Grubbs catalyst (**G-2**) in 1999, which contained, instead of one phosphine molecule, the much more electron-donating mesityl-substituted N-heterocyclic carbene (NHC) ligand.[42]

Structures of Ru catalysts



Mes is 2,4,6-trimethylphenyl

The introduction of the NHC ligand increased the activity up to the level inherent in Mo catalysts; furthermore, the stability of complexes and compatibility with a wide range of functional groups being present in organic molecules increased. These discoveries substantially promoted the investigations on further modifications of the catalyst structure. A significant modification was made by Hoveyda's research group in 2000.[43] The introduction of 2-isopropoxybenzylidene and NHC ligands gave rise to a new generation of catalysts combining the high activity and exceptional stability. The second-generation Hoveyda–Grubbs catalyst (**HG-2**, Fig. 3) is the first catalyst which can be isolated simply by chromatography on silica gel. Moreover, after the reaction and addition of two equivalents (relative to the catalyst) of 2-isopropoxystyrene into the reaction mixture, the catalyst can be regenerated and reused. The simplest and most efficient synthesis of complex **HG-2** consists in the replacement of the phosphine ligand in catalyst **G-2** by 2-isopropoxystyrene (see Scheme 2).

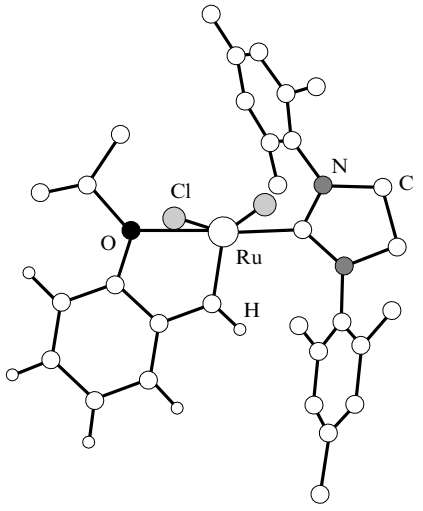
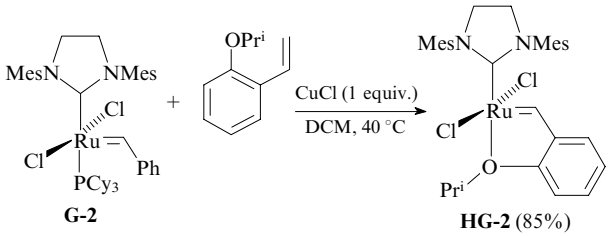


Figure 3. Structure of the Hoveyda–Grubbs catalyst **HG-2** (some of the H atoms are omitted for clairty).[43]

Scheme 2



Catalyst **HG-2** is able to carry out metathesis of various alkenes (terminal and internal, having mono-, di- and trisubstituted C=C bonds) similarly to complex **G-2**. As shown by Wakamatsu and Blechert[44] in 2002, the activity of **HG-2** is slightly lower than that of **G-2**; however, modification of the structure *via* the introduction of the phenyl group in the *ortho*-position relative to the isopropoxy group (the Blechert catalyst, **B-1**) increases the catalyst activity towards RCM, ROMP and CM reactions by almost an order of magnitude, and the amount of the catalyst in RCM can be reduced to 0.05 mol.%. Furthermore, the higher activity of **HG-2** is manifested in the metathesis reactions of electron-deficient alkenes.[45,46] Grela *et al.*[47] found that the introduction of a nitro group into the 2-isopropoxybenzylidene ligand [the Grela catalyst **GL-1** ($R = NO_2$)] also appreciably improves the catalyst activity: for example, RCM and enyne metathesis (see Fig. 2) can be conducted even at 0 °C. Different catalyst modifications, including embedding into a polymer matrix, and the data on catalyst application can be found in reviews.[2–4]

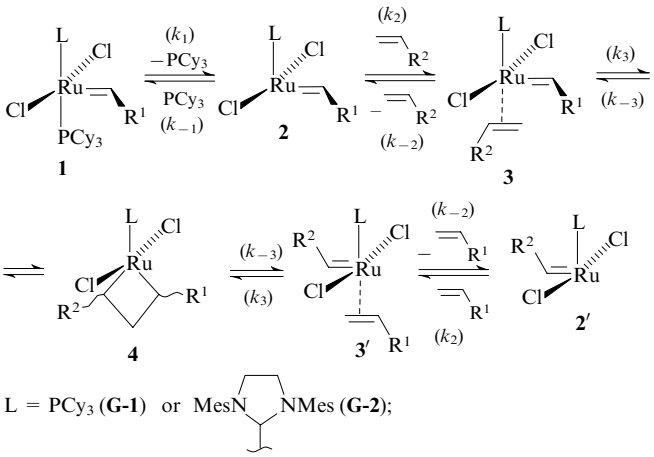
Among a plethora of ruthenium complexes, noteworthy is catalyst **G-3** obtained in 2001 and containing two molecules of 3-bromopyridine (or other substituted pyridines). This complex is sometimes called the third-generation Grubbs catalyst, since it is 1500 times as active as catalyst **HG-2** in initiation of the reaction.[48] However, due to the low stability, complex **G-3** found application mostly in polymerization of cycloalkenes[49] and other unsaturated compounds[50] where the highest possible reactant concentrations are used.

The structure–activity relationship for the Ru catalysts for metathesis was thoroughly studied both experimentally and theoretically (DFT calculations), which played an important role in the evolution of catalytic properties. Nowadays, it is generally accepted that the first step of the reaction with these catalysts is initiation, which may markedly differ for different complexes. Actually, all the characterized catalysts are precursors (precatalysts), and the true active species result from the initiation step. Scheme 3 depicts the mechanism of initiation and formation of a metallacycle for the phosphine-containing Grubbs catalysts, **G-1** and **G-2**, and presents the relative rate constants for reaction steps (k_i).

In the initiation step, complex **1** dissociates with release of the phosphine molecule. The rate of initiation k_1 for complex **G-1** is two orders of magnitude higher than that for catalyst **G-2** due to the difference in the electronic effects of the phosphine and NHC ligands.[51,52] However, the overall catalytic activity of **G-2** is approximately 100 times higher, which is likely to be due to the difference in the rates of

coordination of the alkene and phosphine ligands to 14-electron Ru intermediate **2**.[53,54] In the following step, the coordinated alkene and the benzylidene ligand in complex **3** react giving rise to ruthenacyclobutane **4**.

Scheme 3



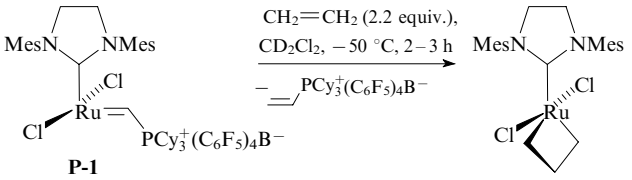
L = PCy_3 (**G-1**) or MesN NMes (**G-2**);

k_1 (rel.) ~ 10^2; k_2 (rel.) = 1;

k_2/k_{-1} (rel.) ~ 10^{-4} (for **G-1**); k_2/k_{-1} (rel.) = 1 (for **G-2**)

Romero and Piers[55] obtained experimental evidence for the formation of these intermediates by NMR spectroscopy using 14-electron cationic complex **P-1** as a catalyst (the Piers catalyst) (Scheme 4). The corresponding ruthenacyclobutane is formed as a single product at −50 °C within 2–3 h and remains stable at this temperature for several hours but rapidly decomposes at −10 °C. The addition of 5 mol.% of diethyl diallylmalonate to the metallacycle (−50 °C) induces metathesis, which is completed upon heating to room temperature.

Scheme 4



P-1

A year later, Wenzel and Grubbs[56] studied in detail the process of formation and the stereochemistry of substituted ruthenacyclobutanes by NMR spectroscopy. It was demonstrated that the coordinated alkene in intermediate **3** (see Scheme 3) is in a dynamic state (rotates around the bond with the Ru atom), while in complex **4**, ruthenacyclobutane adopts the *anti*-configuration (bottom-path) relative to the donor ligand. It should be noted that the DFT calculations also confirm the preferred formation of a ring with such disposition of the NHC ligand;[57] however, it is mentioned that the most favourable route takes into account the balance of contributions of a solvent and steric and electronic effects the total system energy.

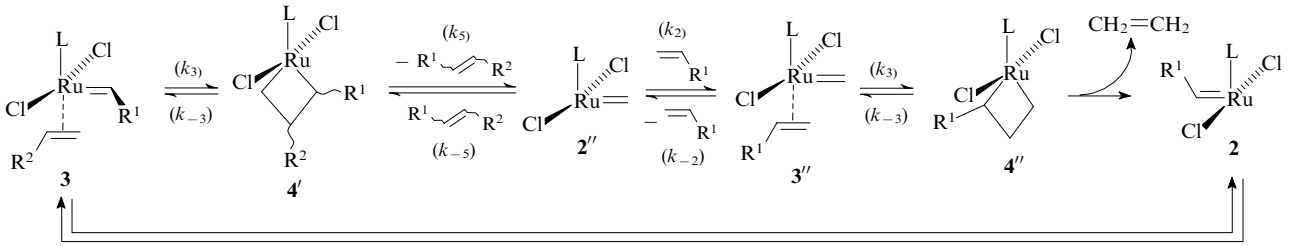
Scheme 3 shows the unproductive metathesis where all the steps are reversible. However, in the real catalytic process, for example, in RCM, the equilibrium shifts to the formation of a cyclic product owing to the release of gaseous ethylene, and the mechanism looks different (Scheme 5): metallacycle **4′** with vicinal substituents R^1 and R^2 is formed and then decomposes to give the product and methylidene complex **2″**. This intermediate not only plays an important role in the catalytic cycle of metathesis, but is also responsible for the catalyst decomposition and reaction stopping as well as for different side processes.[58–63] Elucidation of the mechanism of decomposition of this species is a key to creation of more stable catalytic systems.

Grubbs and co-workers[64] studied in detail the decomposition of phosphine methylidene complexes **MethG-n** (*n* denotes the catalyst generation) which are formed in the course of the reaction from the corresponding complexes **G-*n***. Thus, the final products of decomposition of complex **MethG-2** are methyltricyclohexylphosphonium chloride and binuclear hydride ruthenium complex **5** (Scheme 6).

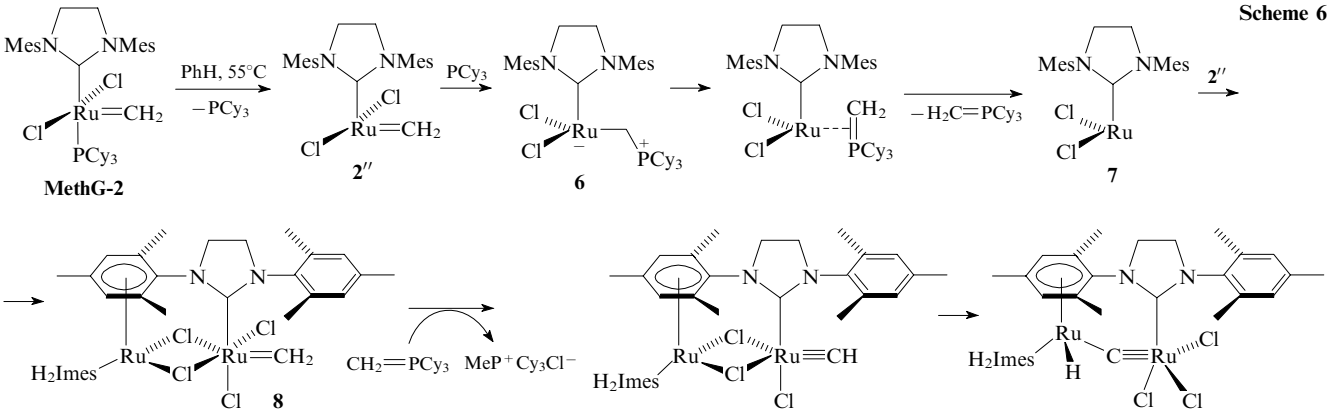
A plausible mechanism of the reaction includes the following key steps: (i) initiation with dissociation of the phosphine ligand; (ii) alkylation of complex **2″** resulting in betaine structure **6**; (iii) elimination of the Wittig reagent giving rise to 12-electron intermediate **7**, which reacts with complex **2″** to afford new ethylidene binuclear complex **8** stabilized by coordination of the Ru atom to the aryl system. In the last step, the Wittig reagent acts as a base and eliminates the proton from binuclear complex **8,** resulting in a phosphonium salt and a methine complex, which rearranges to the final product **5**. Hence, the concentration of the phosphine ligand directly affects the rate of catalyst decomposition. The half-life times for methylidene complexes **MethG-1** and **MethG-2** (PhH, 55 °C) comprise 40 min and 5 h 40 min, respectively, and the rate of decomposition of catalyst **MethG-3** was not measured due to its low stability.

It should be noted that in ethylene atmosphere, these complexes decompose in a different way: the main product is a dimeric complex resulting from insertion of Ru into the C–H bond of the methyl group of the aromatic substituent. Under these conditions, the decomposition of phosphine-free catalyst **HG-2** yields hydride ruthenium complexes, which were not identified. It is assumed that the higher stability of complex **HG-2** is due to the dynamic 'return' (release–return mechanism) of the 2-isopropoxyaryl ligand (the so-called 'boomerang') after completion of the catalytic cycle (Scheme 7).[65–67]

Scheme 5

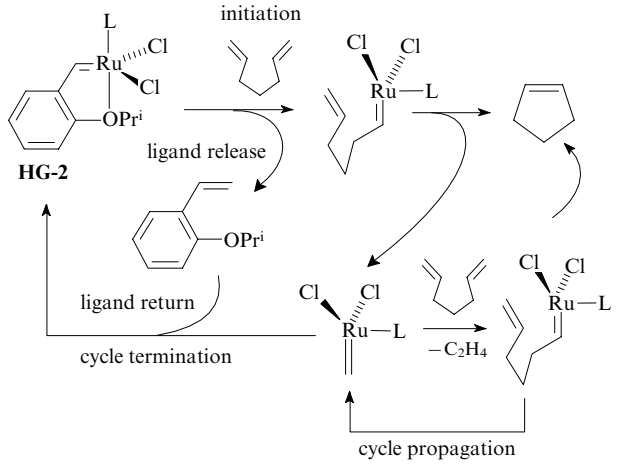


Scheme 6



H_2Imes is 1,3-dimesitylimidazol-2-yl

Scheme 7



The reaction involving complex **HG-2** and analogous catalysts is initiated *via* dissociation of the Ru–O bond; the catalytically active species are similar to those formed from catalyst **G-2** (see Schemes 3 and 5),[48] and the rate of initiation (at 5 °C) is almost 1000 times higher. After initiation, the styrene ligand migrates to the solution, and the metal complex moiety forms a catalytically active methylidene species, which catalyzes the metathesis reaction. When diene is completely consumed, the styrene ligand again forms the initial precatalyst.

The key proof for this mechanism is the fact of recovery of the main bulk of the catalyst and the possibility of repeated use. Moreover, the experiments with the addition of ^{13}C-labelled styrene to **HG-2** showed fast ligand exchange during RCM and CM reactions, which can be considered as an argument in favour of the 'boomerang' mechanism.[68] However, this scheme is likely to be realized only at high concentrations of the catalyst or the styrene ligand added externally. It was found that at low catalyst loadings (0.2 mol.%–0.5 mol.%), the styrene ligand does not add to the ruthenium catalyst after metathesis and remains in the solution. This was confirmed by the experiments using the fluorescent modified ligand[69] and a series of comparative kinetic investigations.[70] Nevertheless, it is recognized that the catalysts based on 2-isopropoxystyrene manifest particular stability the cause of which is still unclear.

A major challenge of almost any catalytic reaction is the choice of a complementary substrate–catalyst couple. As a rule, this problem is solved experimentally by selecting a catalyst, solvent and additives and varying the process conditions. Metathesis is not an exception. As will be shown by the examples below, it some cases, unpredictable situations arise: the loss of catalytic activity or undesirable reaction pathway, which requires additional investigations in each particular case. Nevertheless, there are simple recommendations that help to narrow down the range of problems faced when conducting the RCM. The first problem is the ring size. The least strained five- and six-membered rings are formed most easily,[71] while formation of seven-membered and larger rings is much more difficult. A shift of equilibrium to the cyclic product is achieved owing to the release of gaseous ethylene, which is removed from the reaction area. It is important to utilize the appropriate alkene concentration: the more strained the resulting ring, the lower the required reactant concentration. For five- and six-membered rings, the concentration can be maximum. This follows from the equilibrium nature of metathesis (see Figs 1, 2): the product of intramolecular cyclization is capable of transforming into polymer upon an increase in the concentration and strain in cycloalkene.[72]

Another important problem of metathesis is the interaction of the catalyst with functional groups of the substrate. Table 1 shows the general trend of tolerance of different classes of functional groups of organic compounds to the catalyst. If the five- or six-membered ring is formed and the substrate molecule contains such groups as ester, carbonyl or hydroxyl, then even catalyst **G-1** should operate efficiently. If the ring size is larger, then the use of complexes **G-2** or **HG-2** might be required. While alcohols only decelerate the reaction, aliphatic amines are able to irreversibly block the catalyst. Tertiary amines are least prone to poison the catalyst; in this case, **G-2** and **HG-2** are recommended for various temperatures. Catalyst **G-1** is most sensitive to impurities, it decomposes at $T > 40$ °C. The situation with the selection of the solvent is similar: in most cases, weakly coordinating solvents such as dichloromethane and toluene are used.

Another important factor is the spatial structure of the diene. The more proximate and the less crowded the alkene units, the faster and more efficient the RCM. One should take into account also the possibility of 'non-metathesis' behaviour of the catalyst caused by substrate structural

features and side chemical processes (migration of the double bond, radical reactions, *etc.*).[58–63] There are also other problems faced while conducting RCM, which can be solved upon examining the literature cited in this review.

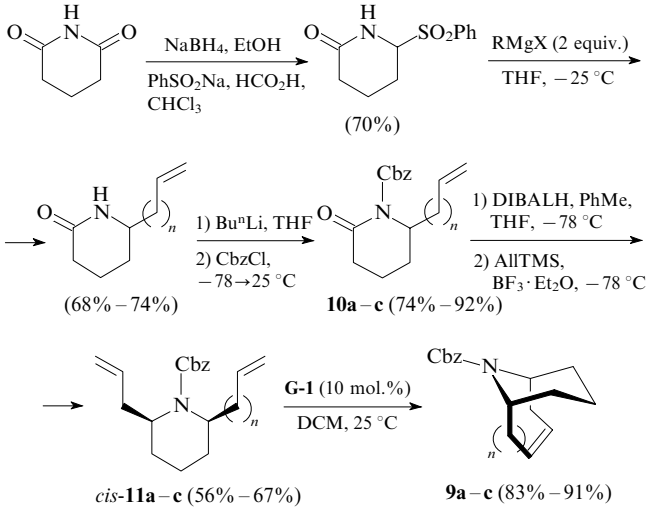
IV. Synthesis of bridged azabicyclic compounds

Bridged azabicycles represent a unique class of compounds with high biological activity. One of the most famous representatives are tropane alkaloids: (−)-scopolamine, (−)-cocaine and atropine, which have been known since the beginning of time (Fig. 4). Among less popular natural compounds with the azabicyclic core, note (+)-ferruginine, (+)-anatoxin-a and (+)-calystegine-B_2. (+)-Ferruginine is a tropane alkaloid isolated in 1979 from *Darlingiana Darlingiana* and *Darlingiana Ferruginea,*[73,74] which possesses neurotoxic action; its unnatural enantiomer (analogue of anatoxin-a) was used as a lead compound in investigation of the impact on acetylcholine receptors.[75,76] Anatoxin-a, produced by blue-green algae *Anabaena flos-aquae*, is the strongest neurotoxin,[77] which is better known as the 'very fast death factor' (VFDF). As it gets into the body, the death can happen in 4 min. For mice, the half-lethal dose (LD_{50}) is 368 μg kg $^{-1}$ of (+)-anatoxin-a hydrochloride and 913 μg kg $^{-1}$ of *rac*-anatoxin-a hydrochloride (intravenously). For humans, the lethal dose is unknown but, according to estimates, it does not exceed 5 mg (Ref. 78). Both toxins are used in the development of medicines for quite a number of diseases, including Alzheimer's and Parkinson's diseases. Another class of natural polyhydroxylated azabicycles is a family of calystegines A–C, which were isolated from *Calystegia sepium* and identified in 1988 and later revealed in various fruits and vegetables. Calystegines manifest surprising similarity in the biological action with monosaccharides and have high therapeutic potential as specific glycosidase inhibitors.[79]

There are different approaches to the formation of an azabicyclic core, for example, conventional synthesis of tropinone by the Robinson cyclization.[80] However, recently novel methods have been developed that utilize the intramolecular metathesis as a key step in the formation of a bicyclic molecule. Several reviews were published (see, *e.g.* Refs 6 and 7), which, however, do not cover all the literature on this topic and do not allow readers to make conclusion about the efficiency of one or another method. The most complex problem in these transformations is the synthesis of the corresponding diene or enyne — the starting compound for metathesis reaction.

In 2002, Neipp and Martin reported[5] the first data on the application of RCM in the formation of azabicyclic cores with different sizes of the larger ring (Scheme 8).

Scheme 8



R = $CH_2{=}CH(CH_2)_n$ [n = 0 (**a**), 1 (**b**), 2 (**c**)]; X = Cl, Br; Cbz is benzyloxycarbonyl, DIBALH is diisobutylaluminium hydride, All is allyl, TMS is trimethylsilyl

Azabicycles **9a–c** were synthesized starting with glutarimide, which was converted *via* seven successive steps using Cbz protection (compounds **10a–c**) to *cis*-substituted *N*-Cbz-2,6-dialkenylpiperidines **11a–c** (~30% total yield, 6%–4% impurity of *trans*-isomers). It should be noted that in the last step, a great number of poorly separable by-products are formed. In the presence of catalyst **G-1** [in the concentration (c) of 0.1 mol litre^{-1}], the dienes obtained in DCM readily underwent the RCM reaction, giving rise to azabicyclic compounds **9a–c** as a mixture with *trans*-isomers **11a–c**.

Subsequently, this scheme was used to obtain various azabicyclic systems.[81] Thus, *N*-Cbz-6-vinylpyridin-2-one **10a** served for preparing tropane skeleton **12** (Scheme 9). Initially, benzotriazole derivative **13** was prepared (as a mixture of stereo- and regioisomers) and then it was treated with a mixture of vinylmagnesium bromide and $ZnCl_2$ in THF to produce a mixture of *cis*- and *trans*-isomers **14** in a moderate yield and 6.8 : 1 diastereomer ratio (*dr*).

The chromatographic separation gave pure diene *cis*-**14** (in the total yield of 26%), which smoothly gave tropane azabicycle **12** in the presence of **G-1** (c = 0.01 mol litre^{-1}).

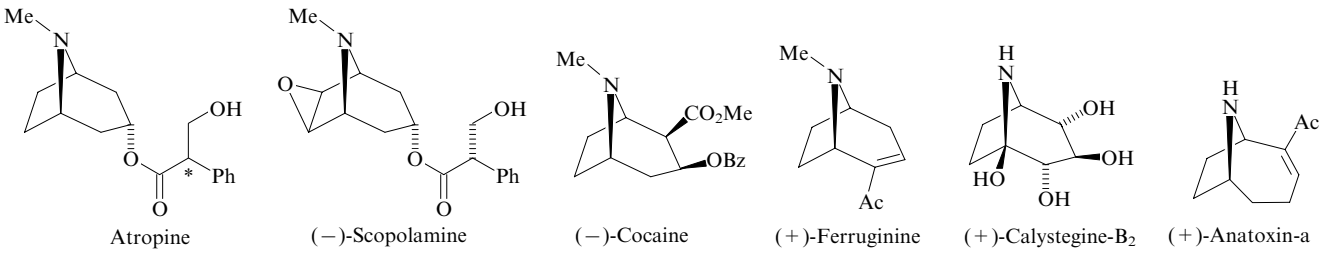
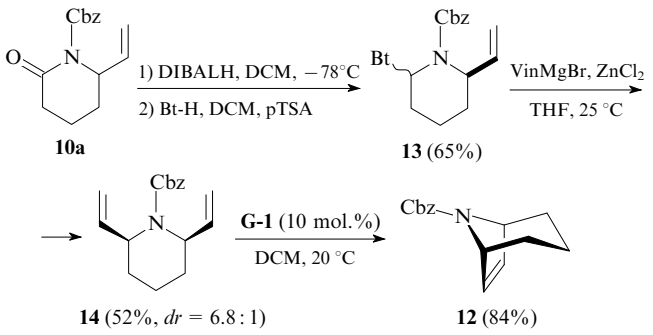


Figure 4. Natural bridged azabicyclic compounds.

Scheme 9

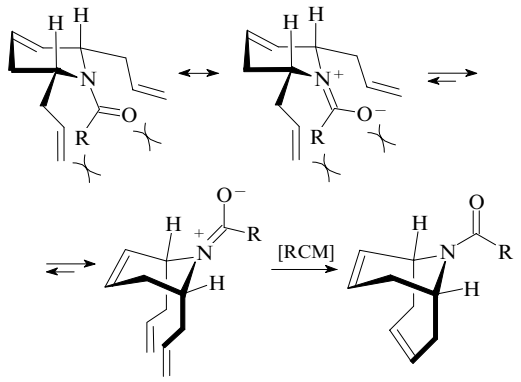


10a **13** (65%) **14** (52%, *dr* = 6.8 : 1) **12** (84%)

Bt-H is benzotriazole, pTSA is *p*-toluenesulfonic acid, Vin is vinyl

Of note is the necessity to introduce an acyl type N-protecting group into the starting diene. This group plays a dual role: first, it suppresses the nucleophilic properties of the amino group and second, it provides for optimal conformation of the molecules with axially located substituents owing to 1,3-allylic strain ($A^{1,3}$ effect) (Scheme 10).[82]

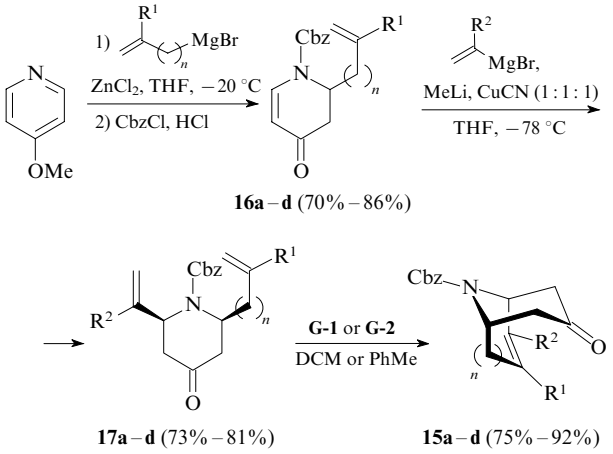
Scheme 10



Azabicyclo[*n*.3.1]alkanones **15a**–**d** methyl-substituted at the C=C bond were obtained from 4-methoxypyridine (Scheme 11). The addition of the Grignard reagent to 4-methoxypyridine activated by the action of CbzCl followed by hydrolysis of vinyl esters give the corresponding dihydropyridin-4-ones **16a**–**d** in good yields. They react with vinylcuprates generated *in situ* to give a mixture of *cis*- and *trans*-isomers **17a**–**c** in (14–20) : 1 ratio; of note is a sharp decrease in the diastereoselectivity of the addition in the case of divinyl derivatives **17a**,**d** upon introduction of the methyl substituent (R^2 = Me). Dienes **17a**–**d** (in the concentration of 0.01 mol litre^{-1}) undergo metathesis giving rise to azabicycles **15a**–**d**. Compound **17a** reacts most easily in the presence of catalyst **G-1** at room temperature, whereas for other dienes, more active catalyst **G-2** is required. Diene **17d** appeared to be most inert, requiring heating to 100 °C and repeated addition of fresh portions of the catalyst, which allows one to obtain product **15d** in 75% yield.

The vinyl derivative of *N*-Cbz-2,3-dihydropyridin-4-one **16a** can be used for synthesis of cocaine and ferruginine (Scheme 12). One-pot reaction involving vinylmagnesium bromide and Mander's reagent (methyl cyanoformate) gives functionalized diene **18** (as a mixture of *cis*- and *trans*-

Scheme 11

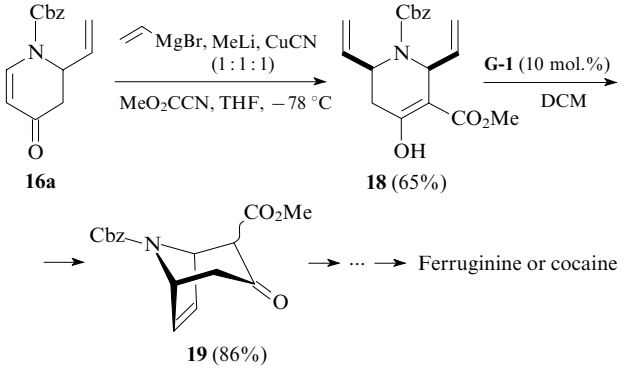


16a–**d** (70%–86%) **17a**–**d** (73%–81%) **15a**–**d** (75%–92%)

Compound	R^1	R^2	*n*	*cis* : *trans*
17a	H	H	0	20 : 1
17b	H	Me	1	14 : 1
17c	Me	Me	1	17 : 1
17d	H	Me	0	9 : 1

isomers in 15 : 1 ratio), which is readily converted to tropane derivative **19**.[83]

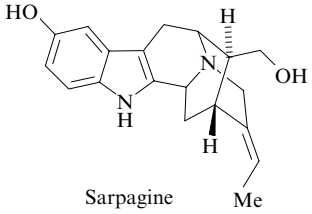
Scheme 12



16a **18** (65%) **19** (86%)

The construction of the tetrahydro-β-carboline core within the azabicycle was reported.[82] A structurally related moiety

Sarpagine structure



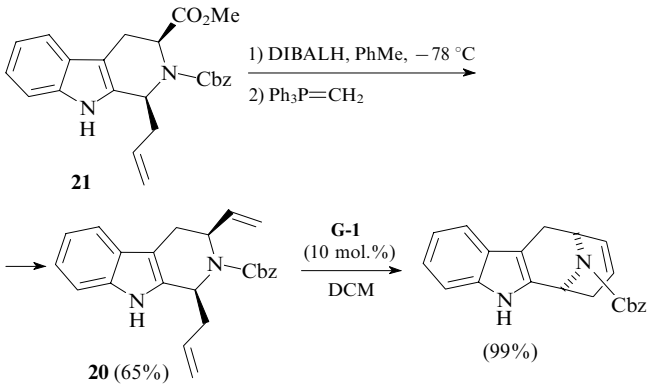
Sarpagine

is present in sarpagine — a representative of the family of indole alkaloids. A key step of the synthesis was the intramolecular metathesis of 2-allyl-4-vinyl derivative **20** obtained from ester **21** (Scheme 13).

In 2002, Kibayashi and co-workers[84] assembled an azabicyclic skeleton of (−)-adaline — the defensive alkaloid

from the two-spot ladybird *Adalia bipunctata* — using RCM.

Scheme 13



The diastereoselective allylation of *N*-acyliminium ion **22** generated *in situ* under the action of $TiCl_4$ was the key step of the formation of the chiral centre in the synthesis of (−)-adaline (Scheme 14). The resulting lactam **23** was subjected to the reductive ring opening using the lithium salt of ammine borane, which allowed the C=C bond of the allyl group to be preserved upon reduction.

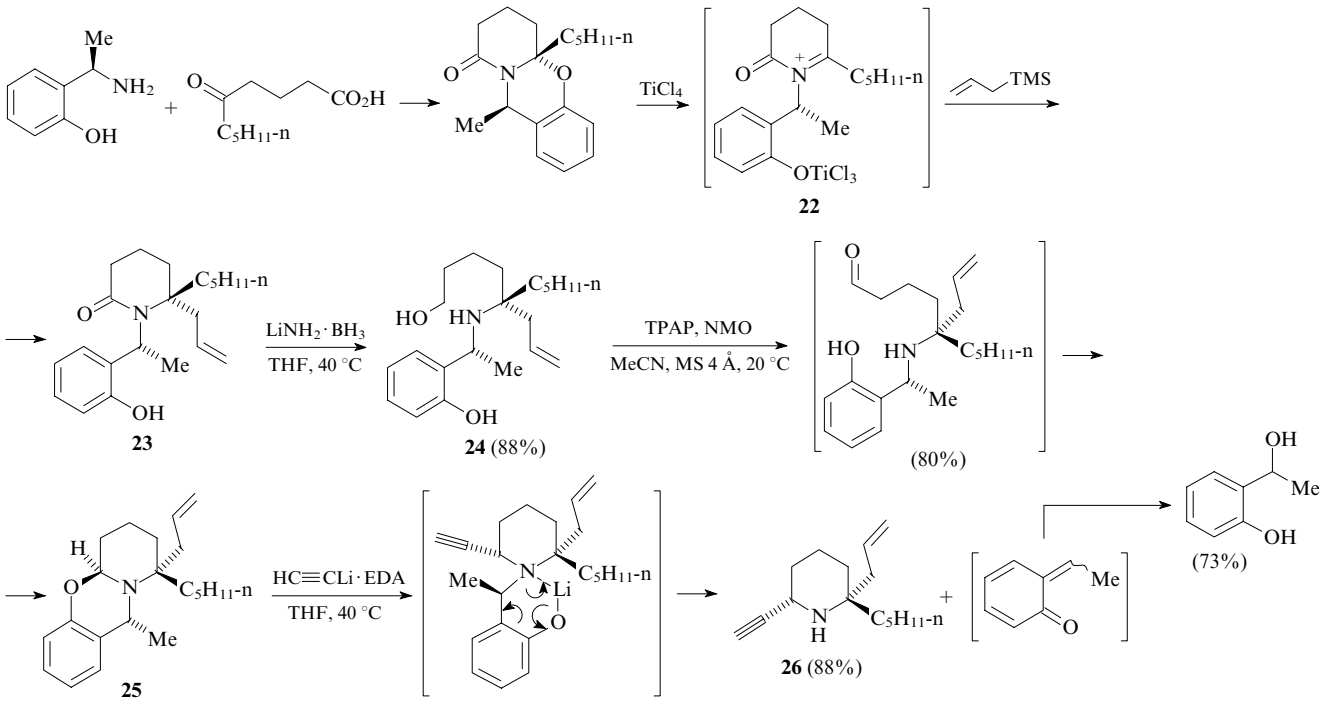
The catalytic oxidation of amino alcohol **24** to aldehyde with a TPAP–NMO system led to aminal **25**. In the following step, the ethynyl group was introduced using 5 equivalents of the lithium acetylide complex with ethylenediamine. This gave (*6S*)-ethynylpyridine **26** and 2-(1-hydroxyethyl)phenol resulting from cleavage of the auxiliary chiral group. For preparation to the metathesis reaction, enyne **26** was converted to the hydrochloride and then formamide **27** (Scheme 15).

The selective reduction of the triple bond over the Lindlar catalyst (Pd–PbO–$CaCO_3$) led to diene **28** in good yield. This product was subjected to RCM in the presence of **G-2** (15 mol.%) giving azabicyclic amide **29** in a quantitative yield. The subsequent route of conversion of amide **29** to (−)-adaline seems to be rather cumbersome, because the outcome of the five-step synthesis is the oxidation of the C=C bond into the carbonyl group. Initially, the osmium-catalyzed *cis*-dihydroxylation of amide **29** was carried out; then, the hydroxyl group in the γ-position of compound **30** was selectively protected. The ratio of products **31** and **32** was 10 : 1 (the total yield was 98%); they were separated chromatographically. The free OH group in aldehyde **31** was reduced by the Barton–McCombie method in the form of a xanthate. Then the silicon-containing protecting group in compound **33** was removed under the action of TBAF, and the corresponding formamide was quenched with lithium in ethylenediamine. The synthesis of (−)-adaline was completed by selective oxidation of the alcohol group in compound **34** with pyridinium chlorochromate. This is an unusual solution, since PCC is a neutral and even weakly basic oxidant, which must oxidize also the amino group. However, it seems that under the reaction conditions the 'protective' protonation of the amino group with pyridinium hydrochloride takes place, which makes it possible to avoid the undesirable oxidation.

In 2004, three research groups — Martine's,[85,86] Aggarwal's[87] and Mori's[88,89] groups — reported almost simultaneously similar syntheses of (+)-anatoxin-a and (+)-ferruginine. In all papers, enyne metathesis was the key step in the assembling of the azabicyclic structure; the initial compounds were derivatives of pyroglutamic acid.

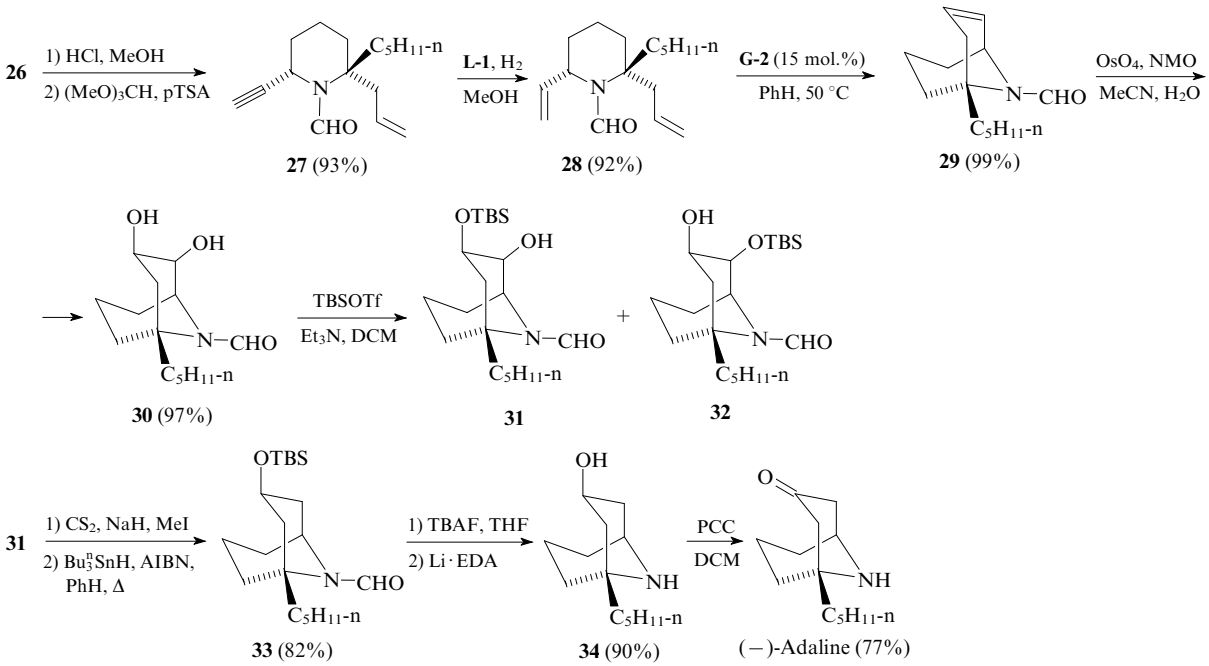
In the studies of Martin and co-workers,[85,86] methyl D-pyroglutamate was converted to N-Cbz derivative **35** (Scheme 16). Treatment of the latter with but-3-enylmagne-

Scheme 14



TPAP = $Pr^n_4N^+RuO_4^-$, NMO is *N*-methylmorpholine *N*-oxide, MS are molecular sieves, EDA is ethylenediamine

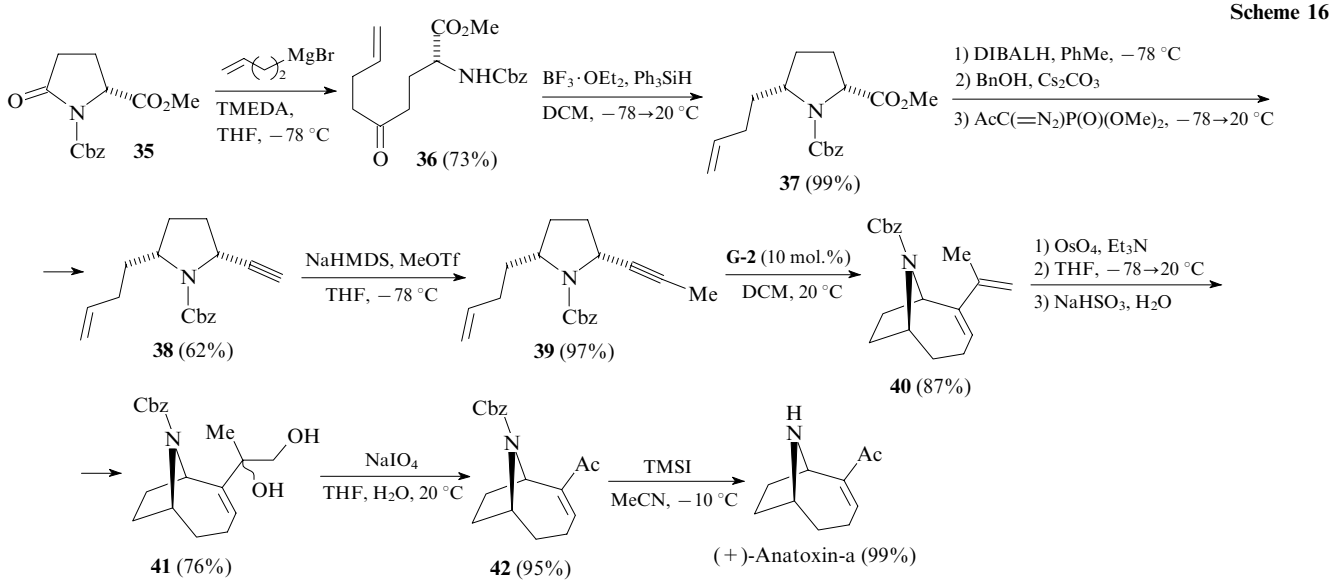
Scheme 15



L-1 is Lindlar catalyst, TBS is *tert*-butyldimethylsilyl, Tf is trifluoromethylsulfonate, AIBN is azobis(isobutyronitrile), TBAF is tetra-n-butylammonium fluoride, PCC is pyridinium chlorochromate

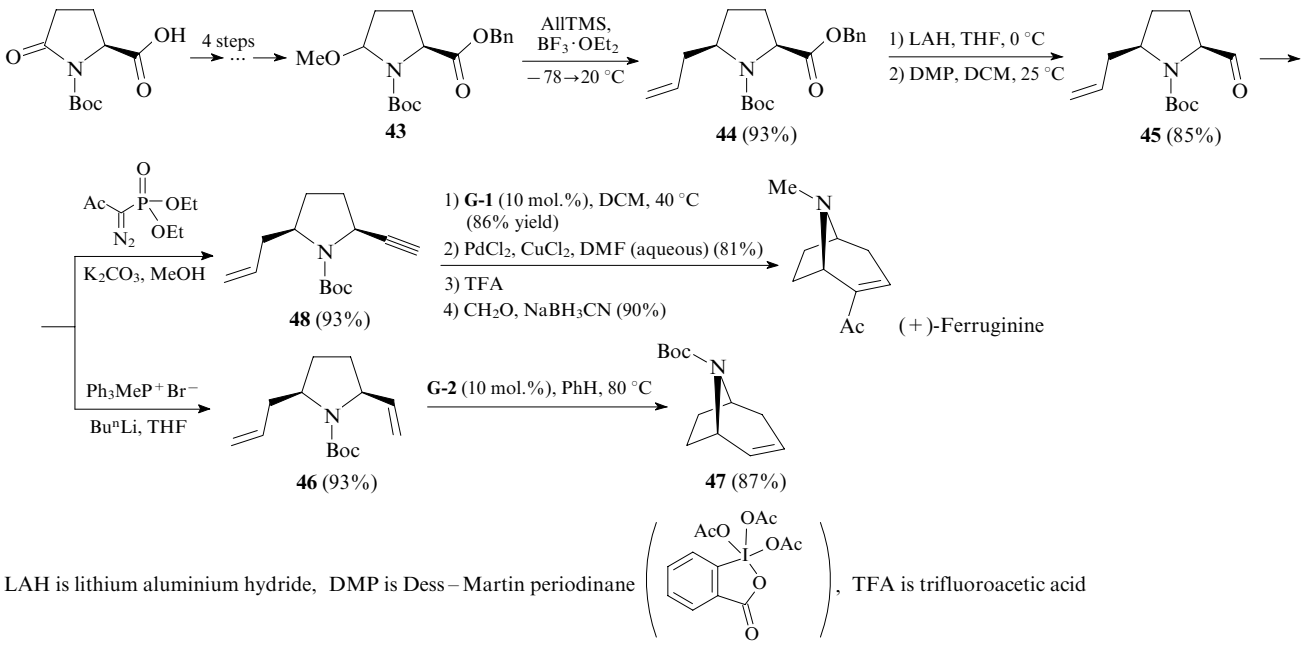
sium bromide in the presence of TMEDA resulted in the addition of the butenyl moiety with simultaneous ring opening and formation of ketone **36**. The addition of TMEDA is required to avoid the alternative reaction of Cbz-group elimination giving rise to methyl pyroglutamate. In the presence of a $BF_3 \cdot OEt_2 - Ph_3SiH$ mixture, the reductive amination of ketone **36** proceeds with a good diastereoselectivity (dr = 11 : 1) to form *cis*-isomer **37**. Then, a two-step one-pot procedure for the transformation of the ester group into the ethynyl group was used. Initially, ester **37** was reduced to aldehyde, and then the latter was treated with BnOH or Pr^{i}OH followed by addition of the Bestmann–Ohira reagent — dimethyl (1-diazo-2-oxopropyl)-phosphonate. The reaction product, pure *cis*-enyne **38**, was obtained in 62% yield after chromatographic purification from the *trans*-isomer. The effective methylation of the ethynyl group was accomplished *via* deprotonation under the action of NaHMDS followed by alkylation with methyl triflate. This led to enyne **39**, which smoothly cyclized in the presence of catalyst **G-2** to give derivative **40**. Then the

Scheme 16



TMEDA is *N*,*N*,*N*′,*N*′ is tetramethylethylenediamine, aHMDS is sodium bis(trimethylsilyl)amide

Scheme 17



exocyclic C=C bond in intermediate **40** was dihydroxylated with a good selectivity in the presence of OsO_4 to give diol **41**, which was cleaved on treatment with $NaIO_4$ in a THF–water mixture to give N-Cbz-substituted anatoxin-a (compound **42**). [It should be noted that an attempt to use the shorter route *via* Wacker oxidation of the N-Boc analogue (Boc is the *tert*-butoxycarbonyl) of diene **40** lacking the methyl group failed; therefore, the additional methylation and splitting steps were introduced.] The synthesis of (+)-anatoxin-a was completed by the removal of the Cbz-protection under action of TMSI in acetonitrile (see Scheme 16). Since the free (+)-anatoxin-a is very unstable, it was converted to hydrochloride.

Under similar conditions, Aggarwal *et al.*[87] assembled the azabicyclic skeleton of (+)-ferrugunine (Scheme 17). Firstly, L-pyroglutamic acid was transformed into aminal **43** by the known procedure,[90] and then, on treatment with allyl trimethylsilane in the presence of $BF_3 \cdot OEt_2$, it was converted to a mixture of allylated *cis*- and *trans*-isomers **44** in 4 : 1 ratio, which were separated chromatographically. The ester group in compound *cis*-**44** was reduced with lithium aluminium hydride to the alcohol group (78% yield), and the intermediate alcohol was oxidized with the Dess–Martin periodinane to aldehyde **45** in 85% yield. The treatment of the latter with the Wittig reagent gave *cis*-diene **46**, which smoothly furnished azabicycle **47** in the presence of catalyst **G-2** (10 mol.%) in a benzene solution (c = 0.005 mol litre^{-1}).

The conversion of the aldehyde group into the ethynyl group using the Bestmann–Ohira reagent gave in one step enyne **48**, which cyclized under the action of catalyst **G-1** (10 mol.%) in DCM (c = 0.01 mol litre^{-1}). As a result, the corresponding azabicycle with a conjugated diene system was obtained. It should be noted that in the case of ferruginine, the selective Wacker oxidation of the exocyclic C=C bond in the presence of the $PdCl_2$–$CuCl_2$ system afforded, as expected, the N-Boc derivative which was converted to the target (+)-ferruginine by a published procedure.[91]

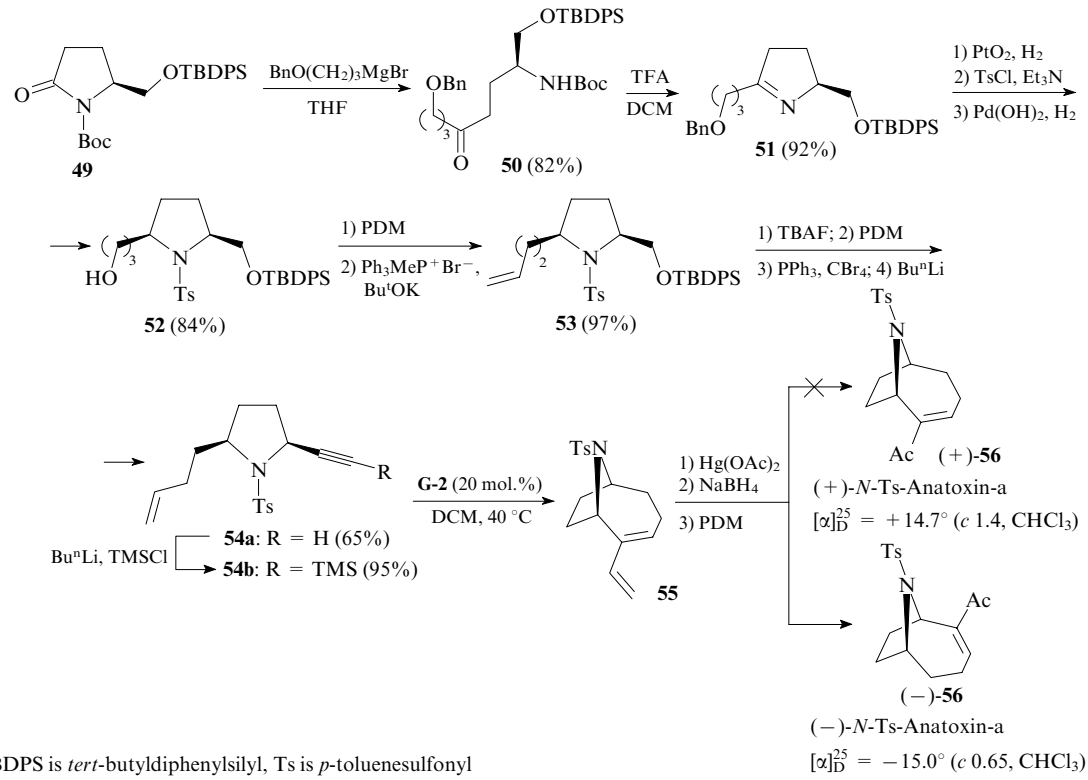
The approach to the synthesis of (+)-anatoxin-a developed by Mori and co-workers[88,89] was less efficient (Scheme 18). However, this approach is interesting owing to combination of the methods for construction of the azabicyclic core described in the above-mentioned studies and clarification of the synthesis details.

The synthesis started from compound **49**, which added to 3-benzyloxypropylmagnesium bromide to give ketone **50**; no introduction of TMEDA was required in this case, unlike Cbz derivative **35** (see Scheme 16). The removal of the Boc protection was accompanied by cyclization, resulting in imine **51**. The hydrogenation of the C=N bond over a platinum catalyst led exclusively to the corresponding *cis*-isomer which, was treated with TsCl without isolation and subjected to repeated hydrogenation over a palladium catalyst, thus deprotecting the hydroxyl group. As a result, N-Ts derivative **52** was isolated in a total yield of 84% in 3 steps. To transform compound **52** into an alkene, the OH group was oxidized with the Dess–Martin periodinane, and then product **53** was obtained in a high yield *via* the Wittig reaction.

In the following step, the enyne required for the metathesis reaction was synthesized. Compound **53** was converted in two steps to the corresponding aldehyde, which was treated with a CBr_4–Ph_3P system (the Corey–Fuchs reaction), leading to *cis*-2-(2,2-dibromovinyl)-5-(but-3-enyl)-*N*-tosylpyrrolidine. Under the action of n-butyllithium, HBr was eliminated from the latter, and the second bromine atom was replaced by lithium; the workup afforded enyne **54a** with the terminal triple bond.

However, the metathesis with compound **54a** gave azabicycle **55** in a yield of only 15%, 7% and 28% with catalysts **G-1**, **G-2** and **HG-2**, respectively. The lower yield in the case of **G-2** was caused by the formation of a considerable amount of a by-product. The introduction of TMS-substituted enyne **54b** into the reaction in the presence of 20

Scheme 18



TBDPS is *tert*-butyldiphenylsilyl, Ts is *p*-toluenesulfonyl

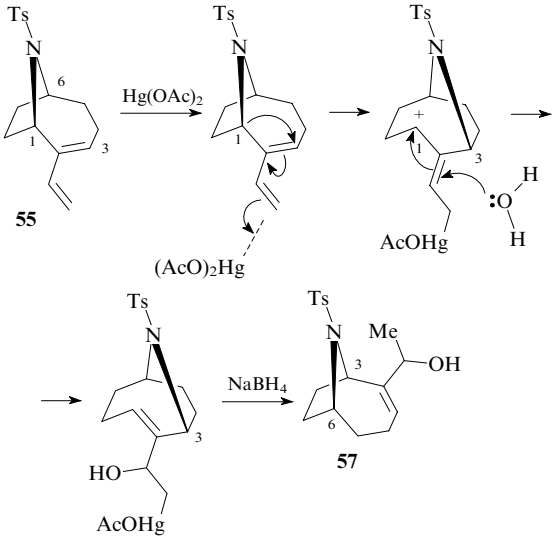
mol.% of complex **G-2** afforded azabicyclic diene **55** in a high yield (85%).

Subsequently, the authors intended to use a two-step route for the conversion of the vinyl group to the acetyl one comprising hydromercuration, reduction of the mercury derivative with sodium borohydride and oxidation of the resulting alcohol with the Dess–Martin periodinane. Indeed, such a sequence led to *N*-Ts-anatoxin-a (**56**); however, determination of the optical rotation angle of the compound showed that the product was its enantiomer, (−)-**56** (see Scheme 18).

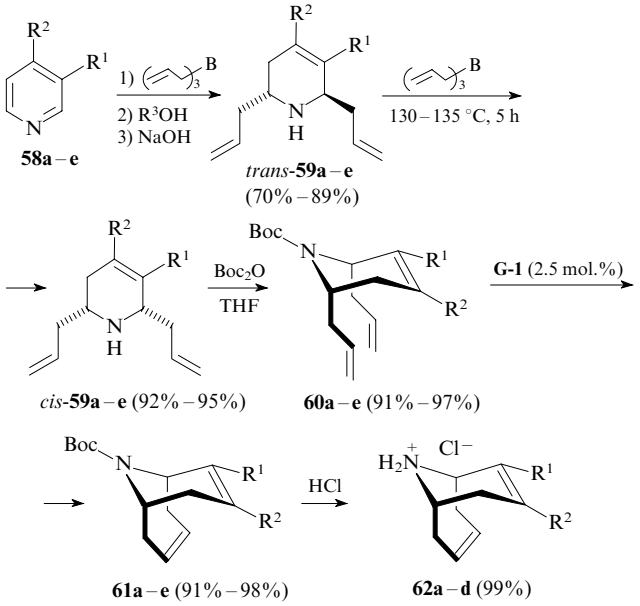
To explain this result, the authors[88,89] assumed that mercuration is accompanied by cationic rearrangement, which leads to enantiomeric alcohol **57** (Scheme 19) and, then, after oxidation, to azabicycle (−)-**56**. It should be noted that the conversion of N-tosylated enyne similar to Cbz derivative **39** in Scheme 16 using the Martin procedure leads to the expected (+)-isomer of anatoxin, although slight racemization is observed, and, consequently, the specific rotation angle decreases to +12.8° (see Scheme 18).

The enhanced lability of the C–N bond in the tosyl bicyclic derivatives is likely to be caused by good stabilization of the negative charge which arises during rearrangement and, therefore, can lead to racemization.

Scheme 19



Scheme 20

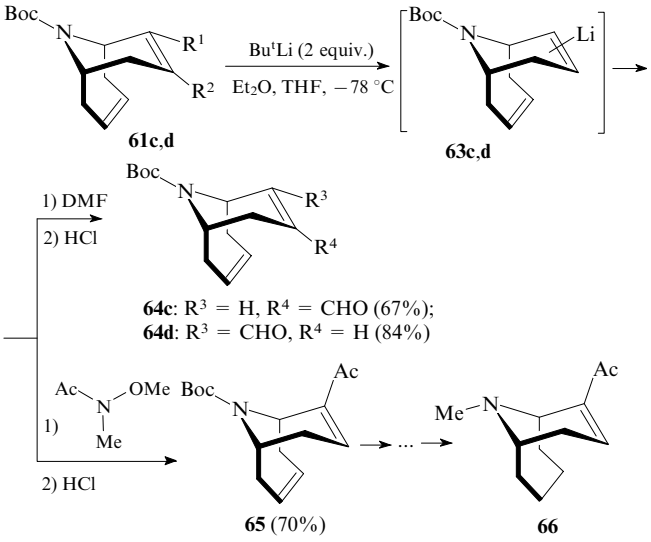


58–**62**: R^1 = H: R^2 = H (**a**), Me (**b**), Br (**c**), OMe (**e**); R^1 = Br, R^2 = H (**d**); R^3 = Me, Et, Pr^i

In 2006–2007, the authors of the present review[92–95] suggested a highly efficient strategy for the synthesis of azabicyclic compounds based on the allylboration of aromatic azaheterocycles (pyridines, isoquinolines and pyrroles) and ring-closing metathesis. According to this protocol, the synthesis of diene precursors was based on two key steps. The first step was diallylboration of pyridines (Scheme 20). The process occurs upon treatment of pyridines **58a–e** with triallylborane and alcohol (the highest yields were achieved in the case of isopropyl alcohol) under reflux or at 50–60 °C (for pyridines with the donor substituents).[96] This gave *trans*-2,6-diallylated 1,2,3,6-tetrahydropyridines *trans*-**59a–e**. On heating with an equivalent amount of triallylborane at 130–135 °C, they give *cis*-derivatives *cis*-**59a–e** (the *trans*-isomer impurity is 2%–5%). Treatment with di-*tert*-butyl dicarbonate yields N-Boc-protected dienes **60a–e**, the starting compounds for metathesis. Under the action of 2.5 mol.% of catalyst **G-1**, these dienes readily undergo cyclization upon heating in DCM, the diene concentration being 0.26 mol litre^{-1}, which is a unique result compared to other studies. The treatment of azabicycles **61a–e** with a dioxane solution of HCl at 70 °C quantitatively yields the corresponding hydrochlorides **62a–d**.

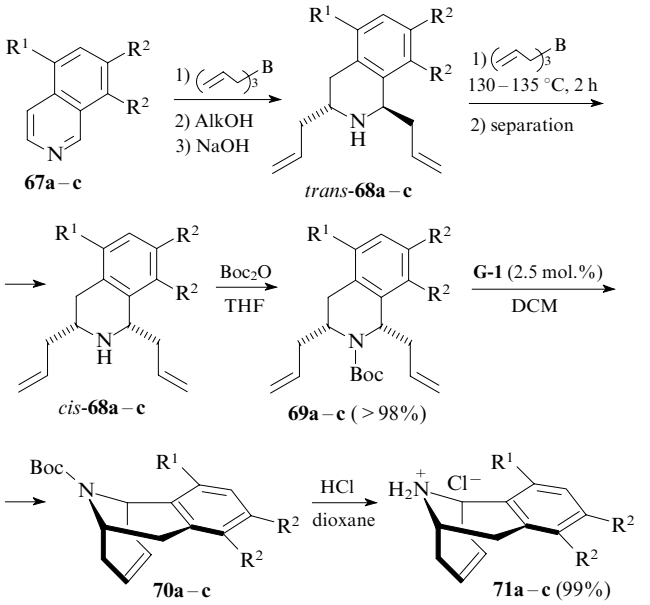
An advantage of this method is the possibility to preserve rather reactive functional groups such as vinylic bromine atoms in bromides **61c,d** or the vinyl ether group in compound **61e**. Thus, bromides **61c,d** were converted to lithium derivatives **63c,d** (Scheme 21), which were used to synthesize bicyclic aldehydes **64c,d** and, upon treatment with the Weinreb amide, ketone **65**. The latter can be transformed into the ferruginine homologue, azabicycle **66**.[93]

Scheme 21



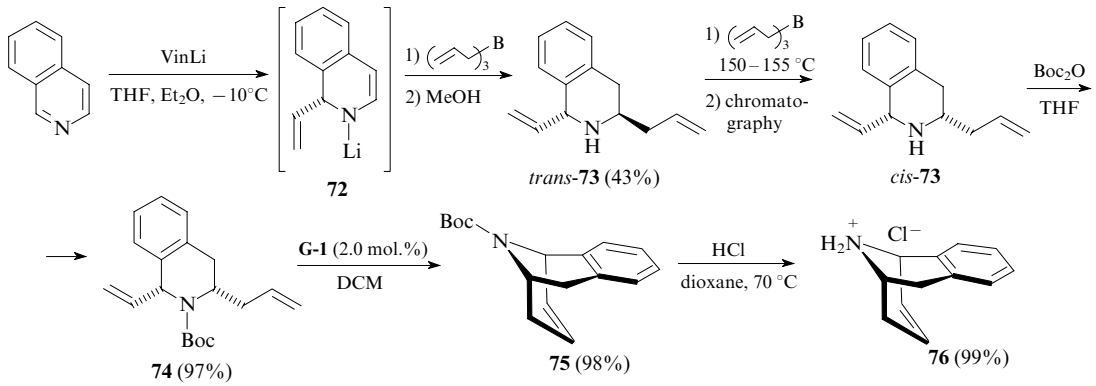
Similar reactions involving isoquinolines **67a–c** lead to benzoannulated azabicycles (Scheme 22).[84,85] The first step of diallylboration of isoquinolines is well optimized and gives *trans*-diallylated compounds *trans*-**68a–c** in high yields. However, the second step, *trans*–*cis* isomerization under the action of triallylborane, leads to equimolar mixtures of isomers from which the required *cis*-isomers *cis*-**68a–c** were isolated by crystallization or chromatography. Free amines were transformed into N-Boc derivatives **69a–c** and then subjected to metathesis (c = 0.14–0.19 mol litre^{-1}) in the presence of **G-1** (2.5 mol.%). As a result, azabicyclic amides **70a–c** were

Scheme 22



Compound	R^1	R^2	Yield (%)		
			trans-**68**	*cis*-**68**	**70**
a	H	H	95	43	93
b	Br	H	99	49	98
c	Br	Br	82	45	98

Scheme 23

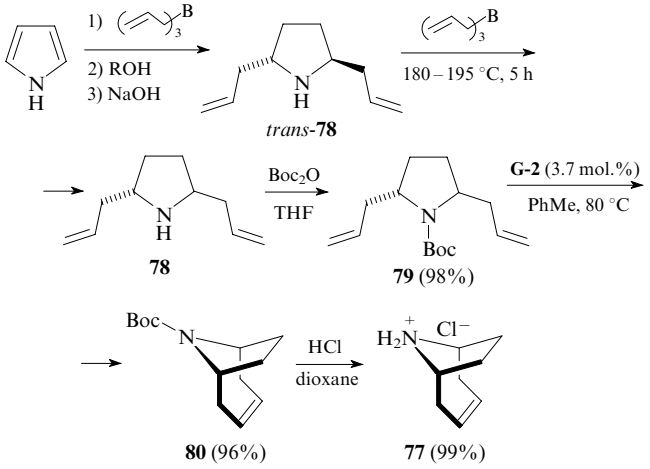


isolated (93%–98%), which gave hydrochlorides **71a–c** in quantitative yields on treatment with HCl.

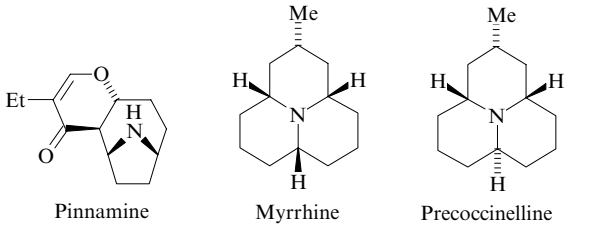
The successive vinylation of isoquinoline and allylboration of intermediate lithium amide **72** led to *trans*-diene *trans*-**73** with the shortened hydrocarbon chain (Scheme 23).[93] Heating of diene *trans*-**73** with triallylborane (150–155 °C) affords an equilibrium mixture of *cis*- and *trans*-isomers **73** (1.6 : 1 ratio) from which the required isomer *cis*-**73** was isolated by chromatography. Note that in the case of substrate **74**, metathesis with the formation of the 9-azabicyclo[3.3.1]nonane skeleton **75** proceeds more intensely than in the case of diallyl derivatives. The deprotection under the action of HCl gives azabicyclic hydrochloride **76** in a quantitative yield.

The same protocol appeared to be efficient in the synthesis of 9-azabicyclo[4.2.1]non-3-ene **77** from pyrrole (Scheme 24).[92] However, in this case, an inseparable mixture of *trans*- and *cis* -isomers of diene **78** is formed in 2.3 : 1 ratio; therefore, they are introduced into the metathesis reaction without separation in the form of N-Boc derivatives **79**. Only application of catalyst **G-2** in toluene at 80 °C gives the high yield of azabicycle **80**, which is transformed into hydrochloride **77** under the action of HCl in dioxane. Prochiral molecule **77** seems to be promising in the development of the synthesis of the poorly explored marine toxin pinnamine.

Scheme 24



Strutures of pinnamine and alkaloids



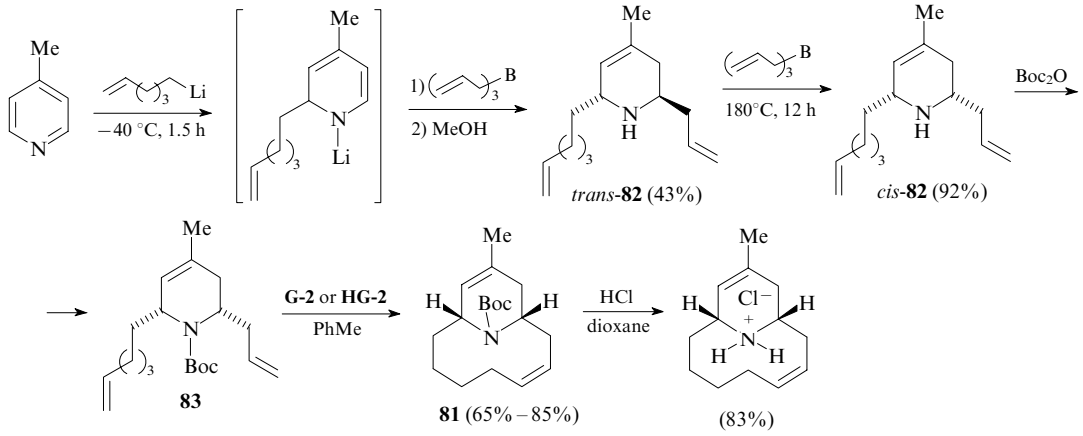
In conclusion, we will present an example of the use of the allylboration–metathesis strategy in the synthesis of macrobicyclic compound **81**.[95] This bicyclic compound was supposed to be converted to myrrhine and precoccinelline, ladybird defensive alkaloids, which are perhydro[9*b*]azaphenalene derivatives.

Using metathesis reaction, the carbon skeleton of the azaphenalene was formed (Scheme 25). Initially, the successive treatment of 4-picoline with hex-5-en-1-yllithium and triallylborane resulted in *trans*-isomer *trans*-**82** which, was converted to isomer *cis*-**82** on heating with triallylborane (*trans*-isomer impurity was 4%). In the presence of catalyst **G-2** or **HG-2**, N-Boc derivative **83** affords oligomeric products, and only dilution of the solution down to a substrate concentration of 2.5 mmol litre^{-1} shifts the equilibrium towards the formation of macrobicycle **81**. Especially difficult was the isolation of the bicyclic compound from the reaction mixture, since even insignificant impurity of the active catalyst leads to polymerization upon increase in the solution concentration. Despite the difficulties, bicyclic product **81** was isolated and transformed into a solid salt the structure of which was confirmed by X-ray diffraction.

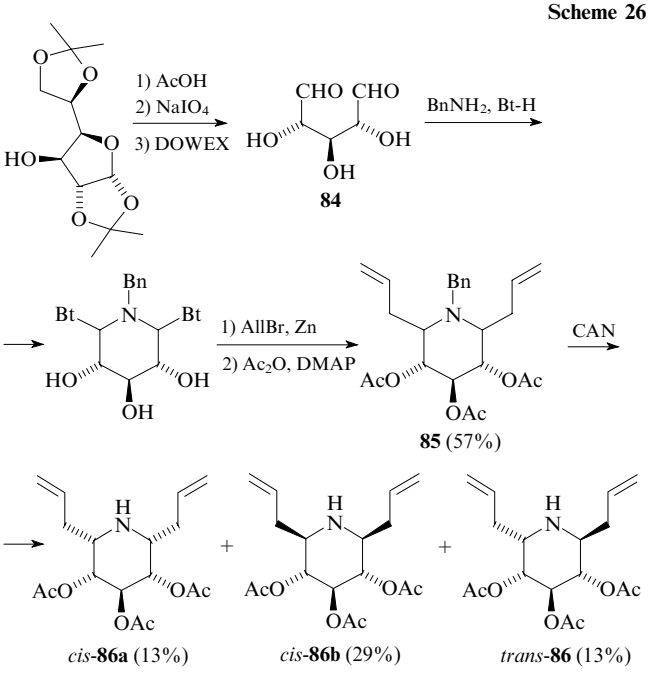
The metathesis of hydroxy-substituted 2,6-diallylpiperidines was also used to prepare tropane alkaloid analogues of the calystegine family.[97] The authors used an approach according to which the polyhydroxylated piperidine ring (Scheme 26) is formed from the aldehyde and amine components, the stereochemistry of the OH groups being initially specified by the starting dialdehyde **84**.

Dialdehyde **84** is obtained from a readily accessible compound: diacetone-D-glucofuranose, in three steps. Then compound **84** is treated with benzylamine in the presence of benzotriazole, resulting in 2,6-bis(benzotriazol-2-yl)-piperidine (45% yield in 4 steps) as a mixture of possible isomers.

Scheme 25



Scheme 26



DMAP is 4-(dimethylamino)pyridine,
CAN is ammonium cerium(IV) nitrate

Treatment of the isomers with allylzinc bromide (5 equiv.) in THF leads to diallylated piperidine as a mixture from which triacetoxy derivatives **85** are isolated. The benzyl protection is removed by oxidative elimination, then *cis*-(*cis*-**86a**,**b**) and *trans*-isomers (*trans*-**86**) are separated by chromatography.

Compounds *cis*-**86a**,**b** required for metathesis were used as N-Troc derivatives (Scheme 27). The corresponding dienes were refluxed in DCM in the presence of catalyst **G-1**, which led to azabicyclic products **87a**,**b** in high yields. It should be noted that the authors used rather unusual Troc-protection containing a CCl_3 group, which could be active towards the **G-1**-catalyzed addition to the double bond with Cl atom transfer.[58–63]

Azabicycles **87** were used to obtain polyhydroxylated derivatives in order to study their biological activity. Thus, *cis*-dihydroxylation followed by the Troc deprotection resulted in compounds **88a–d** (see Scheme 27). Amino alcohol **88d** was deacylated to give product **89** on treatment with MeONa in methanol (conditions *d*), while compounds **90a**,**b** were obtained by treating acetates **87a**,**b** with an excess of allylmagnesium bromide.

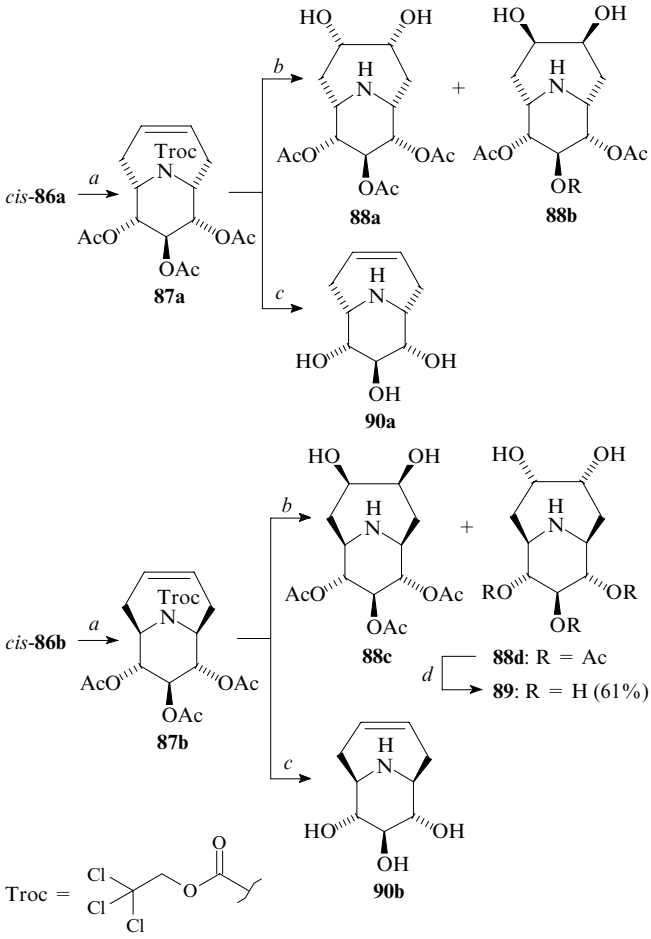
Table 2 summarizes data on the inhibition of enzymes, β-glucosidases from almond and β-glucocerebrosidase; the reference compound was piperidine-3,4,5-triol (1,5-dideoxy-1,5-iminoxylitol, DIX).[98] The highest inhibitory activity in the micromolar concentrations was manifested by aminopentaol **89**, while aminotriol **90b** with similar stereochemis-

Table 2. Half-maximal inhibitory concentrations (IC_{50} /μmol litre^{-1}) for calystegine analogues.[97]

Enzyme	DIX	**90a**	**90b**	**89**
Almond β-glucosidases	180	–	240	2.0
β-Glucocerebrosidase	2.3	–	77	1.2

Note. A dash means the lack of inhibition.

Scheme 27

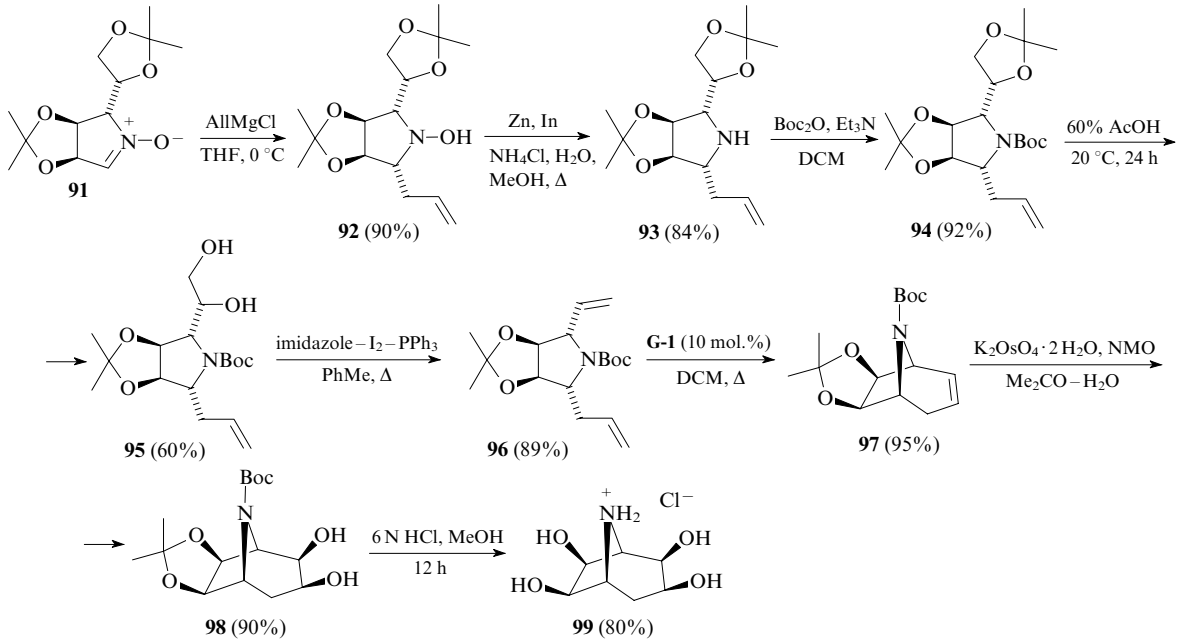


Substrate	Step	Conditions	Product yield (%)			
			a	**b**	**c**	**d**
cis-**86**	*a*	1) TrocCl, pyridine, DCM	73	88	–	–
		2) **G-1** (10 mol.%)	96	98	–	–
87	*b*	1) OsO_4, NMO; 2) Zn (dust), AcOH	15	43	18	37
87	*c*	1) Zn (dust), AcOH	83	81	–	–
		2) AllMgBr	100	90	–	–

try of substituents showed a 1–2 orders of magnitude lower activity, and stereoisomer **90a** did not demonstrate any noticeable activity.

In the same year of 2009, the synthesis of a series of new tropane analogues of calystegines was reported.[99] As the chiral precursor, well-known nitrone **91** was used (prepared from D-mannose), the benefit of which is related to the presence of two protected hydroxyl groups and to the possibility of rapid functionalization of the C=N bond with organometallic derivatives. Thus, the reaction of compound **91** (Scheme 28) with allylmagnesium chloride in THF proceeds stereoselectively to give *cis*-isomer **92** (90%). To obtain an amine, the N–O bond in compound **92** was cleaved on treatment with zinc (4 equiv.) with addition of 18% of indium dust in a mixture of aqueous solution of NH_4Cl and MeOH; allylpyrrolidine **93** was further converted to N-Boc derivative **94**. In the following step, the selective removal of the acetonyl protection in 60% AcOH was less efficient; it is likely that a considerable part

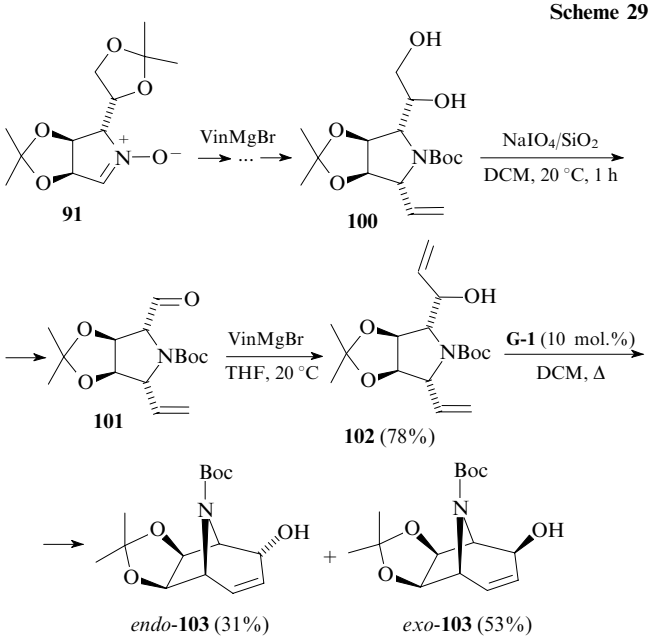
Scheme 28



of diol **95** is further hydrolyzed; therefore, the product yield is 60%. On treatment with a mixture of imidazole (4 equiv.), iodine (3 equiv.) and triphenylphosphine (4 equiv.) under reflux in toluene, diol **95** was converted to precursor diene **96**. In the presence of catalyst **G-1** in DCM, diene **96** (c = 0.005 mol litre^{-1}) underwent metathesis giving rise to azabicyclic alkene **97**. Potassium osmate-catalyzed *cis*-dihydroxylation of the C=C bond occurred selectively with the formation of *exo*-diol **98**, which was converted to bicyclic aminocyclitol **99** after complete deprotection.

For the synthesis of other analogues of calystegines, nitrone **91** was converted to vinyl-substituted diol **100** (Scheme 29), which smoothly formed aldehyde **101** under the action of sodium periodate supported on silica gel. The treatment of aldehyde **101** with vinylmagnesium bromide

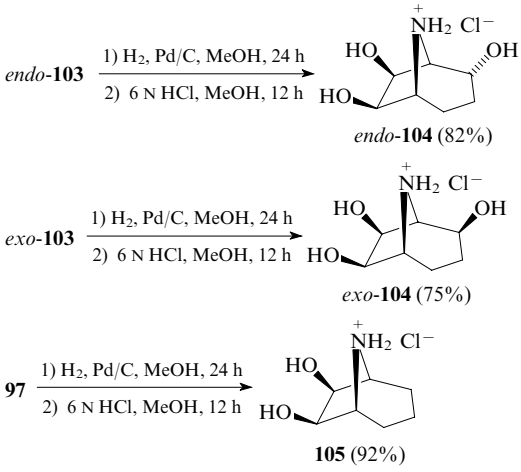
Scheme 29



(3 equiv.) led to the formation of an inseparable mixture of diastereomeric alcohols **102**. The mixture of isomers **102** was converted under the action of catalyst **G-1** to azabicyclic alcohols **103** which were isolated in moderate yields and separated.

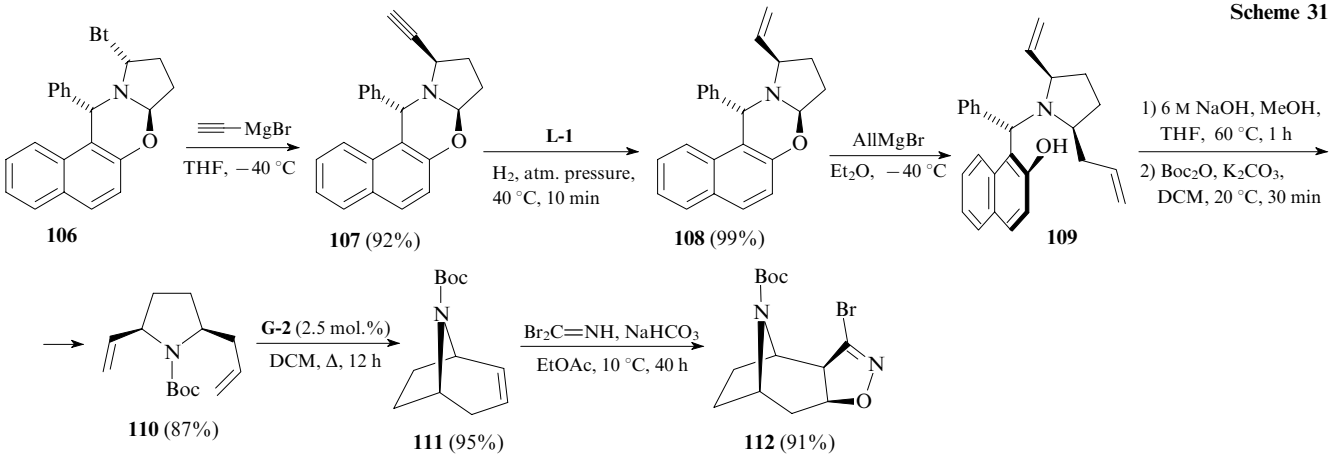
The hydrogenation of the C=C bond over Pd/C in compounds **103** and **97** followed by deprotection led to compounds *exo*-**104** and **105**, which manifested inhibitory activity relative to glycosidases — a mixture of α-mannosidases and *N*-acetyl-β-D-glucosaminidase (Scheme 30).

Scheme 30



These results clearly demonstrate the high efficiency, simplicity and potential of the intramolecular metathesis reaction. The main difficulty consists in the preparation of diene precursors by available and efficient methods. An exactly such approach was developed by Cheng *et al.*[100] for stereoselective synthesis of (−)-cocaine and (−)-ferruginine. The method is based on the stereoselective alkynylation of the Betti base derivative **106** (Scheme 31), which is carried out with the Iotsich reagent in THF at −40 °C; the

Scheme 31



reaction proceeds with inversion of the chiral center and results in alkyne **107**.

It should be emphasized that alkyl-, allyl-, or vinylmagnesium halides do not provide high diastereoselectivity of substitution. The selective hydrogenation of the triple bond in compound **107** over the Lindlar catalyst affords vinyl derivative **108** in a quantitative yield. The allylation of vinylaminal **108** also proceeds stereoselectively, resulting in the skeleton of the future chiral diene precursor, Betti base **109**. It was cleaved in the presence of 6 M NaOH, and the resulting amine was converted without isolation to N-Boc derivative **110** (87% yield in 2 steps). Under the action of **G-2**, diene **110** smoothly undergoes RCM, giving rise to tropane derivative **111**. Then the double C=C bond in tropane **111** is functionalized *via* 1,3-dipolar cycloaddition involving a highly active 1,3-dipole, dibromoformaldoxime. Annulated 3-bromo-2-isoxazoline **112** serves as a versatile reagent for the synthesis of both azabicyclic alkaloids (Scheme 32).

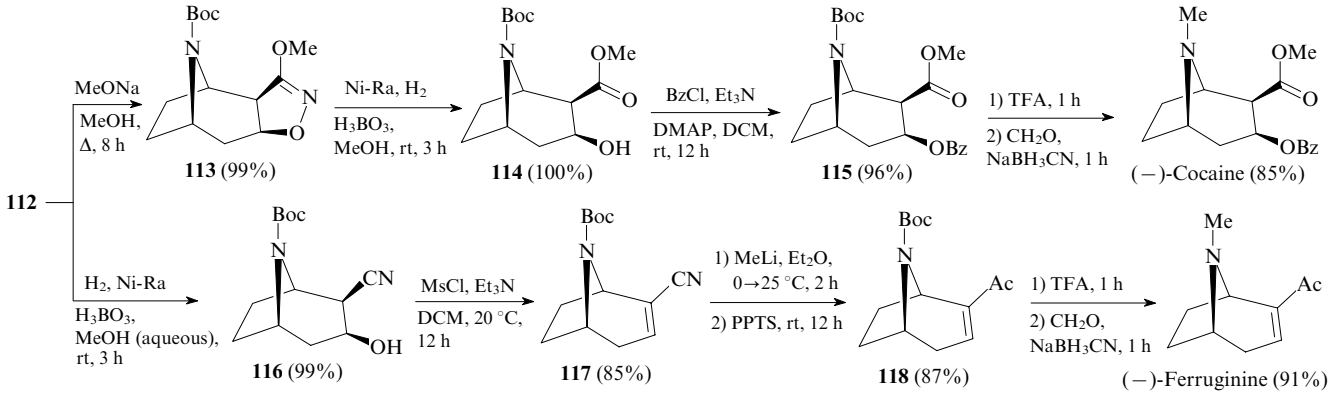
During the synthesis of (−)-cocaine, 3-bromo-2-isoxazoline **112** is initially converted to 3-methoxy derivative **113** and then undergoes the reductive cleavage over Raney nickel (Ni-Ra), resulting in *N*-Boc-methylecgonine **114** in 99% yield over 2 steps. Benzoylation of the hydroxy group in the presence of a catalytic amount of DMAP yields bicyclic product **115**. The Boc protection is removed by treatment with TFA, and then the reductive methylation is performed under the action of formaldehyde with sodium cyanoborohydride. This leads to (−)-cocaine in 81% total yield relative to the starting compound **112**.

The direct reduction of 3-bromo-2-isoxazoline **112** over Raney nickel results in *N*-Boc-ecgonine nitrile (**116**) (99%). The elimination of mesylate leads to acrylonitrile **117** to which methyllithium is added, and the intermediate ketimine is hydrolized in the presence of piperidinium *p*-toluenesulfonate (PPTS) to *N*-Boc-ferruginine (**118**). The synthesis of (−)-ferruginine is completed *via* two-step method: the removal of the Boc-groups under the action of TFA and reductive methylation. The yield of (−)-ferruginine in relation to the initial compound is 67%. It should be emphasized that this method has very high efficiency and can be readily reproduced.

Yet another approach to the synthesis of bridged azabicycles described by Brawn *et al.*[101] represents a combination of Ir-catalyzed allylic amination and intramolecular metathesis (Scheme 33).

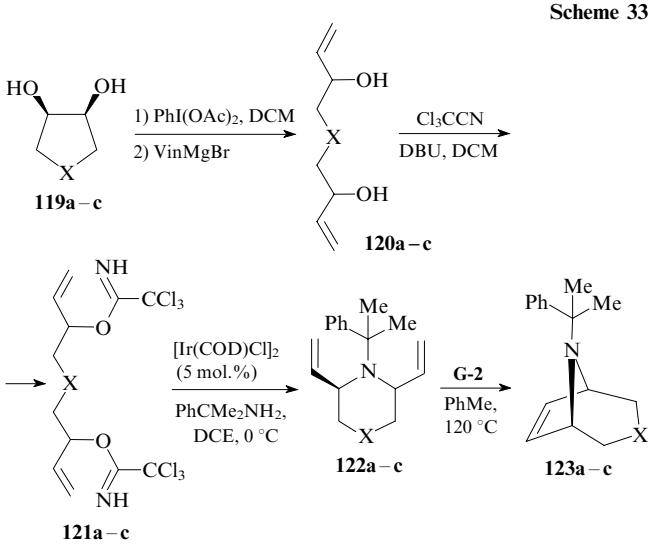
In the first step, the cleavage of commercially available cyclic diols **119a–c** with iodobenzene-1,1-diacetate to dialdehydes followed by the treatment with vinylmagnesium bromide afforded bis(allyl) diols **120a–c**. The attempts to convert diols **120** to acetates or carbonates typically used for amination were unsuccessful. A good alternative was to choose more reactive trichloroacetimidates **121a–c** which were obtained by treatment of diols with trichloroacetonitrile in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

Scheme 32



Ms is methanesulfonyl

Scheme 33



Compound	X	Yield (%)			
		120	**121**	**122**	**123**
a	O	79	72	79	79
b	CH_2	85	67	67	29
c	N-Boc	62	60	84	82

The adjustment of amination conditions for bis(amidates) **121a–c** showed that $[Ir(COD)Cl]_2$ (COD is cycloocta-1,5-diene) was the most convenient and efficient catalyst and benzylamine was the best reagent. However, the reaction with benzylamine led to a mixture of *cis*- and *trans*-isomers in almost equal amounts. Upon introduction of cumylamine to enhance the steric crowding in the undesirable *trans*-isomer, the ratio of isomers changed insignificantly, but application of 1,2-dichloroethane or toluene as the solvent at 0 °C improved the diastereoselectivity. Thus, for morpholine derivative **122a**, the ratio of *cis*- and *trans*-isomers was 5 : 1, for piperidine **122b**, it was 3.5 : 1, and the best result was achieved for piperazine **122c** where the ratio comprised 12 : 1.

Since the substituents in dienes **122a–c** are not fixed in the axial position (no $A^{1,3}$ effect, see Scheme 10), metathesis proceeds less efficiently: high temperature is required, and, in the case of compound **123b**, 10 mol.% of catalyst **G-2** is needed. Nevertheless, this method represents a convenient synthetic route to azabicyclic morpholines and piperazines.

V. Synthesis of 1-azaspirocyclic compounds

The molecules of many natural compounds possess high biological activities and have highly unusual structures that are difficult to synthesize. Among these compounds are 1-azaspirocycles (Fig. 5).

A series of azaspirocycles was isolated from marine organisms — pinnaic acids and halichlorine,[9] facicularine, lepadiformine and cylindricines.[10,11] Of special interest among marine alkaloids are pinnaic acids and halichlorine, which possess biological action related to inhibition of inflammatory processes at the cell level. Particular attention is also drawn to the development of methods for synthesis of hystrionicotoxin alkaloids isolated from dart-frogs (genus *dendrobates*).[12] Undoubtedly, the most important 1-azaspiro derivatives are cephalotaxine alkaloids, since many representatives of this family exhibit high anticancer activity, and alkaloid homoharringtonine was approved in

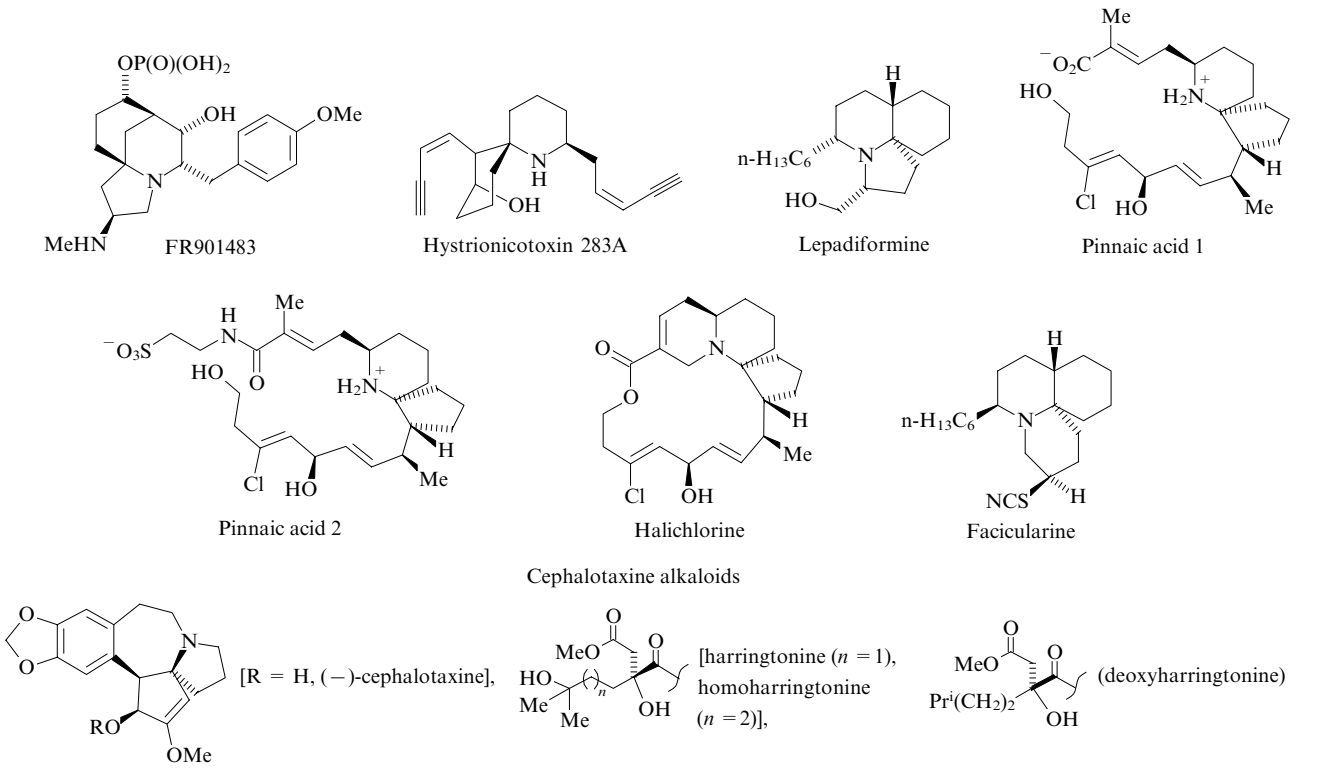
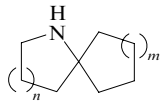


Figure 5. Examples of natural compounds containing 1-azaspirocyclic moiety.

2012 by the FDA (US Food and Drug Administration) as a drug for treatment of chronic myeloid leukemia (blood cancer).[13]

Structures of 1-azaspirocycles



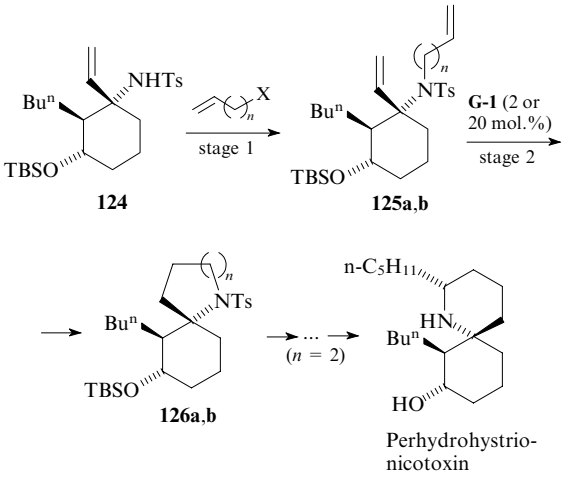
$n, m = 1, 2$

The assembling of the 1-azaspiro bycyclic system incorporated into a molecule is a serious synthetic challenge. Meanwhile, as in the preparation of bridged azabicycles, a considerable progress has been made in the synthesis of 1-azaspiro compounds owing to the application of metathesis reaction.

The methods for synthesis of 1-azaspiro heterocycles are widely described in the literature, which is reflected in the review by Dake[8] published in 2006. Moreover, there are thematic reviews[9–13] devoted to the synthesis of particular natural azaspiro compounds. The present review focuses on the methods of assembling 1-azaspirobicycles using metathesis and on the methods for synthesis of unsaturated precursors.

Tanner *et al.*[102] were among the first to use RCM for closing a spirobicyclic system in the synthesis of (±)-perhydrohystrionicotoxin in 1999 (Scheme 34).

Scheme 34



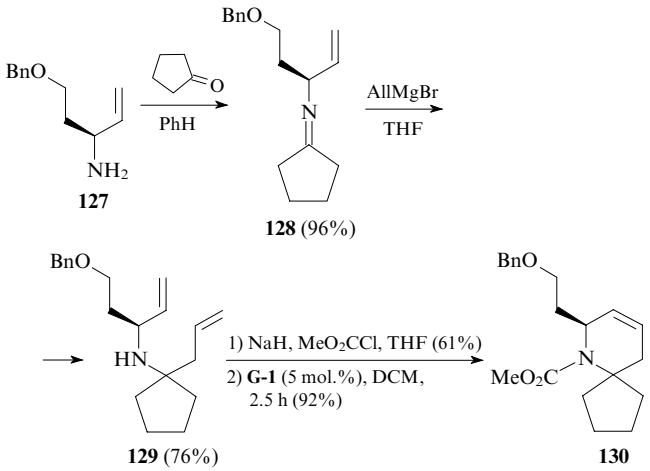
Compound	*n*	Stage 1		Stage 2	
		conditions	yield of **125** (%)	conditions	yield of **126** (%)
a	1	KH, DMF, X = Br	97	PhH, rt, 6 h	99
b	2	Bu^nLi, THF–HMPA (9 : 1), X = OTf	80	PhMe, 90 °C, 48 h	80

HMPA is hexamethylphosphorous triamide.

The starting *N*-Ts-allyl amide **124** (obtained by [2,3]-sigmatropic rearrangement of the corresponding selenium derivative) is converted to the N-anion, which is akenylated at −78 °C with allyl bromide or but-4-enyl triflate. Diene **125a** is obtained in a quantitative yield, while diene **125b** is synthesized in 57% yield, while 29% of the initial amide is recovered unchanged. This corresponds to 80% yield. In the presence of catalyst **G-1**, both dienes undergo metathesis, resulting in spirocyclic compounds **126a**,**b**. However, unlike **126a** (99% yield, 2 mol.% of complex **G-1**), compound **126b** containing the piperidine moiety is formed with difficulty: 20 mol.% of the catalyst and heating in toluene for 2 days are required, which is likely to be due to unfavourable steric crowding. Compound **126b** was further converted to (±)-perhydrohystrionicotoxin according to the published procedures.[103, 104]

The method for the synthesis of the principal spirobicyclic core of halichlorine and pinnaic acids by RCM was developed by Wright *et al.*[105] (Scheme 35).

Scheme 35

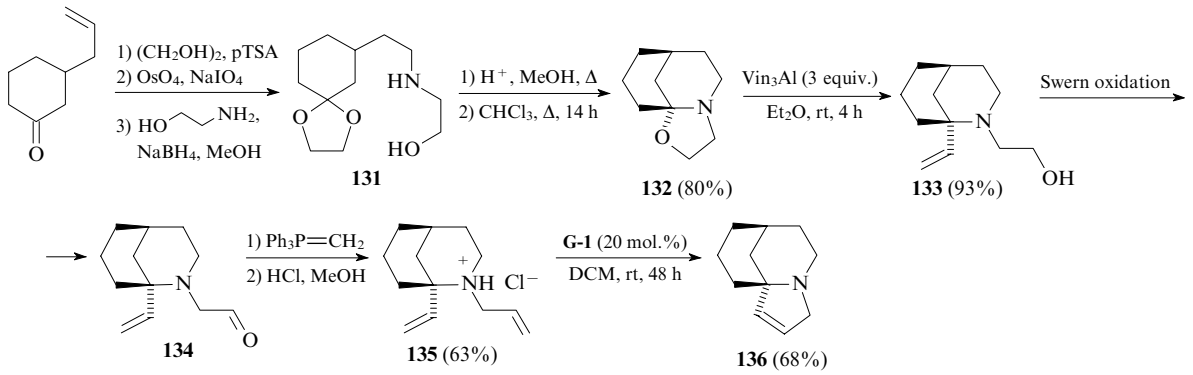


In the first step, chiral allyl amine **127** was transfromed into imine **128**, which was allylated to give dienamine **129**. An attempt to use free amine **129** for metathesis appeared to be ineffective, and, although the transformation into an ammonium salt under the action of pTSA launched the metathesis, the required catalyst loading was 20 mol.%–30 mol.%, which is inadmissibly high. The problem was solved using the carbamate protection: metathesis of the dienamide successfully proceeded in the presence of **G-1** (5 mol.%), resulting in azaspirocyclic derivative **130**.

Kibayasi and co-workers[106] used RCM for construction of a tricyclic core of immunosuppressant FR901483 (Scheme 36), a secondary metabolite isolated from a fermented medium of the fungi *Cladobotryum* in 1996 by researchers of the Japanese Fujisawa Pharmaceuticals company.[107]

The starting dioxolane **131** obtained from 3-allylcyclohexanone in 75% yield in three steps is deprotected upon acid treatment and then, under reflux in chloroform, it is intramolecularly ketolized, giving rise to tricyclic oxazolidine **132**. The application of an original method for reductive vinylation of compound **132** with trivinylaluminium readily furnishes alkene **133**. The oxidation of the hydroxy group in the latter and alkenylation of aldehyde **134** by the Wittig method give the corresponding diene precursor as a free base. This example shows once again the necessity to suppress the nucleophilic properties of the amino group which completely deactivates catalyst **G-1** and arrests the metathesis reaction. The protonation of the amino group with hydrochloric acid solves this problem and allows one to carry out metathesis; however, the application of hydro-

Scheme 36



chloride **135** requires high catalyst loading (20 mol.%) for closing the five-membered ring and formation of the target azatricyclododecene **136**.

Huxford and Simpkins [108] presented a method for stereoselective construction of a spirocyclic precursor for halichlorine (Scheme 37). The same approach to formation of a 1-azaspirobicyclic intermediate was used by Clive's research group [109] with the distinction that it was extended to the synthesis of tricyclic lactams.

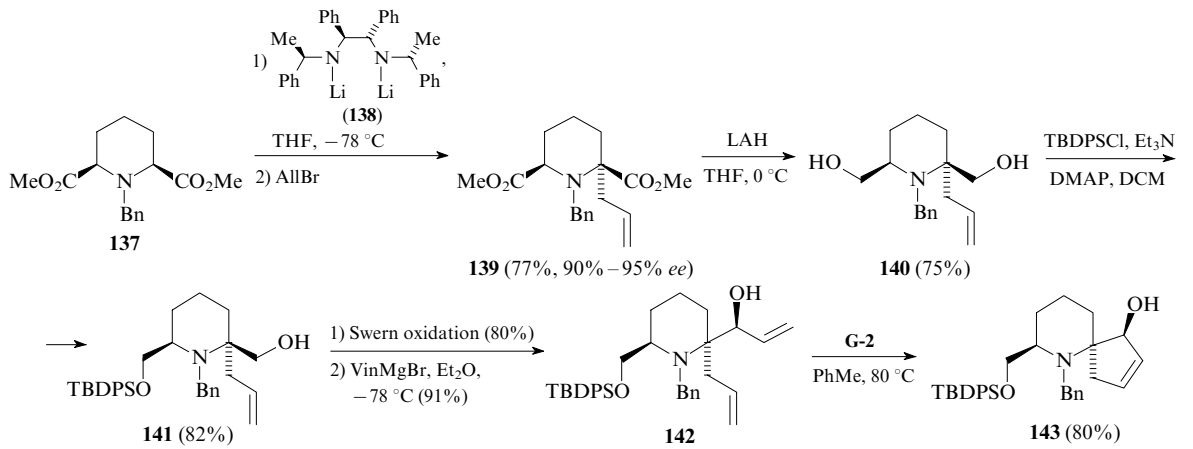
In Simpkin's method, the stereoselective desymmetrization of diester **137** *via* chiral lithium diamide **138** followed by allylation results in alkene **139**. This gives a chiral centre with the quaternary carbon atom serving as the basis for completion of the spiro system. The enantioselectivity (enantiomeric excess, *ee*) in this process reaches 95% but only for loadings of the initial compounds **137** of about 0.1 g; an increase in the loading to 5 g leads to a decrease in *ee* to 67%–55%.[9, 109] The reduction of allylated diester **139** with lithium aluminium hydride gives diol **140** in which the less sterically hindered hydroxymethyl group is selectively silylated with *tert*-butyldiphenylchlorosilane, resulting in ester **141**. The other hydroxymethyl group is oxidized to the aldehyde function by the Swern method. After diastereoselective addition of vinylmagnesium bromide, diene precursor **142** is obtained which, under action of catalyst **G-2** in toluene at 80 °C, affords the target azaspiran **143**.

A tandem of two metathesis reactions was utilized to construct spiro system **144** to be used for the synthesis of hystrionicotoxin analogues (Scheme 38).[110] N-Protected tetraene **145** is transformed in the presence of catalyst **G-1** into monocyclic triene **146** with good stereoselectivity (*dr* = 16 : 1) and high yield (88%). Such a high diastereoselectivity is due to different stabilities of conformers in the chair conformation optimal for ring closure. The second ring is closed in the presence of **G-2** under the same conditions; the ratio of diastereomers in product **147** does not change. It should be noted that the replacement of toluene by DCM allows one to perform tandem reactions in a single step to obtain 1-azaspirocycle **147** in 99% yield and *dr* = 12 : 1.

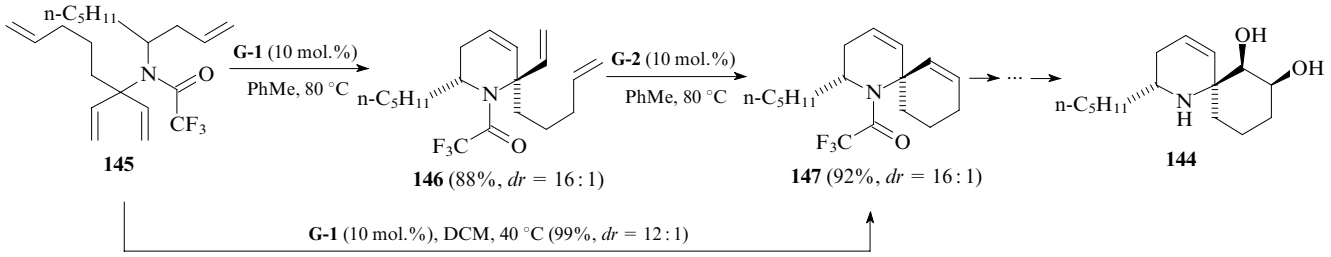
Kim and co-workers [111] suggested a method for the formal synthesis of (−)-lepadiformine using RCM where the diene precursor was obtained by the ester enolate Claisen rearrangement (Scheme 39). The carbonyl group in aldehyde **148** (readily formed from pyroglutamic acid) is oxidized to the carboxyl group with sodium chlorite in a phosphate buffer, then acid **149** is condensed in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) with monosubstituted allyl diol **150**. Ester **151** is subjected to the Claisen rearrangement under the action of LiHDMS through the formation of a cyclic transition state, which leads to diastereomeric unsaturated acids **152** (*dr* = 8 : 1), which were separated chromatographically. The yield of the desired isomer **152** was 70%.

Logically, the next step was esterification of acid **152** to methyl ester **153**. However, all attempts to reduce the ester with lithium aluminium hydride and transform the hydroxymethyl group into the homoallyl substituent were unsuccessful. Therefore, it was decided to use a longer but reliable route, namely, transforming the vinyl substituent in ester **153** into the homoallyl one in the standard way and convert the ester group into the vinyl one. After hydroboration of the vinyl moiety with 9-borabicyclo[3.3.1]nonane (9-BBN), the reaction mixture was treated with thallium(I) ethoxide,

Scheme 37



Scheme 38



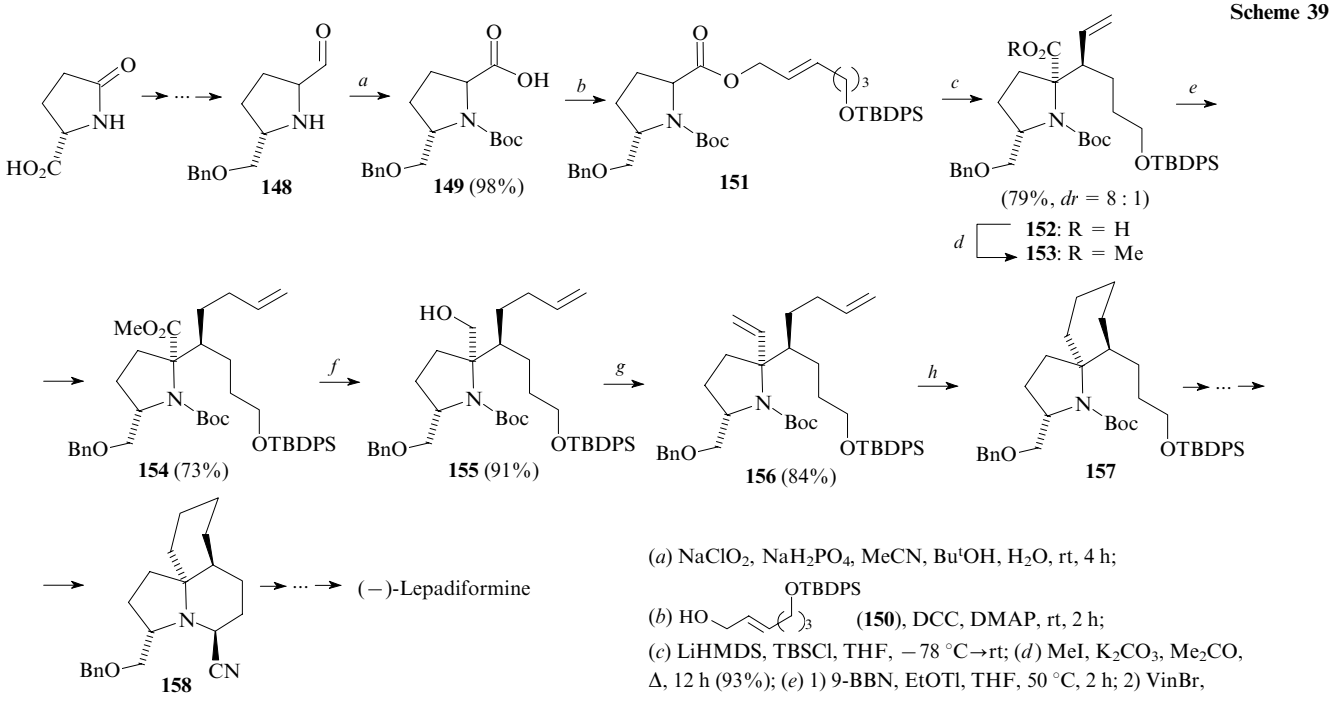
then vinyl bromide and 10 mol.% of the catalyst [a mixture of $Pd(dppf)Cl_2-AsPh_3$, 1 : 1] were added, and the Suzuki–Miyaura coupling of alkylborane with vinyl bromide was carried out to give the target homoallyl derivative **154**. Subsequently, the ester function was reduced with LAH to the hydroxymethyl group in compound **155,** which was oxidized by the Swern method to the aldehyde and was alkenylated by the Wittig reaction, resulting in the desired precursor **156**. A key stage of the spiro system assembly, the RCM reaction, efficiently proceeded in the presence of catalyst **G-2** (5 mol.%), giving rise to azabicycle **157**, which was converted in several steps to tricyclic intermediate **158** to be used in the synthesis of (−)-lepadiformine by the Weinreb method.[10]

Martin's group [112, 113] made an attempt to develop an approach to the tricyclic azaspiro system of the alkaloid FR901483 (Scheme 40). The model substrate was used to work out a rather efficient protocol for the preparation of a tricyclic core applicable for the synthesis of the natural molecule. *N*-Boc-2-pyrrolidone reacts with but-3-enylmagnesium bromide with ring opening resulting in keto derivative **159**. The removal of the Boc protection allows a free base to cyclize into 2-allyl-1-pyrroline **160**. The activation of the imine under the action of CbzCl and treatment of the substituted allyltrimethylsilane in the presence of an equimolar amount of TMSOTf lead to the target diene **161**. The ring closure upon metathesis smoothly proceeds in the presence of catalyst **G-2** (10 mol.%) giving spiro compound **162**. The stereoselective hydroboration of the C=C bond in compound **162** is accompanied by the reduction of the ester group and, after oxidation with sodium peroxoborate, leads to a mixture of diastereomeric diols **163a**,**b** (99% yield, *dr* = 6 : 1), which are isolated in a pure state by chromatography.

The major isomer **163a** has the required configuration of the chiral centres; therefore, in the next step, it was oxidized to give lactone **164**. Under the action of hydrogen in the presence of Pd/C, the hydrogenolysis of the Cbz group results in base **165**. The methanolysis of the latter under microwave irradiation (MW) leads to intramolecular amidation of the intermediate methyl ester, providing the formation of the tricyclic core of the alkaloid FR901483, namely, compound **166**.

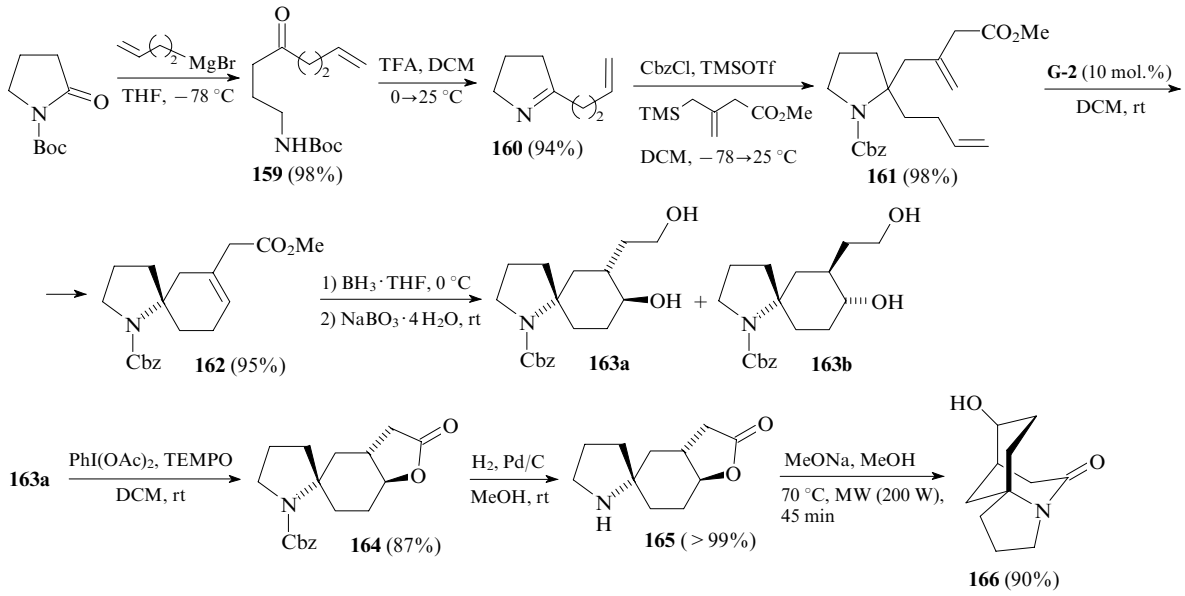
However, as often happens in the synthesis of natural products, the subsequent attempts to accomplish enantioselective synthesis of the alkaloid FR901483 according to the

Scheme 39



(*a*) $NaClO_2$, NaH_2PO_4, MeCN, Bu^{t}OH, H_2O, rt, 4 h;
(*b*) HO–(CH=CH)–(CH$_2$)$_3$–OTBDPS (**150**), DCC, DMAP, rt, 2 h;
(*c*) LiHMDS, TBSCl, THF, −78 °C→rt; (*d*) MeI, K_2CO_3, Me_2CO, Δ, 12 h (93%); (*e*) 1) 9-BBN, EtOTl, THF, 50 °C, 2 h; 2) VinBr, $Pd(dppf)Cl_2$, Ph_3As, THF, DMF, 40 °C, 2 h; (*f*) LAH, THF, 0 °C, 0.5 h; (*g*) 1) Swern oxidation; 2) Wittig reaction; (*h*) 1) **G-2** (5 mol.%), DCM, 40 °C, 1 h (98%); 2) Pd/C, H_2, Et_3N (10 mol.%), MeOH, 12 h (95%); dppf is bis(diphenylphosphino)ferrocene

Scheme 40

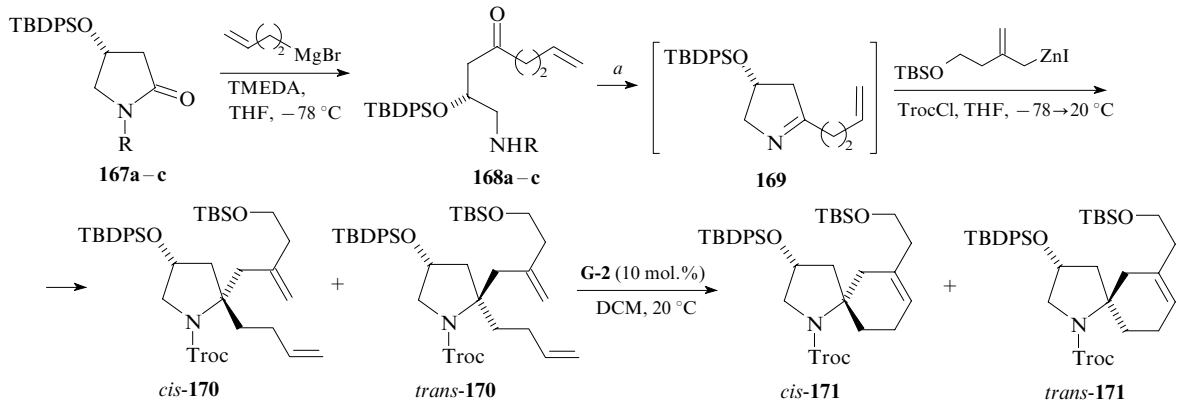


developed protocol from commercially available (*R*)-4-hydroxypyrrolidin-2-one were unsuccessful (Scheme 41).

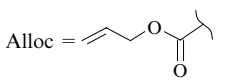
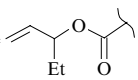
After modification of the proton-donor groups, O-TBDPS-N-Boc-pyrrolidone derivative **167a** is treated with but-3-enylmagnesium bromide to yield ketone **168a**; however, an attempt to remove the Boc protection (conditions *a*) does not afford the target product **169**; instead, elimination of the TBDPSO group with formation of α,β-unsaturated ketone and a pyrrole derivative takes place. The replacement of the Boc group by the allyloxycarbonyl moiety (pyrrolidone **167b**) essentially decreases the yield of ketone **168b** due to more ready decomposition of the Alloc group on treatment with the Grignard reagent even in the presence of TMEDA. In the next step, the Alloc protection is efficiently removed by $Pd(PPh_3)_4$ (20 mol.%) with morpholine; however, the resulting unstable 2-allyl-1-pyrroline **169** cannot be separated from *N*-allylmorpholine (the yield of the mixture is 53%). Despite the successful cyclization, the low yield of product **168b** in the previous step hampers implementation of this route. Therefore, the authors used a bulkier protecting group (EtAlloc), which enabled the synthesis of ketone **168c** in an acceptable yield.

The removal of the EtAlloc groups under similar conditions occurs too slowly, but replacement of morpholine by pyrrolidine substantially accelerates the reaction. However, the problem of separation of 2-allyl-1-pyrroline **169** from N-substituted pyrrolidine complicates the application of this method, since in this case, the next step (reaction with substituted allyltrimethylsilane, see Scheme 41) affords compound **170** in low yield. A search for other conditions showed that a good substitute for pyrrolidine is benzotria-

Scheme 41

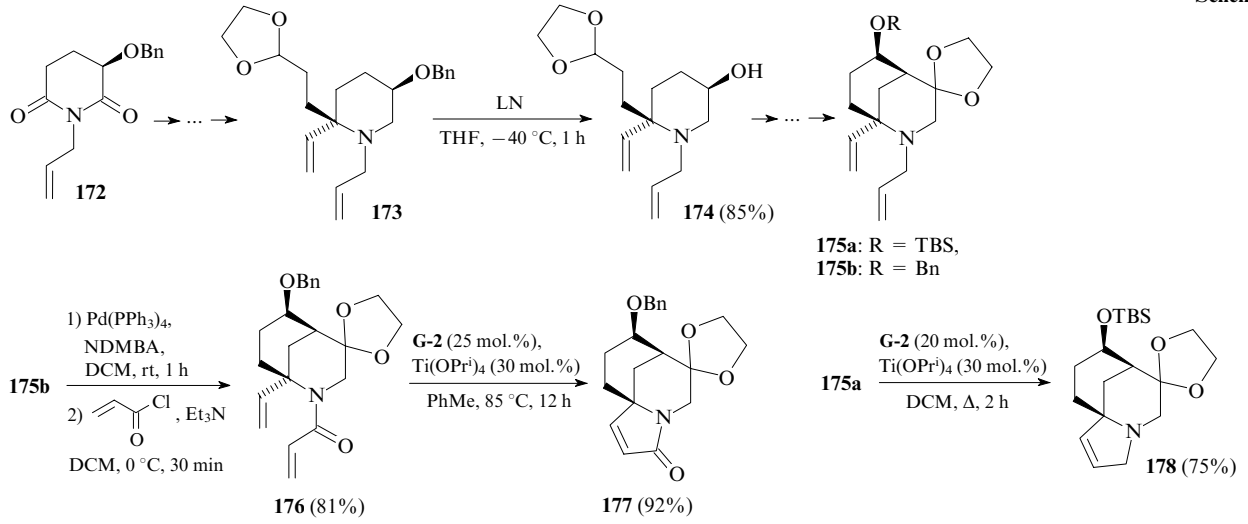


R = Boc, Alloc, EtAlloc;

Alloc = , EtAlloc = 

Compound **167**	R	Yield of **168** (%)	Conditions *a*
a	Boc	59	TFA or TMSI
b	Alloc	15	$Pd(PPh_3)_4$, morpholine
c	EtAlloc	58	$Pd(PPh_3)_4$, morpholine, or pyrrolidine, or Bt-H

Scheme 42



LN is lithium naphthalide, NDMBA is *N*,*N*′-dimethylbarbituric acid

zole; furthermore, the product of its alkenylation is easily separated from pyrroline **169**.

Then another problem arose, namely, the impossibility of application of acid catalysis in allylation by analogy with the model reaction, since the TBDPSO group can be readily eliminated from compound **169**, giving rise to the corresponding substituted pyrrole. The application of an organozinc reagent along with TrocCl leads to an unseparable mixture of isomeric dienes **170** (37%, *dr* = 1 : 1). After the metathesis step in the presence of catalyst **G-2**, the mixture of spiro compounds **171** (99% total yield) was separated, but the synthesis was not further continued. Hence, in the real synthesis of the alkaloid FR901483, almost all of the model results proved to be useless, since it was not taken into account that the chemical behaviour of 3-hydroxypyrrolidines is largely determined by their easy conversion to unsaturated and pyrrole derivatives. Nevertheless, the spiro system closure upon the metathesis reaction was very efficient.

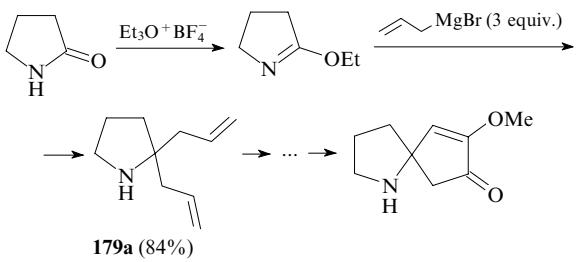
Zhang and Huang and co-workers [114, 115] developed a successful method for enantioselective total synthesis of the immunosuppressant (−)-FR901483 and its isomer (+)-8-*epi*-FR901483, in which the chirality was transmitted from (*R*)-1-allyl-3-benzyloxyglutaramide **172** (Scheme 42) and the final step of the tricyclic core construction involved closure of a six-membered rather than five-membered ring.We will consider only several key intermediates in order to understand the logic of synthesis of the diene precursors. Thus, after selective reduction of one of the carbonyl groups in compound **172**, the second C=O group was subjected to the double reductive alkylation with Grignard reagents, which gave monocyclic diene **173** as a mixture of isomers (*dr* = 9 : 1) in 59% total yield over three steps. The selective debenzylation was accomplished with lithium naphthalide; a mixture of diastereomers was separated by chromatography, and the main isomer **174** was further introduced into the following transformations: (i) Swern oxidation to ketone; (ii) deketalization; (iii) intramolecular aldol type condensation, and, finally, (iv) introduction of the dioxolane protection of the keto group, as well as TBS (**175a**) or Bn protection (**175b**) of the hydroxy group, which completed the formation of a bicyclic system.

In diene **175b**, an acryloyl group was substituted for the allyl group to give diene **176** in two steps: Pd-catalyzed deallylation and acylation of the amino group with acryloyl chloride. Dienes **175a** and **176** appeared to be rather inert in the RCM process in DCM: no reaction took place with catalysts **G-1** or **G-2**. Only upon heating of diene **176** with **G-2** (25 mol.%) at 85 °C in toluene, tricyclic compound **177** was formed in 30% yield (60% of the initial substance was recovered from the reaction mixture). However, the most pronounced effect was achieved upon addition of 30 mol.% of $Ti(OPr^i)_4$ — the reaction products **177** and **178** were isolated in 92% and 75% yields. The influence of $Ti(OPr^i)_4$ can be attributed to cleavage of the Ru–O coordination bonds between the catalyst and the substrate, which arrests the catalytic process. On the whole, it can be noted that the method *via* construction of a five-membered ring was much more efficient.

The studies discussed below show different methods of double alkenylation of lactams, since the efficiency of the whole route of construction of a spiro system is, as a rule, determined by the ease of the synthesis of the diene precursor.

In 1975, when the Grubbs and Schrock catalysts were not discovered as yet, Semmelhack *et al.*[116] described the synthesis of the cephalotaxine alkaloid. A key starting compounds in this transformation was 2,2-diallylpyrrolidine **179a**, which was obtained in 84% yield by the action of allylmagnesium bromide (3 equiv.) on 2-ethoxypyrroline according to the method developed in 1961 by Lukes and Cerny [117] for 2,2-diallylpiperidine (Scheme 43).

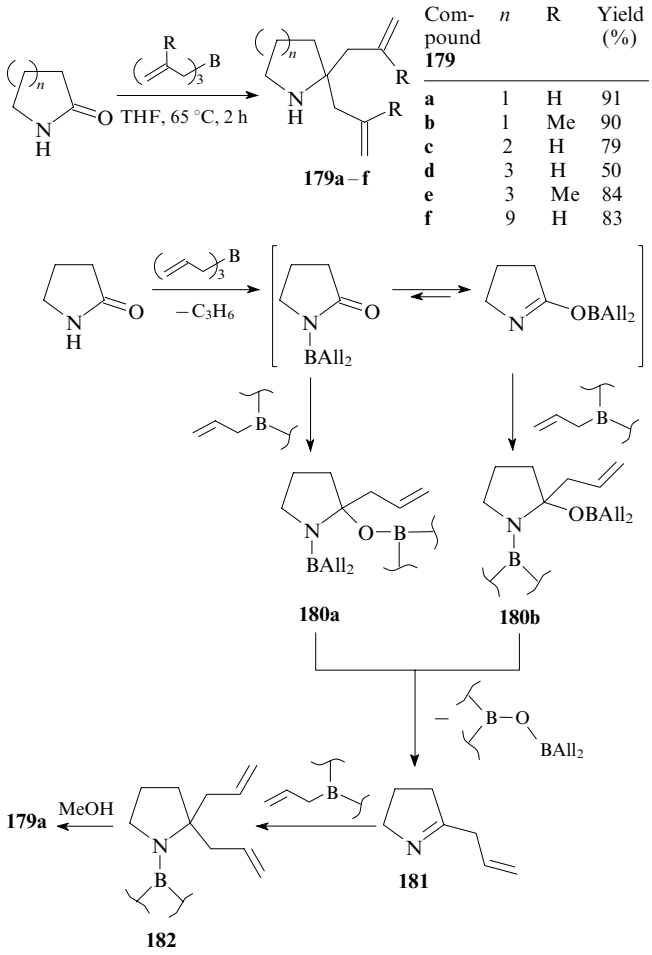
Scheme 43



In 2000, Bubnov *et al.*[118] used triallyl- and trimethallylboranes for allylboration of lactams (Scheme 44). The reaction yielded 2,2-diallylated heterocycles **179a–f**: pyrrolidine, piperidine, azepine and azacyclotridecane derivatives, which were obtained in high yields irrespective of the azacycle size. The most probable mechanism of the process is depicted in Scheme 44 in relation to the synthesis of 2,2-diallylpyrrolidine (**179a**). In the first step, the deprotonation of the NH group accompanied by the release of propylene and formation of the N–B or more stable O–B derivative occurs. Both intermediates react with allylborane moieties, resulting in the formation of monoallylated pyrrolidines **180a**,**b**. Since the compounds containing the heteroatom at the α-position relative to the boron atom are not stable, they undergo β-elimination with release of reactive 2-allylpyrroline **181**, which again reacts with allylborane species, giving rise to 2,2-diallylated derivative **182**. Under the action of MeOH on compound **182**, the protolysis of the N–B bond takes place, and a free amine is generated.

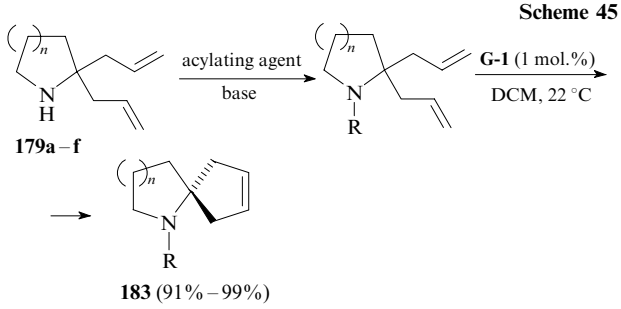
The resulting 2,2-diallylated heterocycles **179a–f** were used for the synthesis of 1-azaspirocyclic compounds **183** by RCM (Scheme 45).[119] An important factor for successful synthesis is the introduction of the acyl type protecting group at the nitrogen atom.

Scheme 44



Compound **179**	*n*	R	Yield (%)
a	1	H	91
b	1	Me	90
c	2	H	79
d	3	H	50
e	3	Me	84
f	9	H	83

Scheme 45

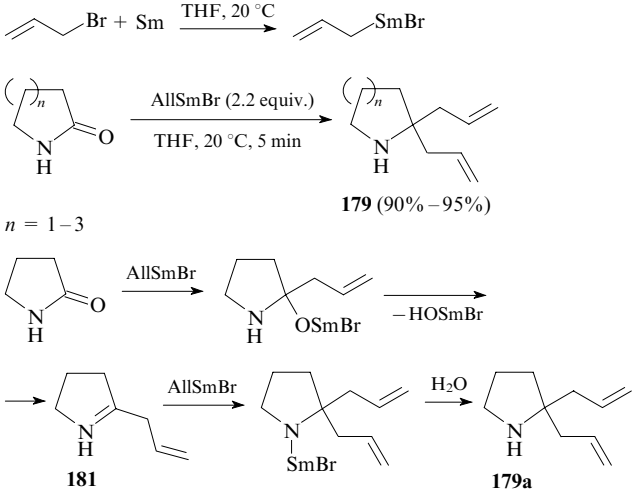


n = 1–3, 9; R = Ac, Bz, Boc, $CF_3C(O)$

Thus, only 1 mol.% of the first-generation catalyst **G-1** is sufficient to achieve the complete conversion and high yields (up to 99%) of N-acylated 1-azaspirans.

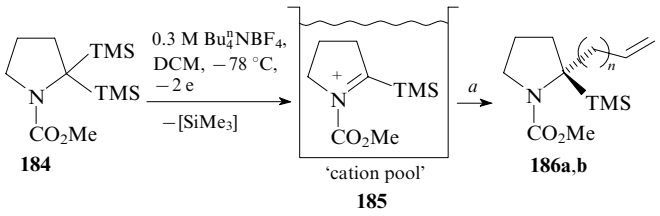
Shortly after the appearance of the report by Bubnov *et al.*,[118] Lia and Zhang[120, 121] demonstrated that lactams can be 2,2-diallylated with allylsamarium bromide in THF in 5 min. The Chinese researchers obtained an analogous series of 2,2-diallylated nitrogen-containing heterocycles **179**. However, the mechanism of reactions involving samarium somewhat differs from that given in Ref. 118 since in this case the N–H bond cleavage step is missing (Scheme 46).

Scheme 46



Suga *et al.*[122] developed the method for electrochemical activation and double alkenylation of *N*-methoxycarbonyl-2,2-bis(trimethylsilyl)pyrrolidine (**184**) (Scheme 47). The electrochemical activation was performed by the 'cation pool' method involving generation and accumulation of *N*-acyliminium cation **185** at low temperature and subsequent direct reaction with C-nucleophiles. This approach has an advantage over conventional processes, since it allows one to use organometallic nucleophiles (organic derivatives of magnesium, zinc and aluminium) without any risk of their oxidation during electrochemical reaction. Thus, pyrrolidine **184** was oxidized at −78 °C in DCM and, after generation of the 'cation pool' **185**, the nucleophile, allyltrimethylsilane or homoallylmagnesium bromide, was added (see Scheme 47).

Scheme 47

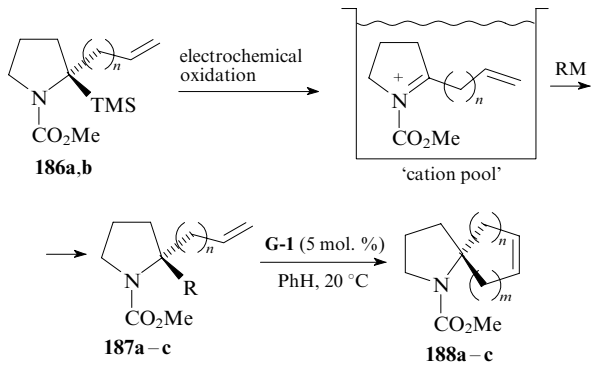


n = 1 (**186a**), 2 (**186b**);

(*a*) TMS (for n = 1) or MgBr (for n = 2)

The resulting alkenes **186a**,**b** were introduced again into the electrochemical reaction for alkenylation by the second nucleophilic agent. Dienes **187a**–**c** were obtained in moderate yields (46%–67%); in the presence of catalyst **G-1** in benzene, the latter were converted to azaspirocyclic alkenes **188a**–**c** (Scheme 48).

Scheme 48



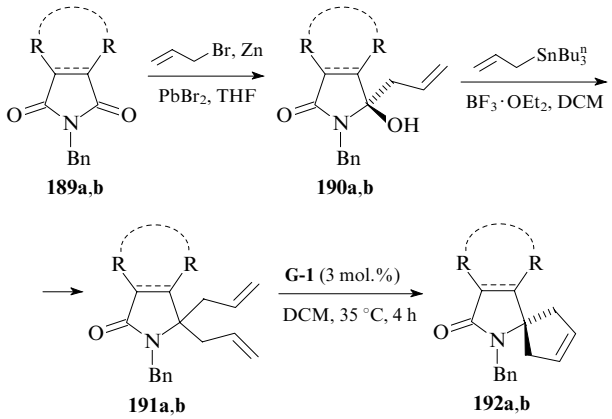
Substrate **186**	RM	Products **187**, **188**	n	m	Yield (%)	
					187	**188**
a	AllTMS	**a**	1	1	46	77
b	AllTMS	**b**	2	1	67	86
	$Bu^nCH{=}CHZnEt$	**c**	2	0	62	92

Alkene **188c** was used in the synthesis of a pentacyclic core of cephalotaxine by the Tietze method.[123]

Kim and co-workers [124, 125] reported the α,α-diallylation of N-benzyl-substituted succinimide (**189a**) and phthalimide (**189b**) (Scheme 49). The method is based on the stepwise allylation of the imides, first, with allylzinc bromide (under Barbier conditions) and then with allyltri(n-butyl)tin. The first step of allylation proceeds rather efficiently, compounds **190a**,**b** being isolated in high yields.

However, the repeated allylation under the action of allyltri(n-butyl)tin proceeds differently for compounds **190a**,**b**. In the presence of boron trifluoride, hydroxy derivative **190a** is largely dehydrated (51%),[124] which is attributable to the slower reaction with the organotin reagent. Diallyl derivative **191a** was isolated only in 23% yield, while **191b** was obtained in almost quantitative yield. Both dienes **191a**,**b** are actively cyclized in the presence of catalyst **G-1** to readily form 1-azaspirans **192a**,**b**.

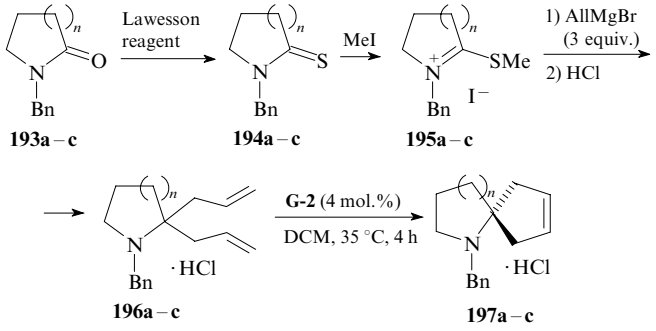
Scheme 49



Compound	R–R	Yield (%)		
		190	**191**	**192**
a	2 H	88	23	98
b	benzo	95	98	98

In another approach developed by Renaud and coworkers,[126] *N*-benzyl derivatives of lactams **193a**–**c** were obtained (Scheme 50). Lactams **193a**–**c** were treated with the Lawesson reagent [2,4-bis(4-methoxyphenyl)-1,2,3,4-dithiadiphosphetane-2,4-disulfide] for substitution of sulfur for oxygen, and then thiones **194a**–**c** were methylated. This gave thioiminium salts **195a**–**c**, the key reagents for this synthesis.

Scheme 50



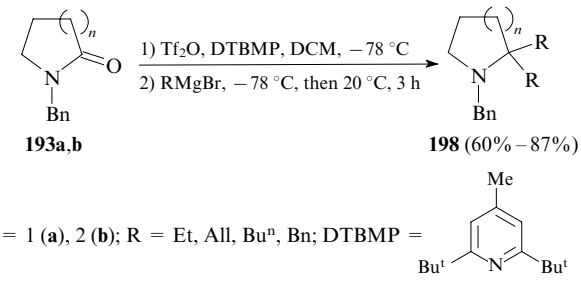
Compound	n	Yield (%)	
		196 (in 3 stages)	**197**
a	1	64	95
b	2	69	87
c	3	52	83

These salts are treated with organomagnesium and -cerium compounds. The addition of 3 equiv. of allylmagnesium bromide to compounds **195a**–**c** gives diallyl derivatives **196a**–**c**. It should be noted that the outcome of addition of organometallic compounds does not depend on the reagent amount. For example, the reaction with 1 equiv. of AllMgBr in DCM at −78 °C results in 40% of product **196a** and the starting lactam **193a** (recovered after hydrolysis). This is associated with the fact that the addition of one allyl group gives rise to the much more reactive pyrrolinium cation, an analogue of cation **195a** which immediately adds the second molecule of the nucleophile.

Hydrochlorides of diallyl derivatives **196a–c** form spiro compounds **197a–c** in high yields in the presence of **G-2**. This method is not limited to the allyl substituents and can be used for the synthesis of other 2,2-disubstituted derivatives.

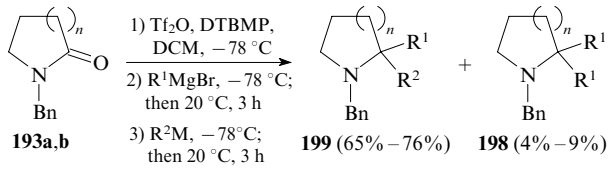
The activation of N-benzyl-substituted (in the general case, N-alkyl-substituted) lactams and amides and their conversion to 2,2-disubstituted amines are possible using the direct acylation of the carbonyl group with Tf_2O, which was accomplished by Huang and co-workers [127] (Scheme 51).

Scheme 51



The sequential treatment of lactams **193a,b** with Tf_2O (1.2 equiv.) in the presence of DTBMP and RMgBr (3 equiv.) at −78 °C gives 2,2-disubstituted amines **198** in good yields. Ethyl-, n-butyl-, benzyl- and allylmagnesium bromides can be used with the same efficiency. Moreover, this method is applicable for two-step alkylation with different organometallic reagents: 1 equiv. of the first reagent is added, and, in a certain period of time, the second reagent is added (Scheme 52). The reaction yields disubstituted amines **199** with two different substituents; the amount of homosubstituted by-product does not exceed 4%–9%.

Scheme 52

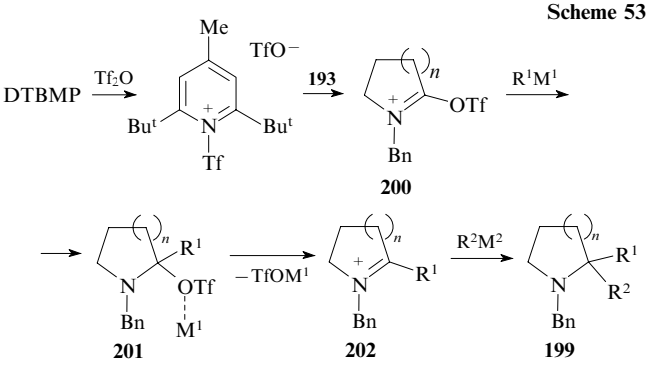


n	R^1	R^2	M
1	Et	Bu^t	MgBr
1	Et	All	MgBr
1	Et	Bn	MgBr
1	Et	Bu^n	Li
2	Et	All	MgBr
2	Bu^n	Et	MgBr
2	Bu^n	Vin	MgBr

The supposed mechanism of the alkylation can be conceived as follows: initially, *N*-trimethylsulfonylpyridinium triflate is formed and then it acylates the carbonyl group to afford acylium cation **200** (Scheme 53).

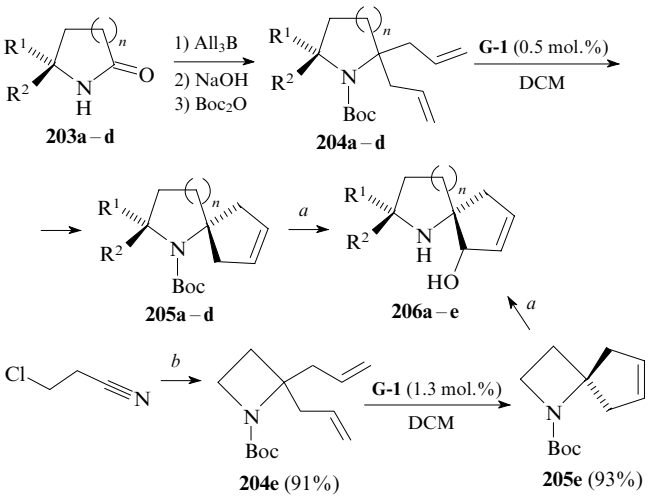
The addition of 1 equiv. of R^1M^1 gives adduct **201** the stability of which is responsible for the selectivity of monoalkylation. At elevated temperature, this adduct decomposes with the formation of acylium cation **202**; the second equivalent of R^2M^2 is added to the latter, resulting in disubstituted amine **199**. Although the metathesis reaction was not carried out in Ref. 127, it is obvious that the reaction is potentially possible under Renaud conditions (see Scheme 50).

Scheme 53



As can be seen, different efficient methods for the synthesis of symmetrical 1-azaspirocyclic alkenes (see Schemes 45, 48–51) have been developed. However, the synthesis of natural compounds requires their unsymmetrical analogues (*e.g.*, compound **188c**, see Scheme 48). Therefore, in 2008 the authors of the present review [128] proposed a method for the synthesis of a series of novel 1-azaspirocycles and chiral spiro-β-amino alcohols based on them (Scheme 54). The allylboration of lactams **203a–d** and 3-chloropropionitrile with triallylborane leads to monocyclic 2,2-diallylated heterocyclic compounds (even with the azetidine ring), which are converted further to Boc derivative **204a–e** in high yield.

Scheme 54



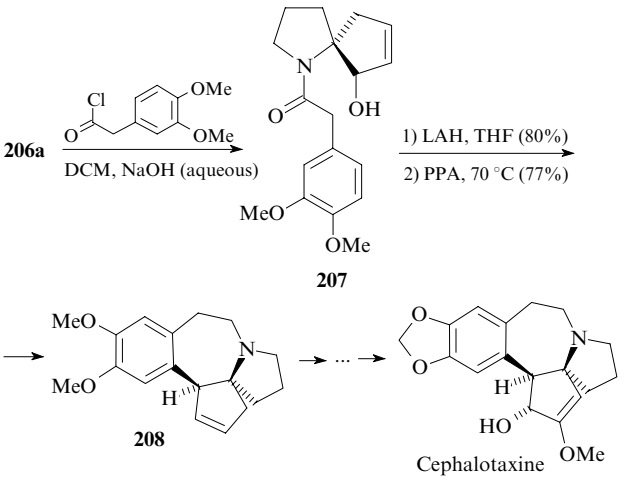
(*a*) 1) NBS, DCE; 2) Bu^{t}OK, THF; 3) $MgBr_2$, THF; 4) NaOH, MeOH
(*b*) 1) All_3B, 110 °C, 1 h; 2) NaOH; 3) Boc_2O;
n = 1: $R^1 = R^2 = H$ (**a**), Me (**b**); $R^1 = H$, $R^2 = CH_2OH$ (**c**);
n = 2, $R^1 = R^2 = H$ (**d**); *n* = 0, $R^1 = R^2 = H$ (**e**);
DCE is dichloroethane

In the presence of catalyst **G-1**, compounds **204a–e** smoothly form spirocycles **205a–e**; in the case of compound **204c** with the unprotected hydroxy group, 2.0 mol.% of the catalyst is required. Further transformation of pyrrolidines **205a–e** in free spiro-β-amino alcohols **206a–e** is carried out in four simple steps, which utilize cheap and available reagents. In the first step, the reaction with *N*-bromosuccinimide (NBS) takes place, resulting in desymmetrization of

alkene with the formation of a tricyclic bromourethane. Under the action of potassium *tert*-butoxide, HBr is eliminated, and then, in the presence of the Lewis acid ($MgBr_2$), the allyl rearrangement results in tricyclic 1,3-oxazolidin-2-one, which is hydrolyzed to give amino alcohols **206a–e** in high yields. Only in the case of compound **206e**, the product yield over elimination and rearrangement steps was ~50%.

To obtain cephalotaxine, spiran **206a** is acylated with homopiperanyl chloride (Scheme 55), and amide **207** is converted to a tetracyclic compound, a key intermediate in the synthesis of cephalotaxine by the Mori method.[129]

Scheme 55



PPA is polyphosphoric acid

* * *

In conclusion it should be emphasized that the combination of alkenylation and intramolecular metathesis is an exceptionally reliable and efficient method for the preparation of 1-azaspirocyclic and bridged azabicyclic compounds. The presence of different efficient catalysts for metathesis along with good understanding of the mechanism of their action allows one to plan and successfully accomplish the most complex synthetic tasks, including those related the synthesis of natural and biologically active compounds.

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