=== **REVIEW** ===

Reactions of Alicyclic Epoxy Compounds with Nitrogen-Containing Nucleophiles

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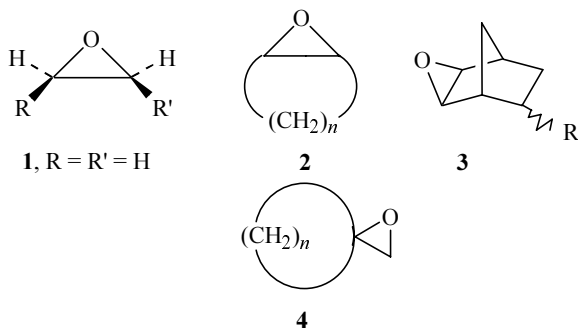[2] *Organisch-chemische Laboratory, Rheinisch-Westfalische technicshe Hochschule, Aachen, Germany*

Abstract—The review considers reactions of alicyclic epoxy compounds and their analogs with nitrogen-containing nucleophilic reagents, such as amines, azides, hydrazines, etc., biological aspects of these reactions, and properties of amino alcohols which are practically important organic products and synthons. Reaction mechanisms, including radical and radical ion reaction paths, the results of quantum-chemical studies, stereo- and regioselectivity aspects, and activation of epoxy substrates with achiral and chiral catalysts are discussed. The formation of nitrogen-containing heterocyclic systems via opening of the oxirane ring is described.

I. INTRODUCTION

Reactions of epoxy derivatives with amines were studied since 1860 when Wurtz reported on the reaction of oxirane (**1**) with ammonia [1]. Aminolysis of alicyclic (**2**) and other epoxy compounds was later described in some more general reviews [2–7], specifically in those dealing with reactions of substituted epoxynorbornanes **3** [8] and spirooxiranes **4** [9]. Reactions of epoxy derivatives with amines are important, for they provide one of the most convenient methods for the synthesis of vicinal amino alcohols which are used as building blocks in the preparation of natural and biologically active organic compounds [10–24]. In the recent review, Bergmeier reported numerous examples of isolation of natural compounds and synthesis of pharmacologically active compounds having amino alcohol structural fragments [10]. Various vicinal amino alcohols and their derivatives at the hydroxy group and the nitrogen atom exhibit diverse biological activity and are now used in medical practice [25–27].

II. SOME BIOLOGICAL ASPECTS OF THE CHEMISTRY OF ALICYCLIC VICINAL AMINO ALCOHOLS

Reactions of alicyclic epoxy compounds with nitrogen-containing nucleophiles are included in the metabolism of polycyclic aromatics and other carcinogenic and mutagenic substances containing an oxirane fragment. Some examples of aminolysis of biologically active epoxy compounds are given below. "Bay-region" epoxy diols which are formed by joint action of cytochrome

1, R = R' = H   **2**   **3**   **4**

Scheme 1.

(+)-**5**

(−)-**5**

Scheme 2.

6

7
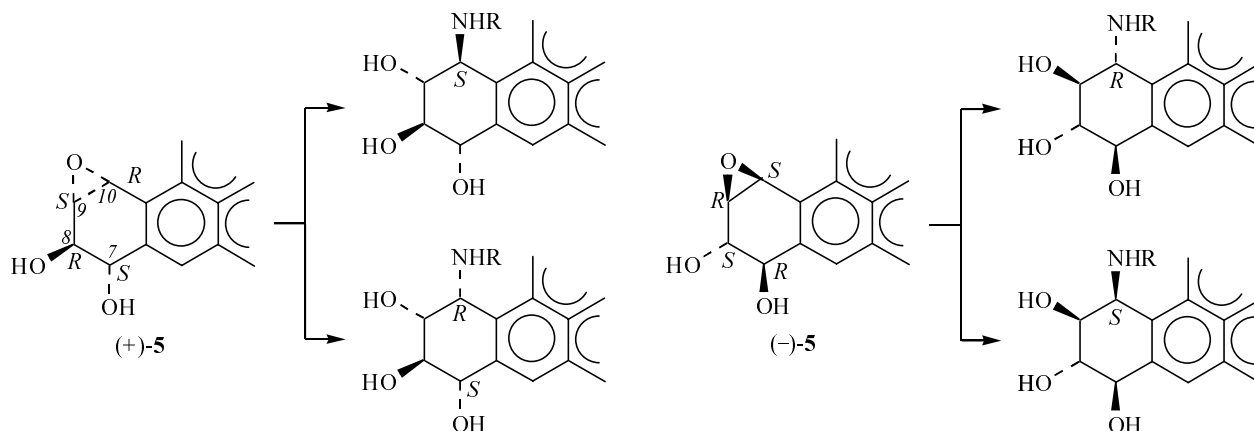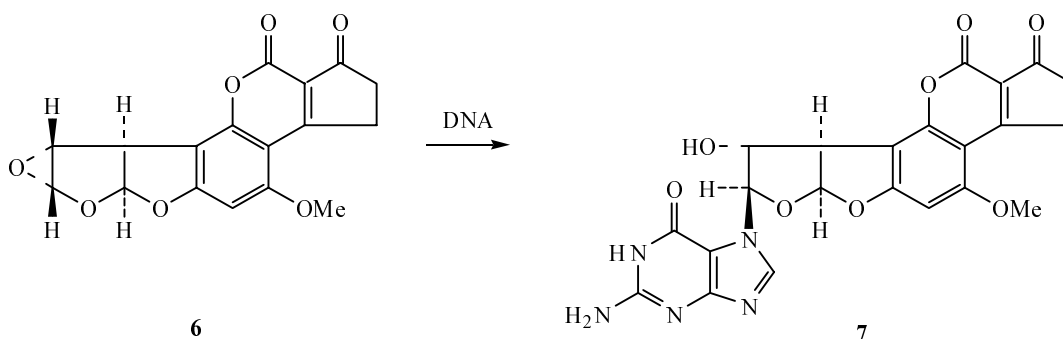
P450 and epoxyhydrolase on polyaromatic hydrocarbons suffer from attack by amino groups and other nucleophilic moieties in living cell molecules at the last stage of metabolism. 9,10-Epoxy-7,8-diols based on benzo[*a*]pyrene [(+)- and (-)-**5**] react with purine bases of nucleic acids through alkylation of exocyclic amino groups in the latter [28]. Enantiomeric epoxy diols (specifically, those diastereoisomers in which the 7-hydroxy group is oriented *cis* with respect to the oxirane ring) undergo mainly *cis*-opening of the three-membered fragment (Scheme 1). Aminolysis and azidolysis of various polycyclic epoxides derived from carbon- and nitrogen-containing polycyclic aromatic systems were studied in detail in [29–31]. In some cases, the amine component was also a polycyclic system, e.g., 5,10-dihydro-7,8,10-trimethylbenzopteridine-2,4(1*H*,3*H*)-dione, etc. [31].

The second example is concerned with activation and binding of Aflatoxin B$_1$ (AFB$_1$), which is one of the strongest carcinogenic and mutagenic compounds and environment pollutants. Baertschi *et al.* [32] reported on a successful metabolic activation of the toxin via epoxidation with dimethyldioxirane and subsequent transformation of epoxy derivative **6** by the action of DNA. The reaction occurs in a regio- and stereoselective fashion at the N^7

atom of deoxyguanosine. The structure of the isolated product (**7**) was rigorously proved (Scheme 2).

One more example of practically important aminolysis is the reaction of stereoisomeric epoxy derivatives of thymidine with amines and b-amino acid ethyl esters [33]. The reaction of (+)-1,3-dimethylthymidine epoxy derivative with amines and b-amino acids was examined as a model of cross-coupling between nucleic acids and proteins. The epoxy derivatives were prepared from optically active bromohydrins. Their absolute configuration was determined by X-ray analysis and by the configuration correlation method [33]. The stereoisomers behave differently in this reaction: Isomer **8** with the amine component forms only the *cis*-adduct, while from isomer **9** both *cis*- and *trans*-adducts are obtained (Scheme 3). The steric structure of the adducts was established on the basis of the known *cis–trans* isomerization by the action of boron trifluoride–ether complex [34]. The reasons for the different reaction stereochemistry were not studied. It was only found that acylation of the d-hydroxy group has no effect on the process [33].

Among biologically active cyclopentanoid analog of nucleosides, there are compounds having an amino alcohol structure, e.g., neplanocin A (**10**), aristeromycin (**11**),

Scheme 3.

$R = H, Ac, X = NHEt, NHPh, NHC_6H_4NO_2\text{-}m, NHC_6H_4NO_2\text{-}p,$
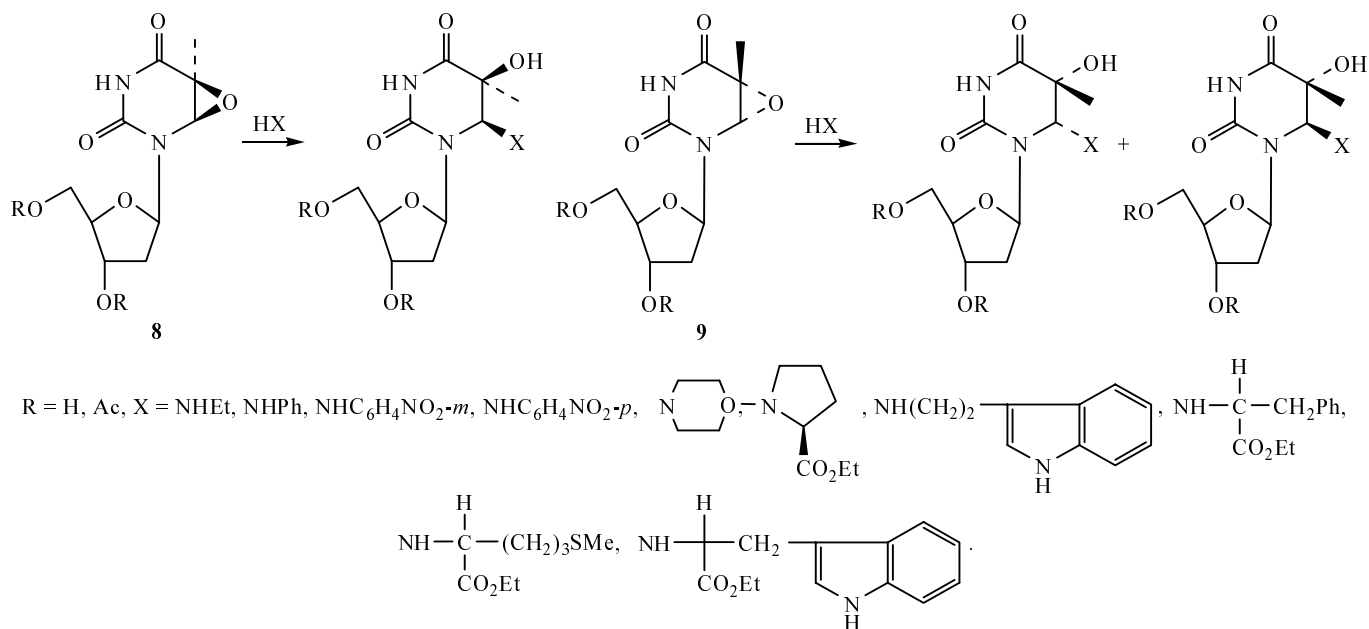
and 2'-deoxyguanosine (**12**). These compounds are used in chemotherapy as antiviral agents which inhibit replication of viruses but do not affect important cell processes [35-37]. Using molecular models, it was shown later that cyclobutane fragment can replace the tetrahydrofuran moiety of natural deoxynucleosides. A new nucleoside

antiviral agent (compound **13**) was synthesized from cyclobutene derivative **14** containing a benzyloxymethyl group which controls the stereochemistry of subsequent processes [37] (Scheme 14). In 1990s, both racemic and optically active *Tsiklobut-A* and its analogs were prepared in a similar way [38–40].

| 10 | 11 | 12 | 13 |

Scheme 4.

Scheme 5.

15   **16**

Scheme 6.

17   **18**

19

Scheme 7.

20

21
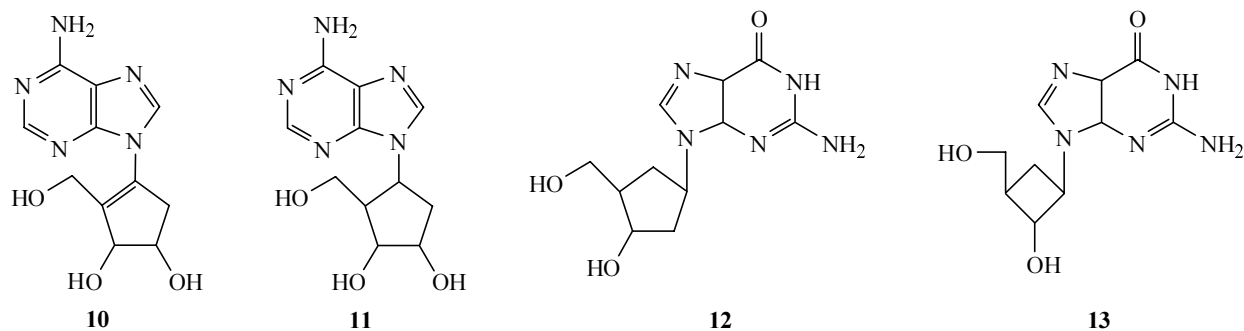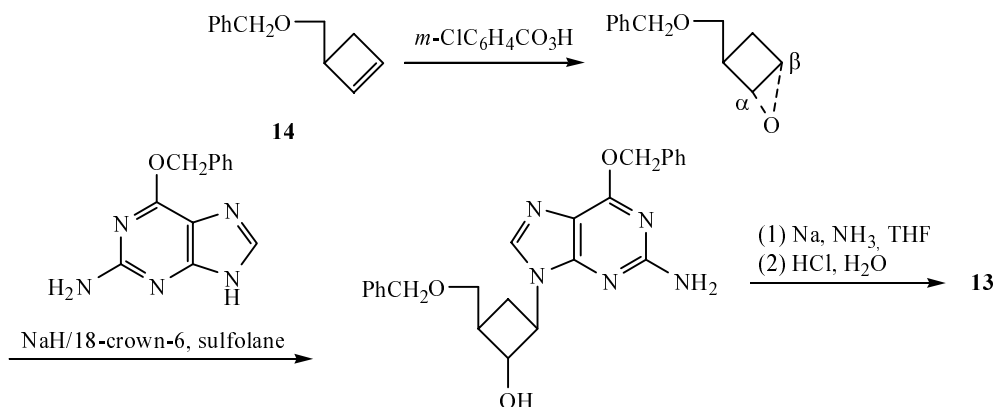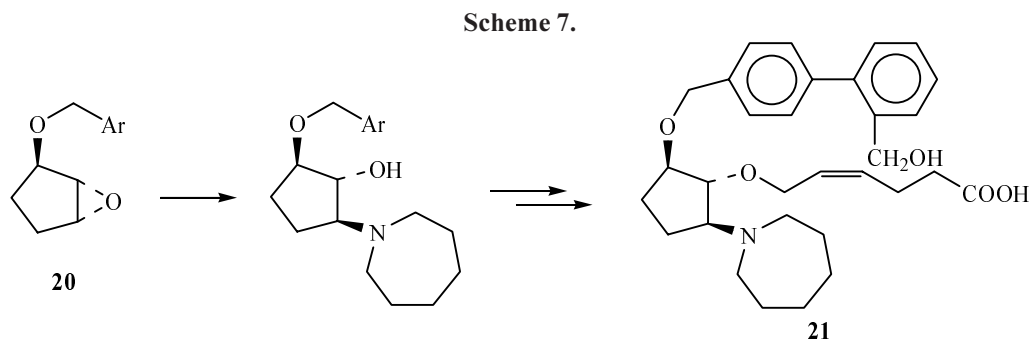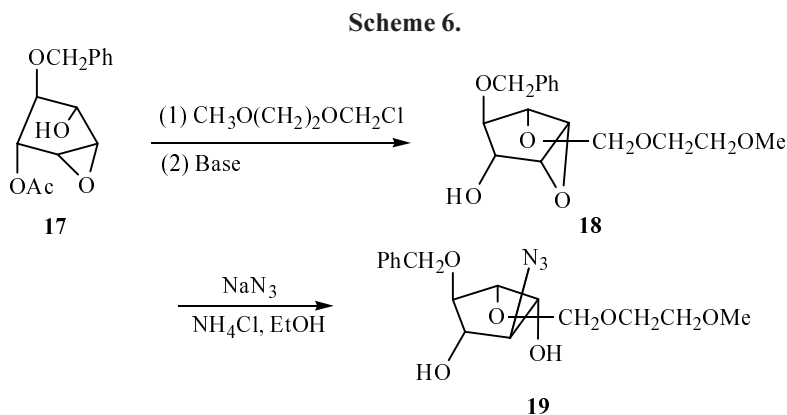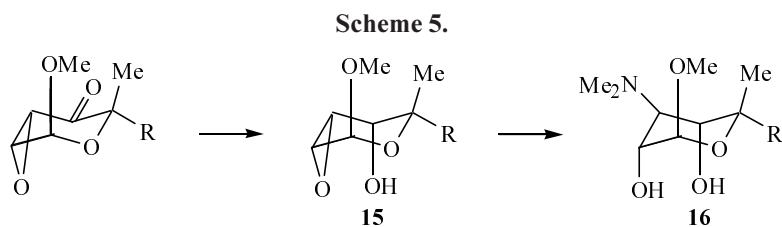
Amino cyclitols of the alicyclic series and their analogs include some antibiotics or their synthetic precursors [41, 42]. Hauser *et al.* [41] described the total synthesis of an anthracycline antibiotic, (+)-*con-o*-methylnogarol (**16**), which is based on the aminolysis of epoxy derivative **15** (Scheme 5). Starting from substituted epoxycyclopentane **17**, Le Grand *et al.*[42] prepared compound **19**, which is an intermediate product in the synthesis of aristeromycin (Scheme 6). Key monoester **18** was isolated as a result of enzymatic hydrolysis; it is responsible for optical activity of the subsequent transformation products [42]. Some amino cyclitols based on 3,4-epoxy-2,2-dimethyl-3,4-dihydro-2*H*-benzopyran were recently found to exhibit cardiovascular activity [16].

A quite interesting synthesis on the basis of epoxy derivative **20** and pharmacological estimation of the activity of new aminoprostanoids have been reported [43]. One of the latter (compound **21**; Scheme 7) is among the most efficient thromboxan antagonists; it is characterized by prolonged action and is used in the treatment of

thromboses. Opening of the epoxy ring in the series of new complex compounds related to Dynemycin A was effected with the aid of propylamine. Study of the chemical transformations of these compounds, in particular of epoxy derivative **22**, (Scheme 8), by the action of amines, alcohols, phenols, thiols, etc., favored elucidation of the mechanism of action of this group of important biologically active compounds [22, 44].

III. MECHANISMS OF REACTIONS OF EPOXY COMPOUNDS WITH NITROGEN-CONTAINING NUCLEOPHILES

General relations holding in the oxirane ring opening, including aminolysis and azidolysis of epoxy derivatives, were established on the basis of the results of studying the reaction kinetics their regio- and stereoselectivity, and conformational features. The generally recognized classical mechanism for transformation of epoxy compounds was proposed in 1959 by Parker and Isaacs [45]. It was then supported by numerous studies performed by both

Scheme 8.
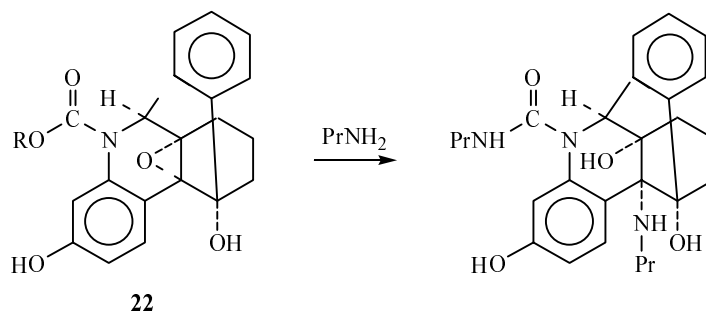
Scheme 9.
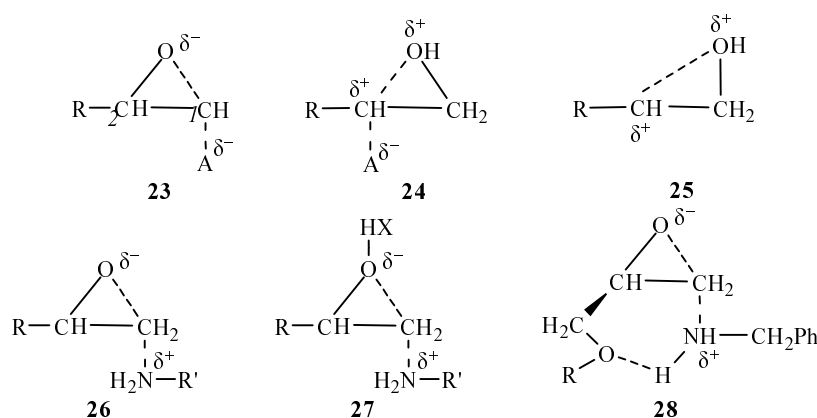
Parker and co-workers [46–48] and other authors [49, 50]. According to the proposed mechanism, the reactions occur as bimolecular nucleophilic substitution at the oxirane carbon atom; here, the departing group is the oxirane oxygen atom. Transition states in neutral (**23**) and acid media (**24**) reflect fundamental reaction features, i.e., bimolecular character and change of the configuration of the carbon atom in the only stage of synchronous process, which distinguish them from transition state **25** typical of S_N1 reactions. *trans*-Stereoselectivity in reactions of epoxy compounds with amines is explained by the structures of transition states **26** and **27** [46, 51, 52] (Scheme 9). The reduced energy of activation in reactions of 2,3-epoxypropyl ethers with benzylamine suggests anchimeric assistance by lone electron pairs on the oxygen atom in the transition state (structure **28**) [49]. The reaction regioselectivity conforms to the Krasusky rule which was discovered while studying aminolysis of alkyl-substituted oxiranes. According to this rule, the formation of alcohols with more substituted carbon atom at the hydroxy group is preferred [53]. The regioselectivity is controlled by steric factor: attack by an amine is directed at less substituted and spatially more accessible terminal carbon atom of the epoxy ring [54–59]. Reactions of epoxy derivatives with azide ion are less selective, pre-

sumably because of greater polarizability of the reagent [11, 60, 61].

The regioselectivity of opening of the oxirane ring in a large series of alicyclic compounds, such as epoxycyclohexanes and epoxy steroids, is determined primarily by conformational factor which favors diaxial mode of ring opening (Fьrst–Plattner rule) [62, 63]. In reactions with dissymmetric 2,3-epoxy-1,1-dimethylcyclo-hexane, alternative attacks are possible which lead to transition states characterized by different energies. In the first case (Scheme 10, structure **29**), *half-chair* conformation of epoxycyclohexane is gradually transformed into *chair* conformation of the addition product (**30**); in the transition state, the cyclohexane fragment has an intermediate conformation (between the above two). In the second case (**31**), alternative attack gives rise to unstable asymmetric *twist* conformation **32** which is then converted into a classical *chair* form. The first path is more favorable from the viewpoint of energy; therefore, the attack by a nucleophile, controlled by conformational factor, is regioselective, and it has no analogies in the series of open-chain epoxy derivatives. The regioselectivity of oxirane ring opening in substituted cyclohexanes and epoxy steroids is usually determined by either consistent or competing effects of conformational, stereoelectronic, and
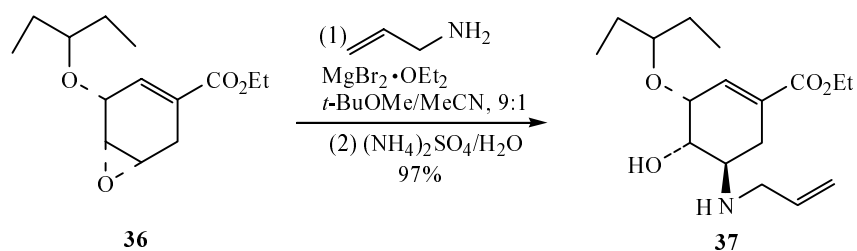
Scheme 10.

**29**   **30**

31   **32**

Scheme 11.

33   **34**   **35**

Scheme 12.

36   **37**
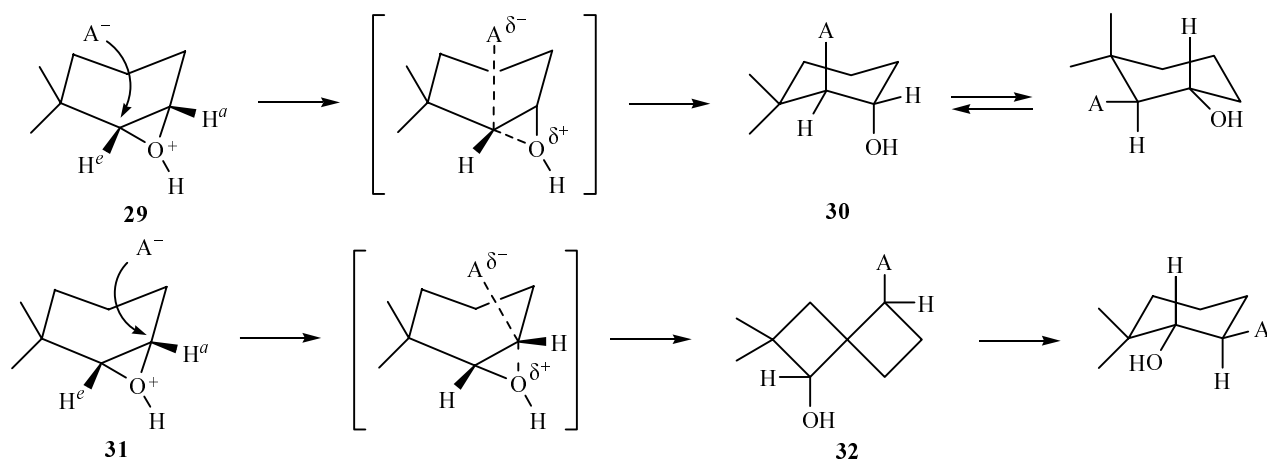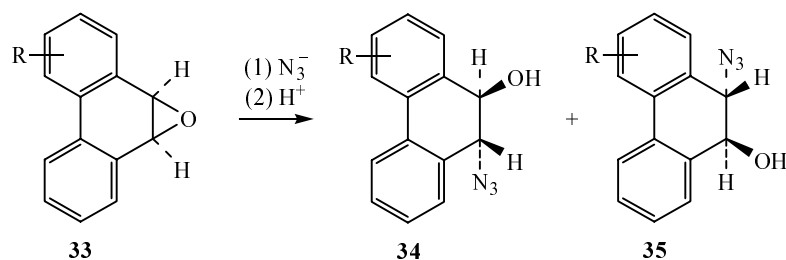
steric factors [64–67]. Shtelzer *et al.* [68] performed experimental and theoretical (by the Hückel method) studies of the reactions of unsymmetrically substituted epoxydihydrophenanthrenes **33** (R = 3-Me, 2-MeO, 3-MeO, 3-Cl) and the corresponding imino derivatives with azide ion. The authors observed a correlation between the product composition and the calculated energies of their ionic precursors [68] (Scheme 11). The regioselectivity of oxirane ring opening by the action of sodium azide and amines (benzylamine and allylamine) was examined using compound **36** which is the key intermediate product in the synthesis of a number of new antiviral agents. A relation was found between the reaction selectivity and the nature of the reagent and catalyst.

Hydroxy amine **37** was formed in high yield [11] (Scheme 12). In the reaction of **36** with benzylamine in the presence of both magnesium bromide–ether complex and ytterbium trifluoromethane-sulfonate, a considerable fraction (up to 15%) of another regioisomer was obtained. The reaction with sodium azide (NH_4Cl, $EtOH/H_2O$) afforded exclusively amino alcohol **37** analog [11].

Crotti *et al.* [60, 69–73] performed a systematic study of the mechanisms of oxirane ring opening in substituted epoxycyclohexanes by the action of various nucleophiles. The reaction of 1,2-epoxy-1-phenylcyclohexane (**38**) with sodium azide in the presence of an acid

38   **39**   **40**   **41**   **42**
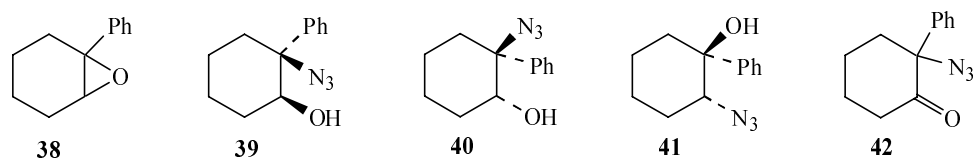
afforded amino alcohols **39** and **40** at a ratio of 21 : 79; their oxidation gave the same ketone **42**. In the absence of an acid in DMSO, isomers **40** and **41** were obtained at a ratio of 24 : 76 [60]. It is very interesting that different regioisomers (**40** and **41**) were formed via *trans*-opening of the oxirane ring in **38** in different media. In the early 1990s, the same authors revealed acceleration and regioselectivity control in the reactions of stereoisomeric 4-(benzyloxy)-1,2-epoxycyclohexanes with sodium azide and diethyl- and *tert*-butylamines in the presence of metal ions (lithium and ytterbium) [69, 70]. Interesting regioselectivity aspects were observed in the aminolysis of *cis*-4-benzyloxy-1,2-epoxycyclohexane (**43**) in the presence of ytterbium tris(trifluoromethanesul-fonate) and lithium perchlorate [70], which gave products resulting from attack on the C^2 (**45**, 97%) and C^1 atoms (**47**, 92%) of the oxirane ring (Scheme 13). Unlike lithium cation, Yb^{3+} ion is incapable of coordinating at two oxygen at-

Scheme 13.

**43**   **44**   **45**

46   **47**
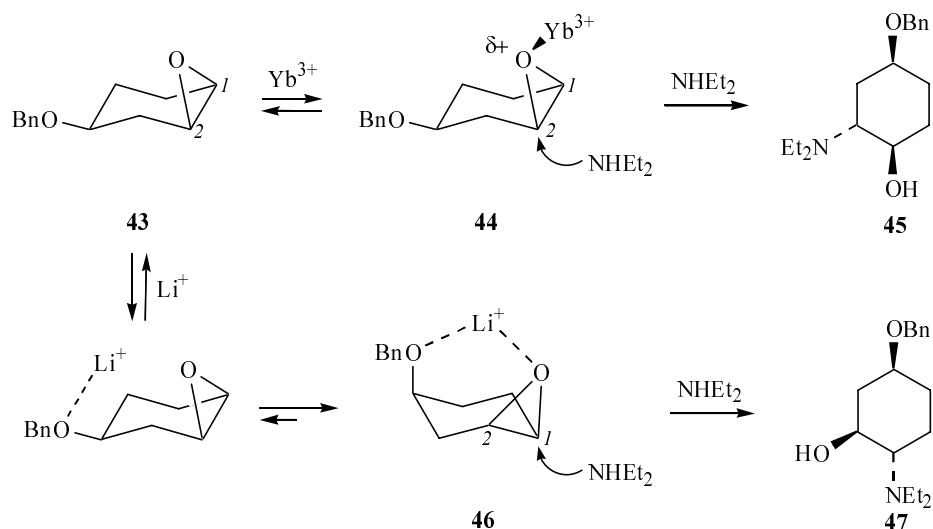
oms to give a chelate moiety; therefore, amino alcohol **45** is formed via axial attack on epoxy derivative **43** at the C^2 atom (complex **44**) according to the Fürst–Plattner rule [62]. Lithium perchlorate gives rise to conversion of the epoxycyclohexane fragment, and diaxial opening of the oxirane ring in complex **46** involves attack on the other reaction center (C^1) [70].

The *cis* isomer of 3-(benzyloxymethyl)-1,2-epoxycyclohexane (**48**) is also capable of forming complexes with lithium ion, and the reaction is characterized by controlled regioselectivity [71]. The catalyst accelerates the reaction with sodium azide, which involves intermediate chelate **49** and leads to product **50** via predominant attack by azide ion at the C^1 atom (86%). *trans*-Isomer **51** cannot give rise to an analogous complex, and a mixture of regioisomeric azido alcohols **52** and **53** is obtained (Scheme 14).
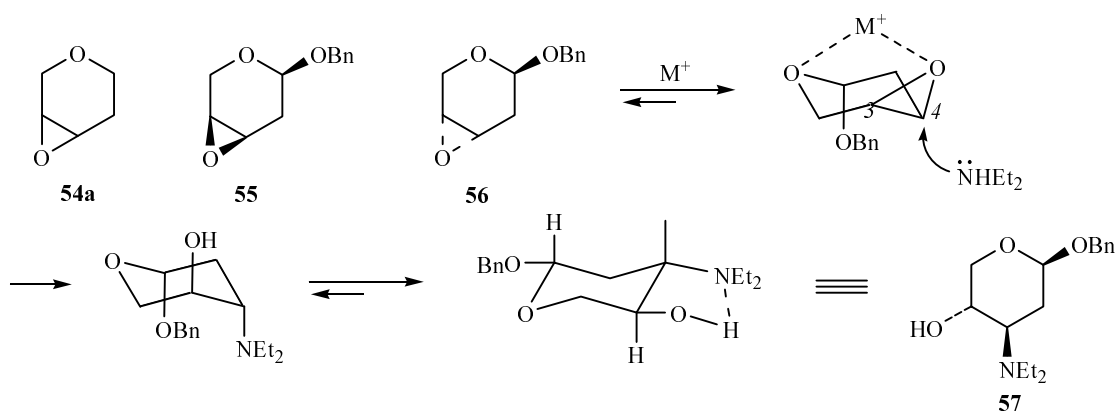
The presence of an oxygen atom in cyclic system **54a** affects the regioselectivity of the process [74], while introduction of a 2-benzoyloxy group increases the num-

**58**   **59**   **60**   **61**   **62**
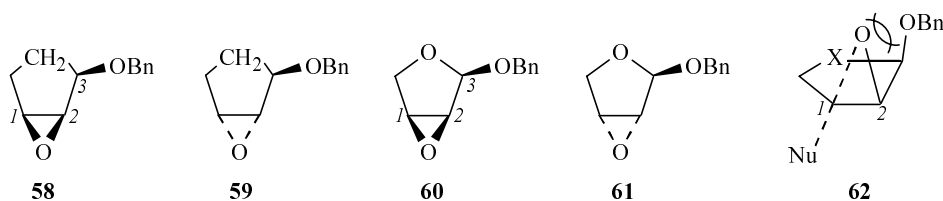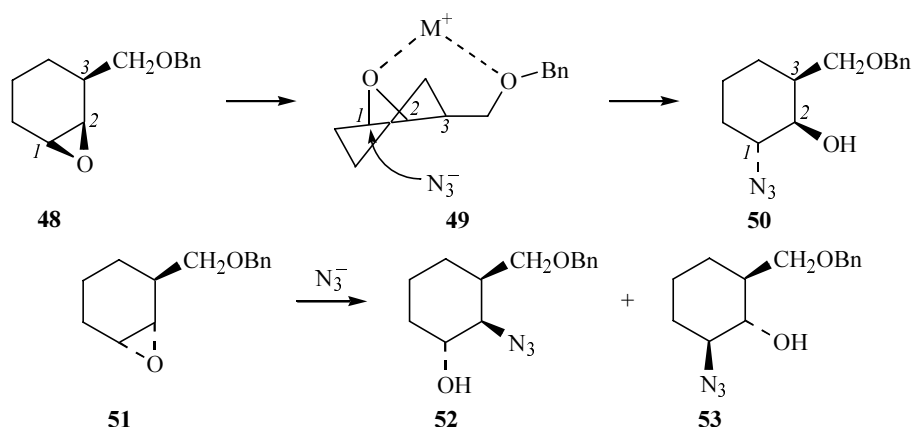
Scheme 14.

Scheme 15.

ber of possible bidentate chelation modes. As a result, intermediate chelate structures can be formed in reactions of both *cis* isomer **55** and *trans* isomer **56**, the latter being converted into amino alcohol **57** as the major product [71] (Scheme 15). Crotti *et al.* also studied aminolysis and azidolysis of *cis*- and *trans*-epoxides **58**–**61** derived from 3-benzyloxycyclopentenes and 2-benzyloxy-

2,5-dihydrofurans [72]. In these reactions, products formed by attack at C^1 were usually the only or the major ones. Intermediate chelation increased the selectivity for the attack at C^2 in the reactions with *cis*-epoxy derivatives **58** and **60**. The regioselectivity in the absence of a catalyst was interpreted in terms of both stereoelectronic (polar) and steric factors, the latter resulting from the

Scheme 16.

Attack at C^1

Attack at C^2
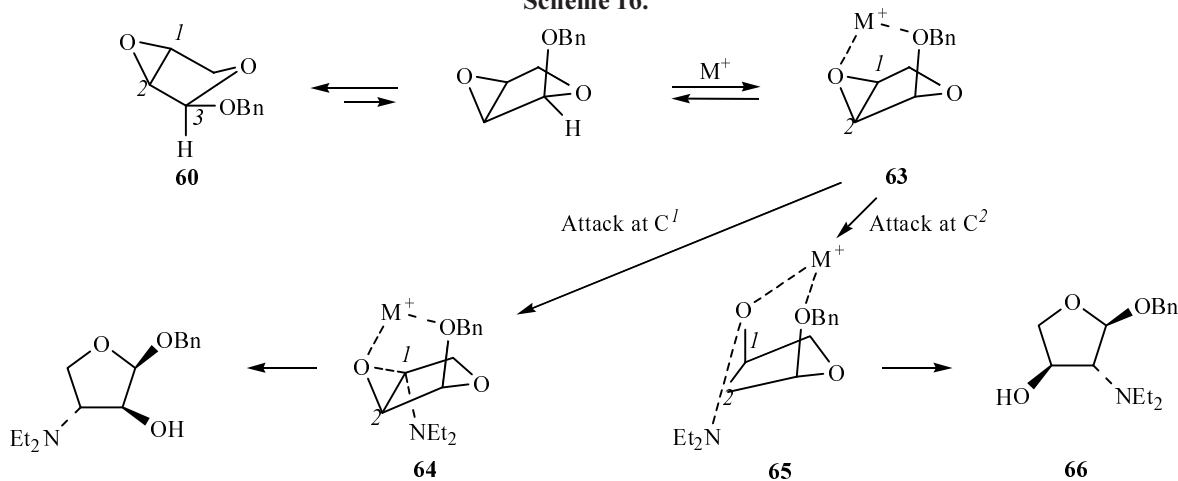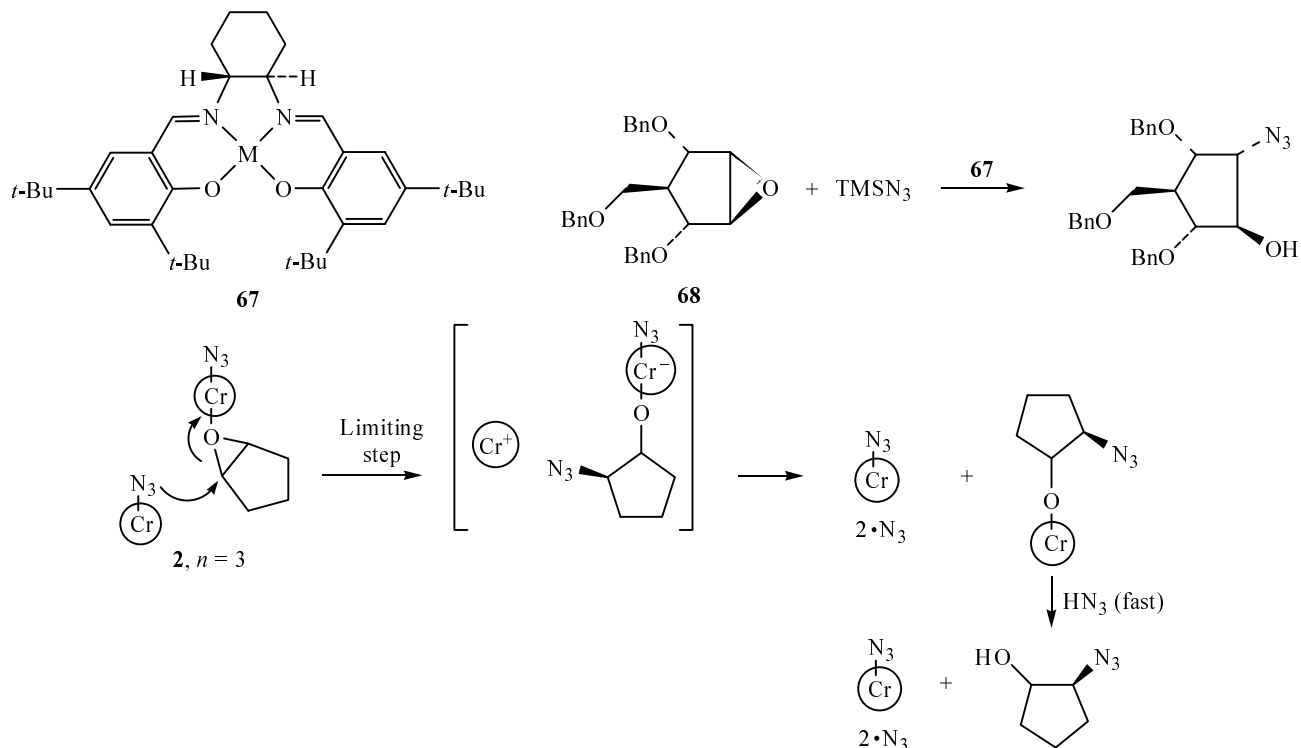
Scheme 17.

Scheme 19.

Scheme 18.

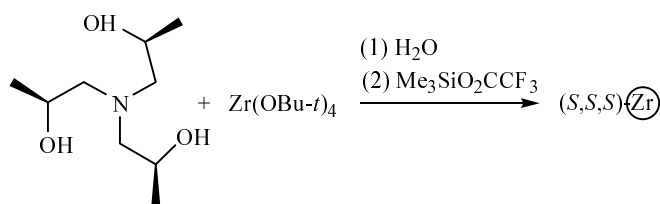presence of a benxyloxy group in the transition state (structure **62**). The observed variation in the regioselectivity of reactions with *cis*-isomers **58** and **60** under chelation conditions and formation of alternative products, e.g., **66**, was explained by the greater stability of *chair*-like six-membered complex **65** relative to five-membered complex **64** where torsion strains are possible [72] (Scheme 16).

The mechanisms of catalytic desymmetrization of *meso*-epoxy derivatives in reactions with trimethylsilyl azide (TMSN$_3$) were studied. The most effective catalysts were chromium complexes **67** (M = CrCl) [75]; Scheme 16 shows an example of stereo- and enantioselective azidolysis of substituted epoxycyclo-pen-tane **68**. The mechanism of desymmetrization of epoxycyclopentane **2** (*n* = 3) was discussed in review [75]. Desymmetrization of *meso*-epoxy derivatives was also effected with the aid of zirconium catalyst prepared

Scheme 20.

Scheme 21.

Scheme 22.

IV. QUANTUM-CHEMICAL STUDIES OF THE REACTION MECHANISMS
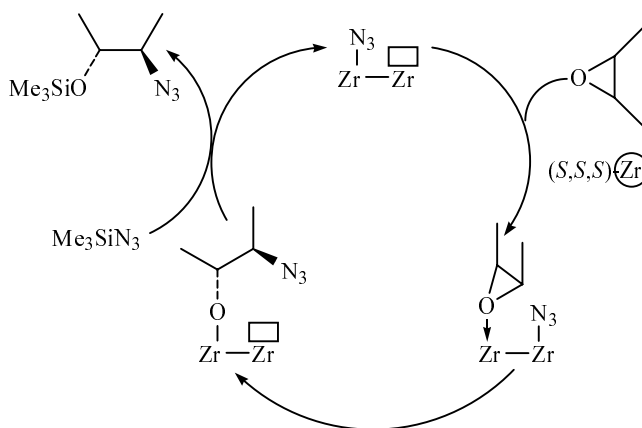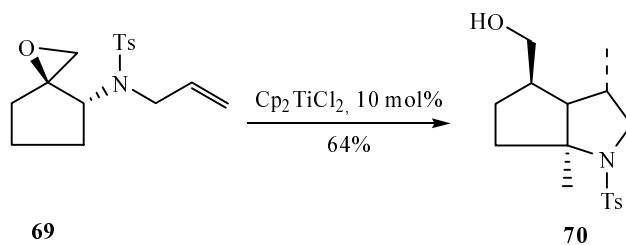
by reaction of tris(2-hydroxypropyl)amine with zirconium(IV) *tert*-butoxide [76] (Scheme 18). Catalytic desymmetrization of epoxy derivatives in the presence of zirconium complexe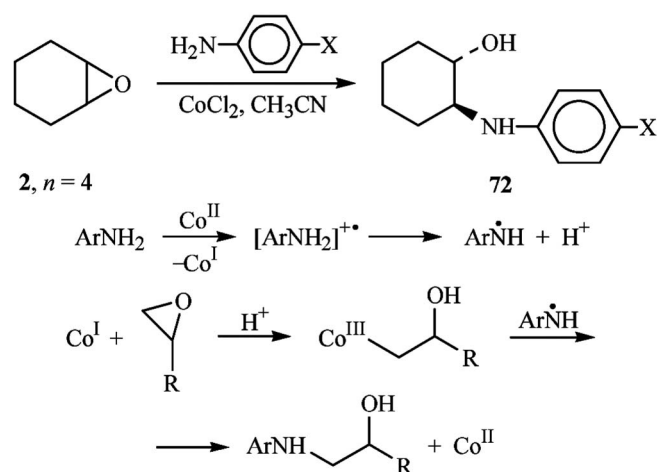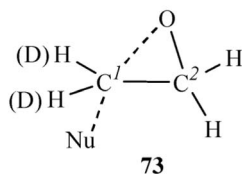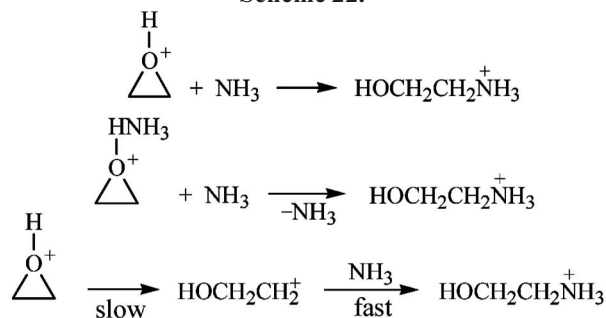s involves two metal centers: on of these activates the azide nucleophile, and the other, the epoxy substrate [76] (Scheme 19). An example of intramolecular opening of the oxirane ring in compound **69**, which follows a radical mechanism and yields substituted pyrrolidine **70** (Scheme 20) was described in [77].

A specific place in the chemistry of epoxy compounds is occupied by reactions involving intermediate formation of radical ions. These species were previously postulated as intermediates in aliphatic nucleophilic substitution [78], and in the recent years they were assumed to be formed in reactions of epoxy derivatives with alcohols [79, 80], sulfur-containing compounds [81], and amines [82]. Various epoxy compounds, e.g., **2** ($n = 4$) reacted with aniline and *p*-methoxyaniline in the presence of cobalt(II) salts to afford products **72** in high yields. The reaction mechanism shown in Scheme 21 was proposed [82] on the basis of supernucleophilic properties of cobalt(I) ion, which ensures high stereoselectivity of the process. The chemoselectivity of this reaction originates from the possibility for generation of $ArNH_2^{+\cdot}$ radical ion which is much more stable than the corresponding intermediates derived from aliphatic amines. Just this factor is responsible for the failure of benzylamine and aliphatic amines to react under similar conditions [82].

Some reactions of epoxy compounds with ammonia and amines were examined with the use of quantum-chemical calculations. These studies also included theoretical estimation of the nucleophile power, role of electrophilic activation of the oxirane oxygen atom, and effect of the solvent. Some results obtained by semiempirical methods were reviewed in [67]. Despite certain differences in the geomtric parameters of transition states, fairly similar values of E_{act} (162.4–167.9 kJ/mol) [83–87] for *trans*-opening of the oxirane ring were obtained by different methods. An alternative process involving frontal approach of the ammonia molecule is less favorable from the energy viewpoint [E_{act} = 200.7 kJ/mol (B3LYP/6-31G(d)] [84]. The high activation barriers indicate a complex mechanism of the reaction in the absence of a catalyst. The energy of activation considerably decreases under conditions of base catalysis; for example, E_{act} for the reaction of oxirane with NH_2^- ion is lower by more than 120 kJ/mol, as compared to the reaction with neutral ammonia [86].

Glad and Jensen [85] performed an important study from the viewpoint of methodology. The authors examined reactions of oxirane with seven nucleophiles (H^-, NH_2^-, OH^-, F^-, SH^-, Cl^-, NH_3) and found a correlation between the calculated secondary kinetic isotope effects (SKIE) and geometric parameters of transition states **73**. The transition state in reactions with NH_2^- and NH_3 becomes later as the nucleophilic power decreases. The values of SKIE calculated by the MP2/6-31+G(d) method are 1.011 and 0.916, respectively, which confirm S_N2 mechanism of the above reactions [87]. The variation of SKIE as a function of the C^1–O bond length (which is broken) suggests a close relation between the kinetic isotope effects and geometric parameters of the transition states. Tereshchenko and co-workers [67, 83] performed an MINDO/3 study of the reaction of ammonia with oxirane activated by proton and ammonium ion in the gas phase with account taken of nonspecific sol-


73

Scheme 23.
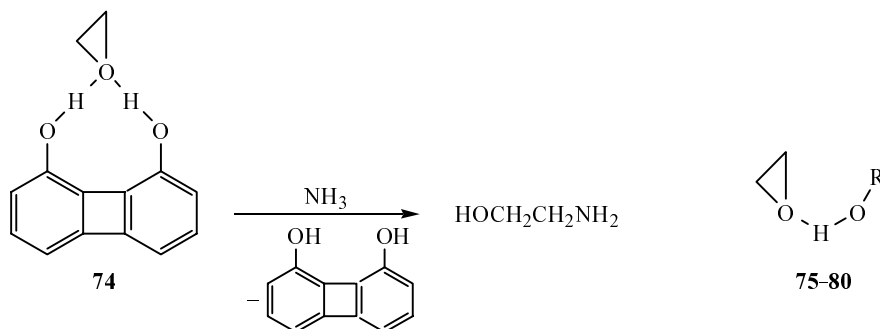
75, R = Ph; **76**, R = p-ClC$_6$H$_4$; **77**, R = p-NCC$_6$H$_4$; **78**, R = p-OCHC$_6$H$_4$; **79**, R = Me; **80**, R = H.

vation using Germer's solvaton model [67]. Ammonium ion is the most probable species that activate the epoxy substrate toward ammonia. The calculated values of E_{act} indicate predomant reaction path with participation of the nucleophile rather than S_N1 mechanism; in this case, the rear attack is characterized by considerably lower activation barrier. As might be expected, ammonium ion is a weaker activating agent than proton [88, 89] (Scheme 22).

The relation between the nature of acid catalyst and its ability to reduce the activation barrier for oxirane ring opening was studied using the reaction of oxirane (**1**) with biphenylene-1,8-diol (**74**) and some complexes **75–80**

Scheme 24.
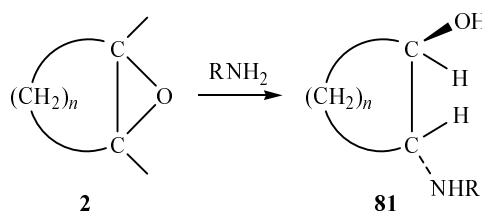
with unidentate ligands [84] (Scheme 23). For comparison, E_{act} values (kJ/mol) for the ammonolysis of **1** were calculated by different methods:

Comp. no.	**1**	**74**	**75**	**76**	**77**	**78**	**79**	**80**
B3LYP/6-31G(d)	162.6	58.7	93.1	87.0	81.4	82.9	107.9	109.5
MP2/6-311++G(d,p)//B3LYP/6-31G(d)	162.3	84.0	115.5	111.7	108.1	108.9	130.8	133.6

In the above series, water and methanol (complexes **79** and **80**) turned out to be the least efficient activators. Among phenols, those containing electron-withdrawing groups in the *para*-position of the benzene ring were the most effective. According to the calculations, biphenylene-1,8-diol catalyzes the reaction much more efficiently than it might be expected on the basis of the Brønsted correlations [90, 91]. Omoto and Fujimoto [84] analyzed complex **74** in terms of the Coupled Fragment Molecular Orbital Method [92–95] and showed that the high activity of biphenylene-1,8-diol originates from more effective interaction between orbitals localized on the O–H bonds and those corresponding to lone electron pairs on the oxirane oxygen atom. A detailed analysis of the electron density distribution in complexes **74–80** and the respective transition states revealed two effects arising from addition of an acid catalyst. First, electrophilicity of the oxirane carbon atoms increases due to displacement of electron density from oxirane to the acid; second, the acid stabilizes transition state via electron density transfer from the nucleophile to oxirane and then to the acid molecule.

V. REACTIONS OF AMINES WITH EPOXYCYCLOALKANES AND DIEPOXY DERIVATIVES

The stereochemistry of reactions of amines with epoxycycloalkanes is determined by specific features of the S_N2 mechanism which includes rear attack by nucleophilic reagent [45] and *trans*-diaxial opening of the oxirane ring according to the Fürst–Plattner rule [62]. As a result, epoxycycloalkanes **2** are converted into amino alcohols **81** ($n = 3$–6; R = H, Me, Et, Pr, Bu, Bzl; Scheme 24) [96, 97]. The formation of primary adducts may be accompanied by their subsequent reaction with the epoxy substrate [97].

According to the results of kinetic studies, in the reaction of epoxycyclohexane (**2**, $n = 4$) with concentrated aqueous ammonia under severe conditions *trans,trans* and *cis,trans* isomers of 2,2'-dihydroxydicyclohexylamine are also formed. Nevertheless, such compounds were not detected among products of the reactions of the same substrate (**2**, $n = 4$) and substituted epoxycyclohexanes **82–84** with stereoisomeric cage-like amines **85** and **86**,
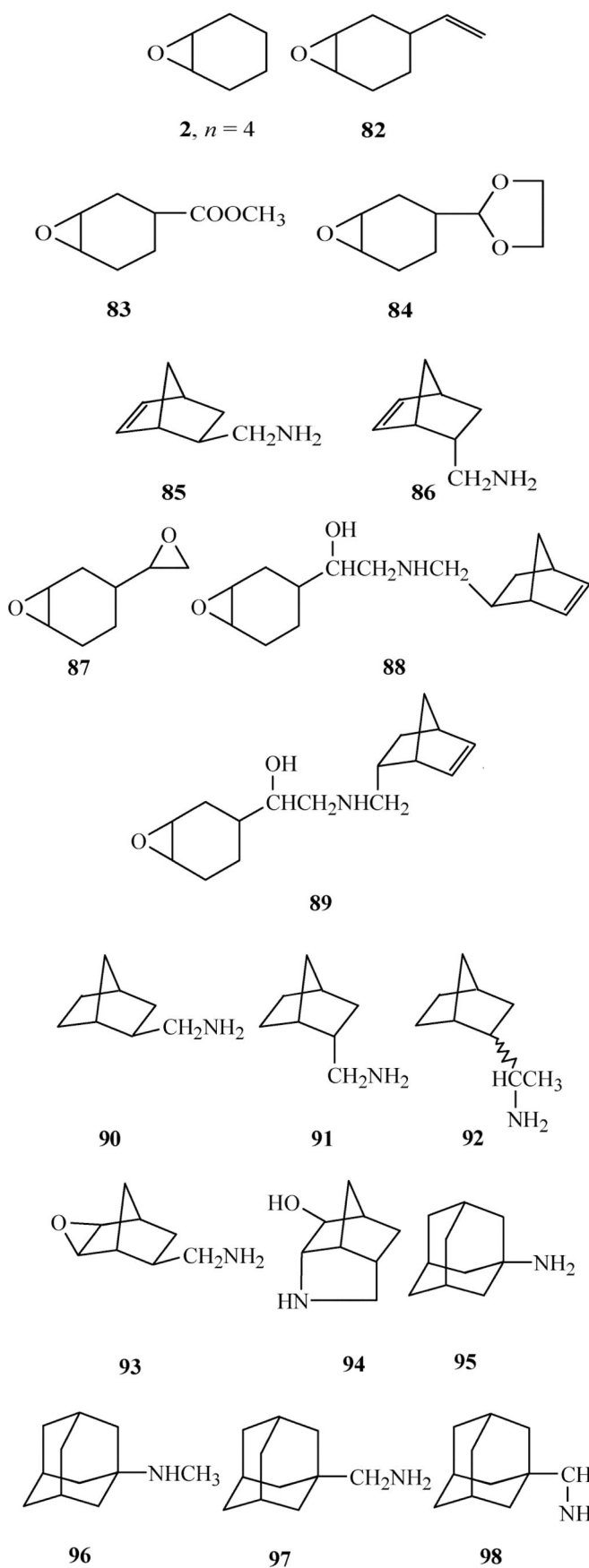
which were carried out under mild conditions (*i*-PrOH, 20°C) with equimolar amounts of the reactants [55]. The reactions of epoxycyclohexanes **82** and **84** with alkyl- and arylamines under analogous conditions were reported in [98, 99]. It should be noted that the ester moiety in compound **83** remains unaffected, in contrast to the electron density distribution in the substrate molecule calculated by semiempirical quantum-chemical methods [55].

Diepoxy derivative **87** stands out against the above series. Its reactions with amines **85** and **86** occur in a chemo- and regioselective fashion at the monocyclic oxirane fragment to afford amino alcohols **88** and **89** [55]. Reactions of a large number of cage-like amines, including amines **85** and **86**, their saturated analogs **90** and **91**, the known antiviral agent Deitiforin (**92**), epoxy derivative of **85** (compound **93**) and its tricyclic isomer **94**, and also amines **95**–**98** of the adamantane series, with *p*-nitrophenyloxirane (**99**) and *N*-(2,3-epoxy-propyl)carbazole (**100**) were described in [100–105]. Using spectral methods, it was shown that these reactions involve equimolar amounts of the reactants and that they strictly follow the Krasusky rule presumably due to considerable size and rigid structure of the amine molecules. The resulting amino alcohols, including compounds **101** and **102,** undergo acylation in the presence of bases at the nitrogen atom, while silylation of these compounds occurs chemoselectively at the hydroxy group [105]. The possibility for selective N-acylation of amino alcohols was demonstrated previously, e.g., in the acylation of (1*R*,2*S*)-norephedrine with *p*-toluenesulfonyl chloride [106]. The chemoselectivity in the acylation of amino alcohol **102** was confirmed by the synthesis of bis-acyl derivative **103** in two different ways [105] (Scheme 25). Acylated amino alcohols **105** having cage-like fragments were synthesized by reactions of **104** (R = H, Ph, CH$_2$Ph) with endic anhydride [107] (Scheme 26).

Scheme 25.

102

103

Scheme 26.


104   **105**
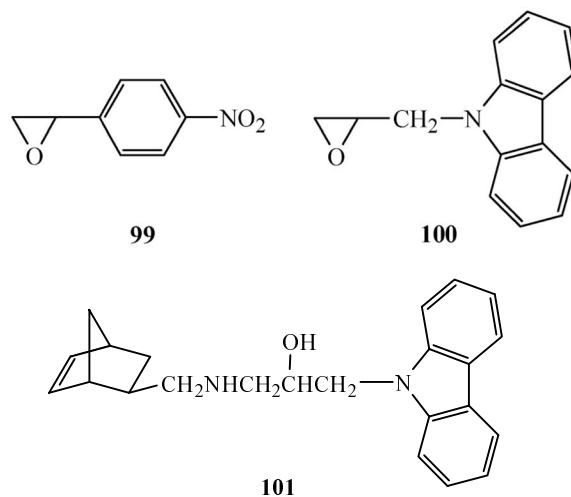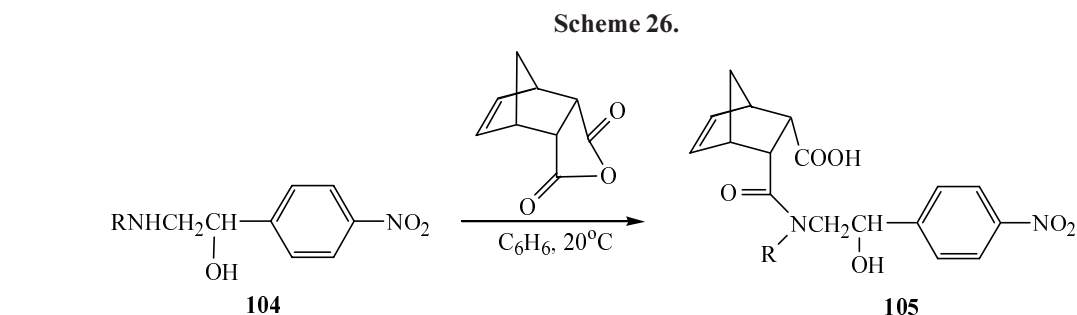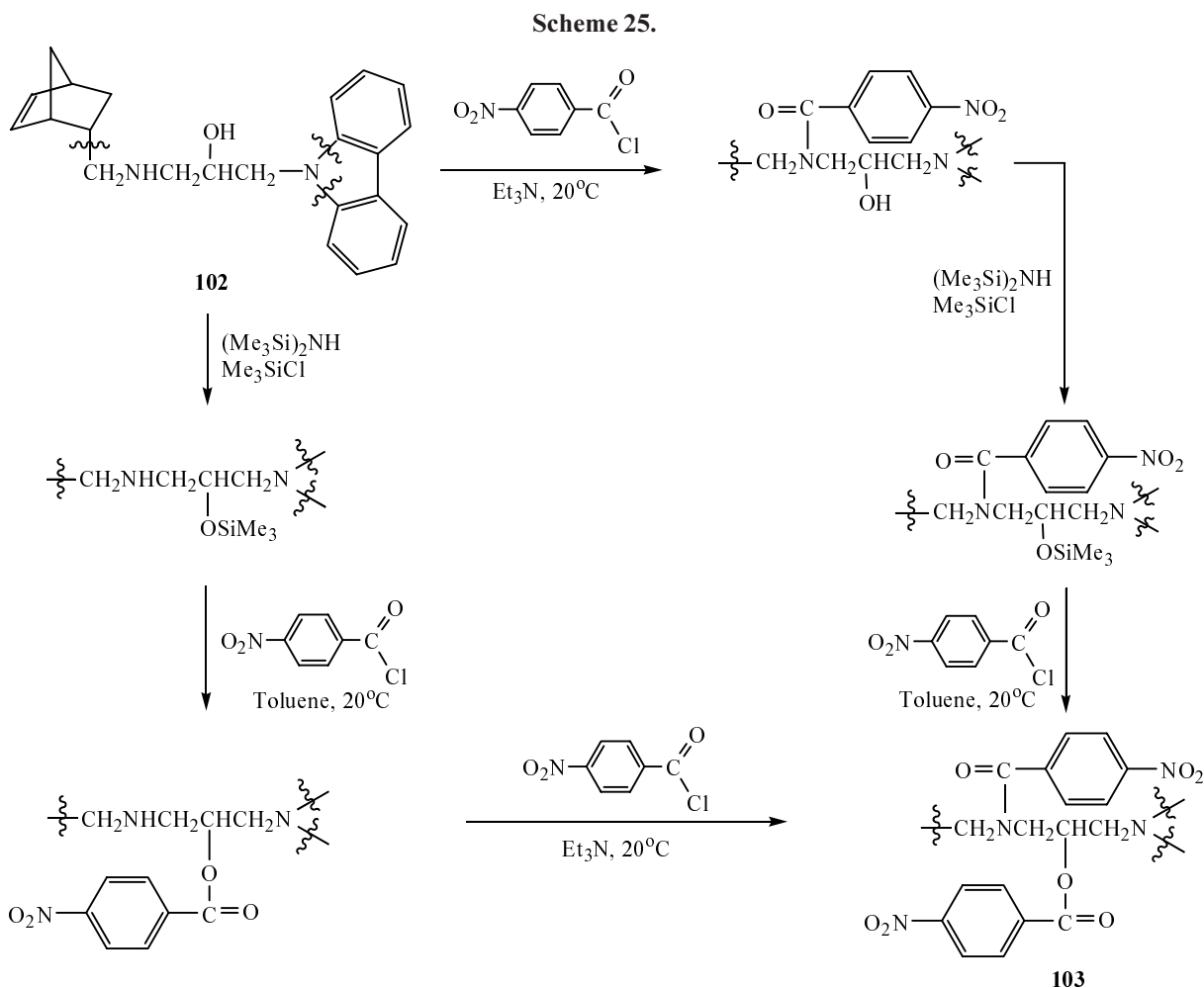
The S_N2 mechanism, which is typical of reactions of amines with epoxy derivatives, is determined mainly by steric factor. Therefore, diepoxy derivative **106** reacts with amines primarily at exocyclic epoxy group. In reactions with bulky amines, such as isopropyl and diethylamine, the isomer of **106** with *cis* arrangement of the epoxy and epoxyethyl groups reacts under more severe conditions [61] (Scheme 27). Chemoselective cleavage of the endocyclic epoxy fragment was observed in reactions of diepoxy derivatives of *p*-menthadiene (*cis*-**106** and *trans*-**106**) with sodium azide. The reactions with both isomers were characterized by strict regio- and

stereoselectivity (Scheme 28); analogous products were obtained from stereoisomeric monoepoxy derivatives of *p*-menthadiene [61]. In all cases, the reaction direction is controlled by the conformational factor. The anomalous behavior of azide ion was explained [62] by its high polarizability which favors delocalization of the negative charge and nucleophilic attack at the most substituted carbon atom. Craig *et al*. [108] studied reactions of diepoxy derivatives of 1,4-cyclohexadiene with nucleophiles, in particular with amines, and found that the *cis* isomer undergoes nucleophilic attack at the 1,4-positions and that the *trans* isomer reacts at the 1,3-positions. It
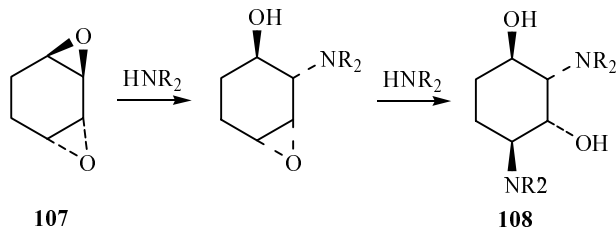
Scheme 27.

**106**

Scheme 28.

cis-**106**
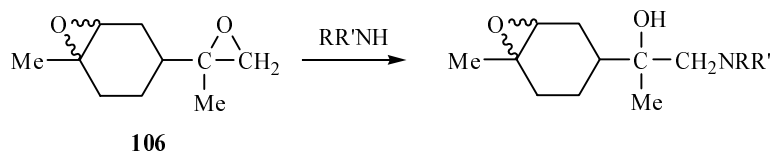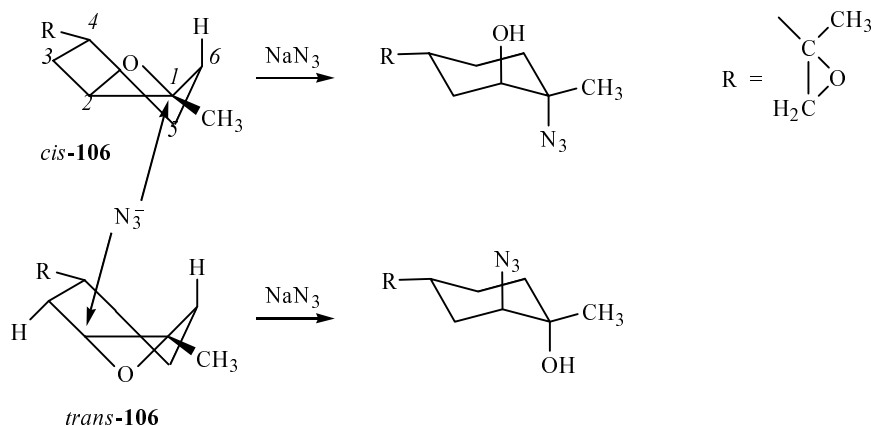
trans-**106**

was presumed that the reaction involves intermediate formation of *trans*-disubstituted epoxycyclohexanes, preferentially with diequatorial arrangement of the substituents. The reaction of *trans*-1,2:3,4-diepoxycyclohexane (**107**) with secondary amines follows Scheme 29 [109]. According to the data of low-temperature ^{1}H NMR spectroscopy, product **108** is a mixture of conformers **A** and **B** (Scheme 30) whose ratio depends on the substituents in the amino group. Analogous stereochemistry is typical of the reaction of compound **107** with sodium azide [110]. *trans*-1,2:3,4-Diepoxycyclopentane (**109**) reacts with
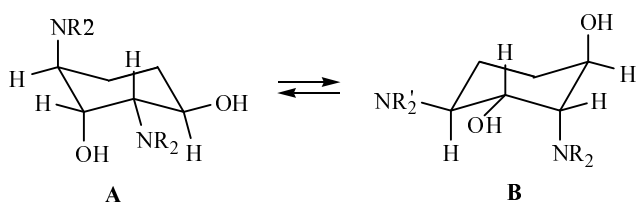
amines in a more complicated fashion. The reaction at both epoxy groups yields diamino diol **111** as the only isomer, while adducts at one epoxy group (compounds **110** and **112**) have different structures [111]. The formation of regioisomeric amino alcohols **110** and **112** was explained by migration of the epoxy group which could accompany formation of the oxide moiety (Scheme 31). The predominant formation of one or another regioisomeric monoadduct is determined by the size of the amine molecule and reaction conditions [111].

The reactions of 3,4-epoxycyclohexene (**113a**, $n = 2$) [112] and 3,4-epoxycyclopentene (**113b**, $n = 1$) [113] with primary and secondary amines are regio- and stereoselective (Scheme 32). The structure of product **114a** was proved by chemical methods, and the structure of **114b** was confirmed by ^{1}H NMR spectroscopy. In both cases, the attack by nucleophile is directed at C^3 $R^1 = R^2 = Me$, Et, Bu, etc..

The reaction with sodium azide is important for the synthesis of 1,3-diimino[14]annulene (**115**) [114] (Scheme 33). The high selectivity of the process made it possible to accomplish stereocontrolled syntheses of 4-deoxyfortamine (**117**) and fortamine (**118**) (Scheme 34) which are precursors of biologically active compounds [115]. The isomerization of epoxy derivative **116** into allyl-like alcohol was completed by the synthesis of fortamine (**118**). Regioselective azidolysis was observed in the reaction with compound **119** [116] (Scheme 35). When the double

Scheme 29.

107   **108**

Scheme 30.

A   **B**

Scheme 31.

109   **110**   **111**   **112**
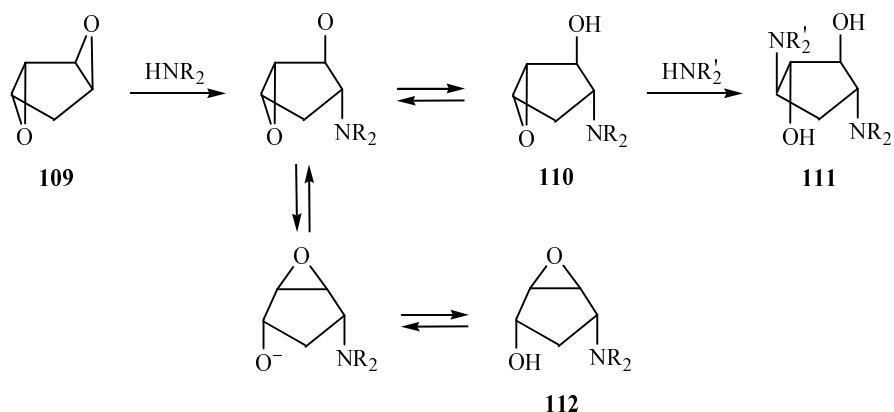
bond is exocyclic, the reaction is less selective [117]: the ratio of regioisomeric products **120** and **121** ranges from 4 : 1 to 1 : 1, depending on the amine structure. 3,4-Epoxycyclohexene (**113a**) reacts with sodium azide in a similar way. In the presence of palladium(0) complexes, 3-cyclohexenone is formed together with 2-azido-3-cyclohexenol, though monoepoxy derivatives of acyclic dienes, e.g., 1-cyclohexyl-2-vinyloxirane, react with sodium azide following regioselective 1,4-addition pattern

Scheme 32.

113a, b   **114a, b**

Scheme 33.

115

Scheme 34.

116

117

116 →

118

Scheme 35.

119

120   **121**
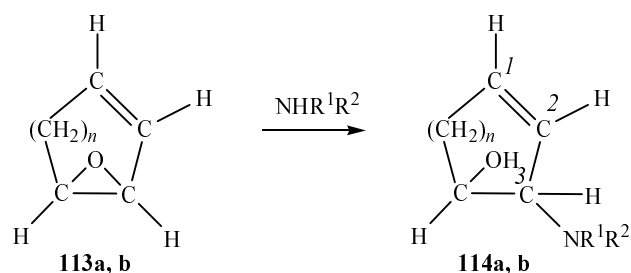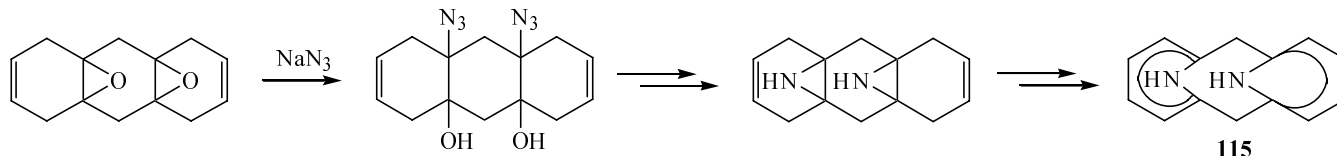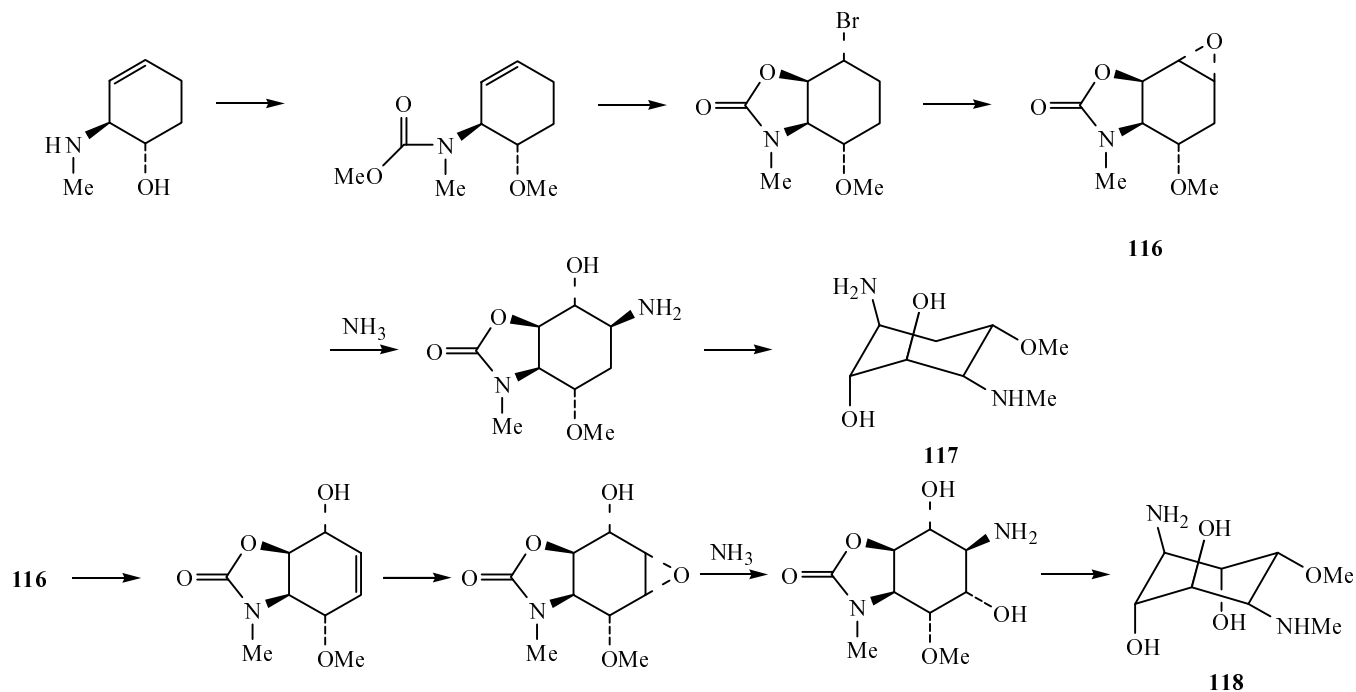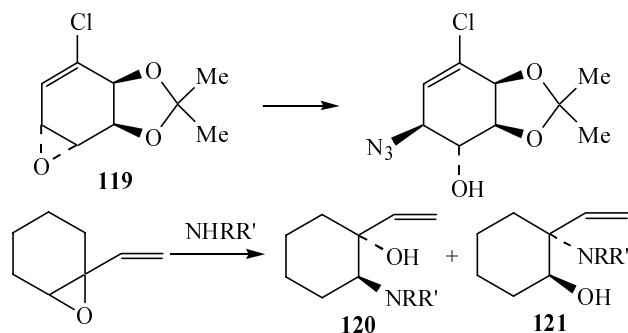
(Scheme 36). As a result, 4-azido-1-cyclohexyl-2-buten-1-ol (**122**) is formed in high yield [118]. A probable intermediate is dipolar π-allylpalladium complex **123**. Protonation of this complex with water precedes its reaction with sodium azide, which is accompanied by regeneration

of the catalyst. The reaction of polycyclic epoxy derivative **124** with sodium azide may be regarded as the first stage of the aromatization process involving intermediate aziridine **125** [119] (Scheme 37).

The mode of transformation of the epoxy fragment in reactions with sodium azide strongly depends on the ring size and nature of substituents in the cyclic fragment [120]. The high regio- and stereoselectivity of the reaction of epoxy alcohol **126** with sodium azide is favored by anchimeric effect of the axial hydroxy group. The transition state (structure **128**) is additinoally stabilized by formation of hydrogen bond with the oxirane oxygen atom [121]. The different regioselectivity in the reaction with epoxy ketone **127** results from the presence of electron-withdrawing carbonyl group which increases the positive charge on the C^3 atom (Scheme 38).

Scheme 36.

122   **123**

Scheme 37.

124

125

Scheme 38.

126   **127**   **128**

Scheme 39.

129   **130**

129 → **131** → **132**

Scheme 40.

133
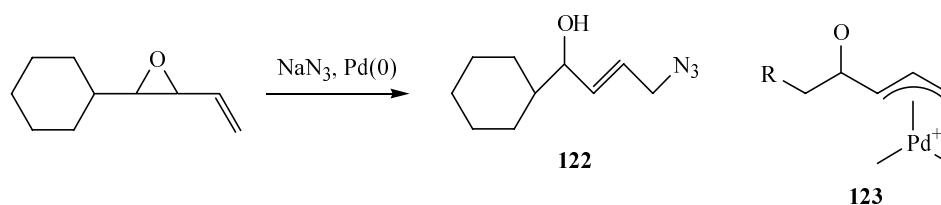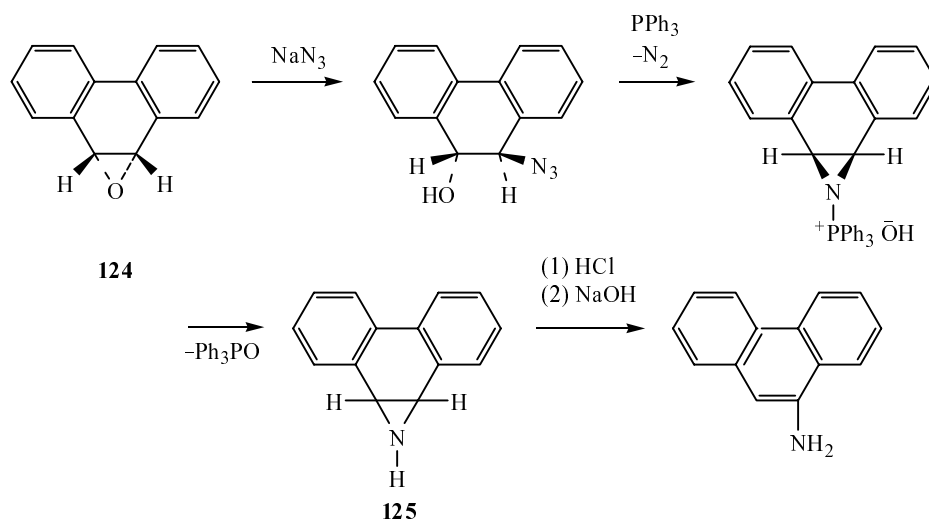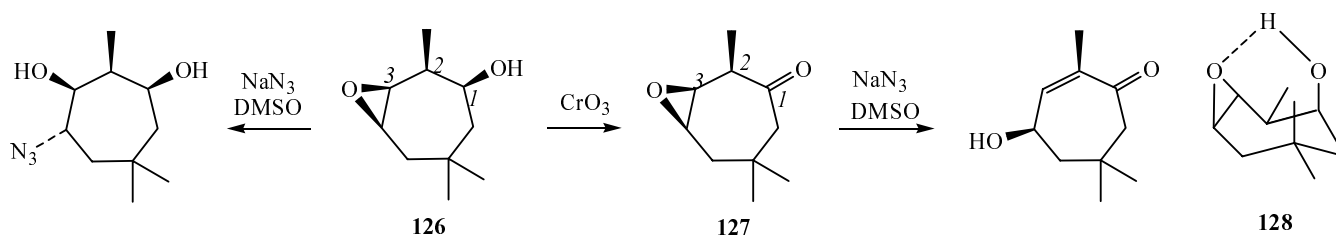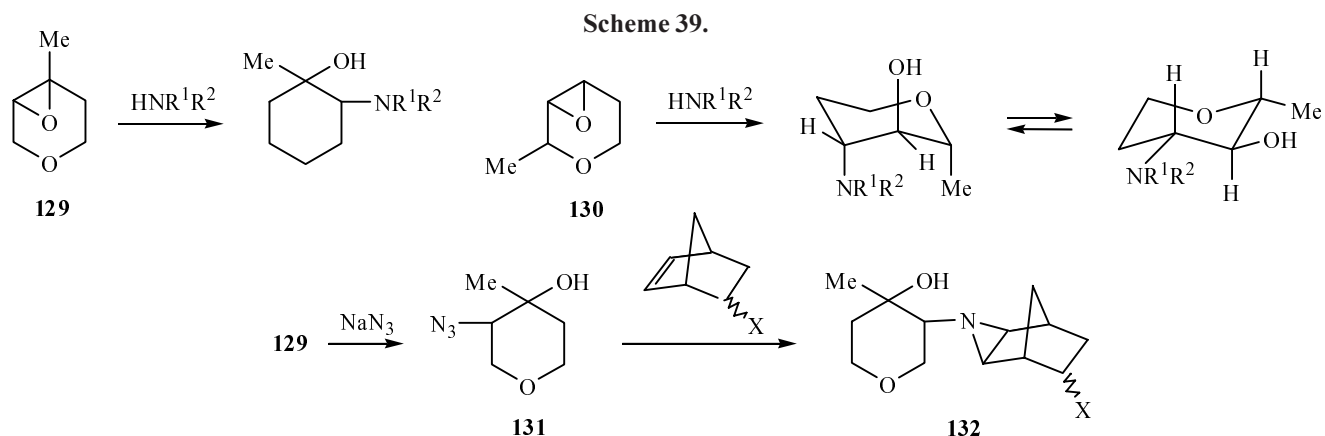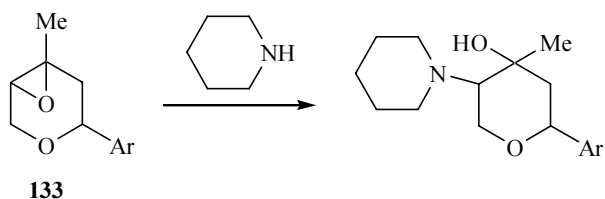
VI. AMINOLYSIS AND AZIDOLYSIS OF EPOXY DERIVATIVES WITH HETEROCYCLIC FRAGMENTS. ANOMALOUS REACTIONS

Studies on the aminolysis and azidolysis of epoxy derivatives having various heterocyclic fragments have been reported [54, 116, 122, 123]. Ibatullin *et al.* [122] exam-

ined the aminolysis of isomeric 3,4-epoxy-2- and -4-methyl-tetrahydropyrans **129** and **130** (Scheme 39). The reactions were regioselective: in each case only one of the possible isomers was obtained. In the reaction of **129** with piperazine, bisadducts were also formed together with common monoadducts. All reactions followed the Fürst–Plattner rule [122]. Compound **129** reacted with sodium azide to give hydroxy azide **131** whose reactions with substituted norbornenes led to formation of aziridine derivatives **132** [124]. A number of aminolysis products were obtained from 2-aryl-4,5-epoxy-4-methyltetrahydropyrans **133** (Ar = Ph, m-BrC$_6$H$_4$, o-HOC$_6$H$_4$, p-MeOC$_6$H$_4$) [125] (Scheme 40). Later on, the same authors studied reactions of compound **133** with a large series of amino acids [126], which occurred at both the

Scheme 41.

134   **135**

Scheme 42.

136   **138**

137   **139**

Scheme 43.

140   **141**   **142**

Scheme 44.

143
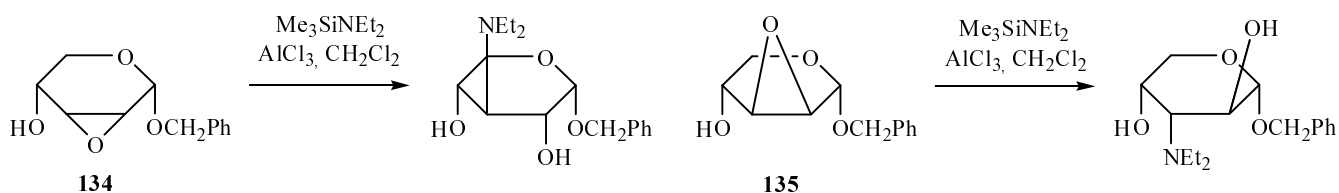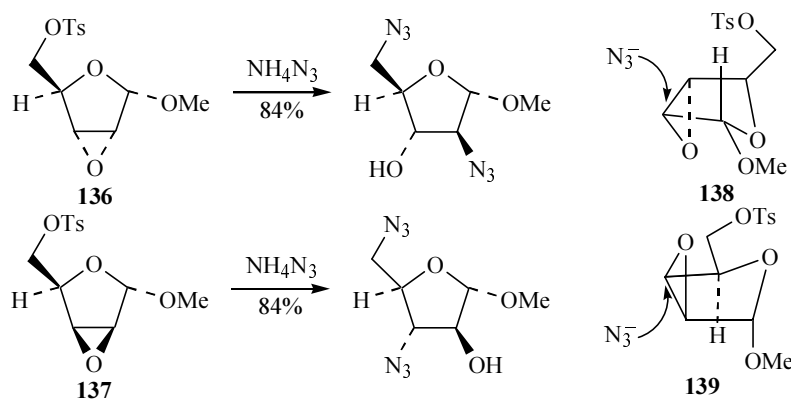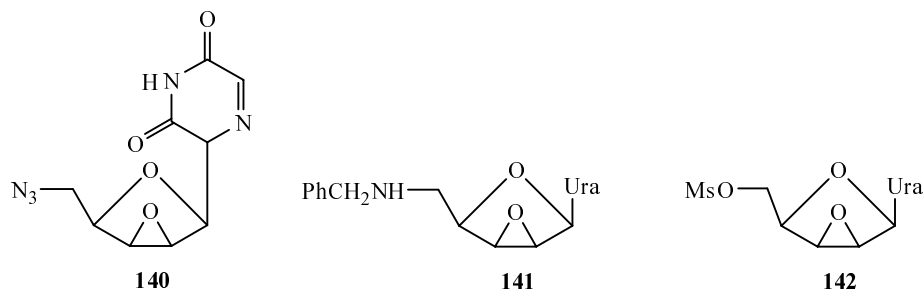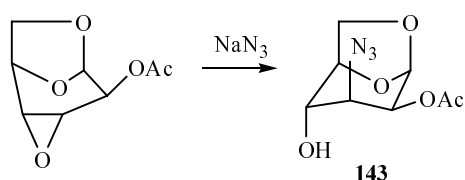
amino and the carboxy group of the reagent. In the first case, aqueous solutions of amino acid salts were used (80°C). The reactions at the carboxy group were effected in chloroform in the presence of *p*-toluenesulfonic acid [126]. The aminolysis of other epoxypyran [127], as well as of epoxybenzopyran systems [16], have been reported. Kazmi *et al*. [128] described a one-step synthesis of *N,N*-dialkylaminosugars by reactions of stereoisomeric epoxytetrahydropyrans **134** and **135** with amines (Scheme 41). A considerable role of steric factor was observed in the reaction of stereoisomeric functionally substituted 1,4-dioxabicyclo[3.1.0]hexanes **136** and **137** with ammonium azide (Scheme 42); this follows from analysis of the structures of transition states **138** and **139**, respectively [65, 123]. The observed inversion of the regioselectivity is determined by conformations of stereoisomers **136** and **137** with account taken of steric hin-

drances created by the substituents (CH$_2$OTs and OMe, respectively [65, 123].

Katalenic and Skaric [129] described the aminolysis and azidolysis of racemic and enantiomerically pure 3,6-dioxabicyclo[3.1.0]hexanes **140–142** having uracil fragments (Scheme 43). Synthetic routes to 3-azido-3-deoxy-D-mannose and its acetyl derivatives **143** were studied in [130] (Scheme 44). Azido alcohol **145** (which is the major product of the reaction of compound **144** with sodium azide) was converted into nitrosourea **146** (Scheme 45); the latter was found to exhibit anticarcinogenic activity with a high therapic index [18]. Epoxy derivatives with nitrogen- [131–133], phosphorus- (**147**) [134], and sulfur-containing heterocyclic fragments (**148**) [135] were subjected to aminolysis and azidolysis (Scheme 46). Robinson *et al*. [133] reported on reactions of substituted epoxy

Scheme 45.

144   **145**   **146**

Scheme 46.

148   **149**

Scheme 47.

150a   +   150b

Scheme 48.

151

(a) 10 kBar, 65°C, 3 days
(b) SiO$_2$, 10 days

prolines with sodium azide. Mono- and diepoxy-cyclo-hexanes reacted with pyrazole derivatives to afford, among other products, racemic 2-(1-pyrazolyl)cyclo-hexanols **149** and **150** (Scheme 47). Enantiomerically

pure compounds **149** and **150** were synthesized by acy-lation in the presence of lipase B from *Candida antarctica* [52]. Imidazoles **151** and pyrazoles reacted with epoxy derivatives at the nitrogen atom both over silica gel and under elevated pressure [136] (Scheme 48).

In 1996, Kotsuki *et al.* [136, 137] discovered an un-usual reaction of epoxy derivatives with indole (**152**), which occurred under elevated pressure in the presence of ytterbium(III) trifluoromethanesulfonate (Scheme 49). This reaction was successfully used in the enantioselective synthesis of (+)-diolmycin A2. Likewise, epoxy deriva-tives reacted with pyrrole and indole over silica gel; how-ever, these reactions were less selective. A carbon–car-

Scheme 49.

152

Scheme 50.

152   153

Scheme 51.

154a   155   156
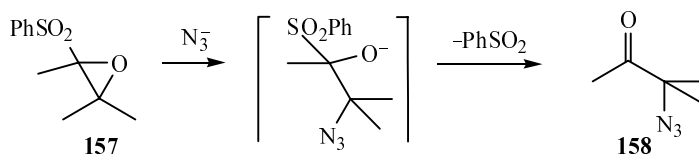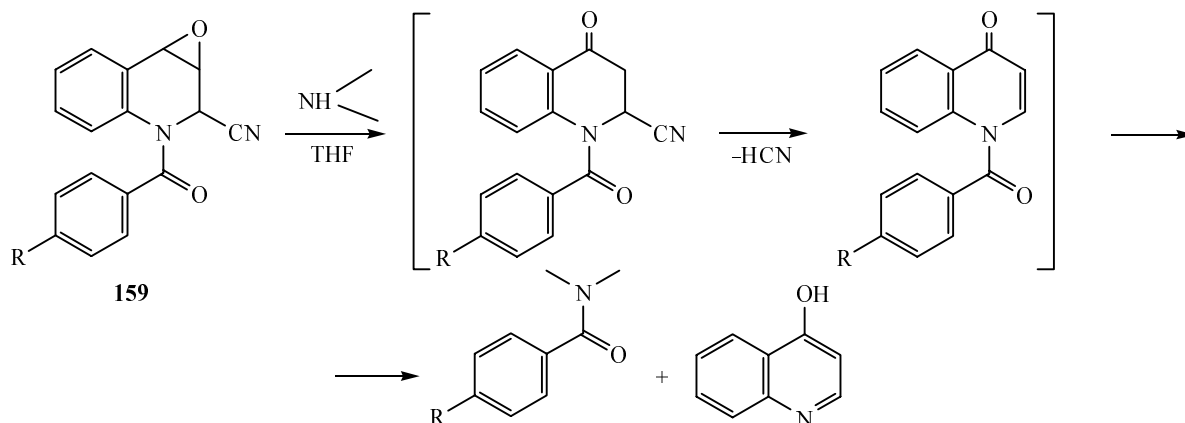
Scheme 52.

Scheme 53.

bon rather than carbon–nitrogen bond was formed in adduct **153** when the reaction of indole with epoxy derivatives was carried out at room temperature [136] (Scheme 50). Cyclic epoxy ketones **154a** and **154b** reacted with 2-propynylamine in a quite unusual fashion. Pyrolysis of the adducts, specifically of **155**, gives rise to an important group of fused pyrroles **156** (Scheme 51) [138].

In some cases, anomalous reaction course in the aminolysis of oxiranes is explained by conjugation in their molecules. Paladium-catalyzed azidolysis of 3,4-epoxy-cyclohexene is followed by isomerization to 3-cyclo-hexenone, whereas its eight-membered analog failed to react under the same conditions [118]. Carbonyl compound **158** was prepared from epoxy sulfone **157** [139] (Scheme 52). The isomerization of epoxy derivative into ketone also occurred as intermediate stage in the anomalous aminolysis of epoxytetrahydroquinoline **159** [140] (Scheme 53).
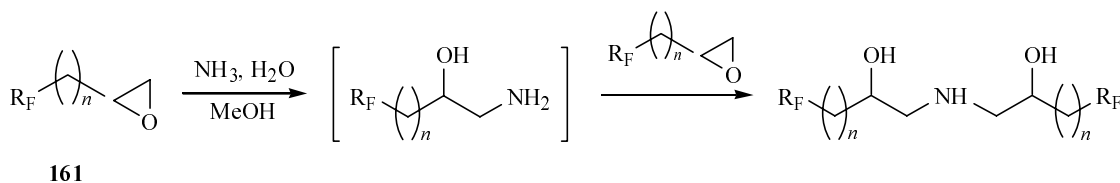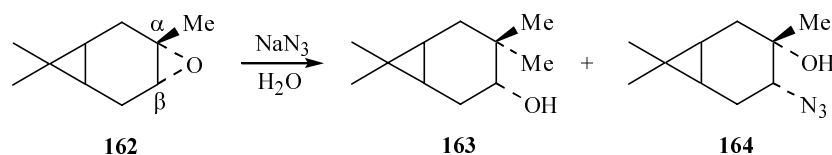
Scheme 54.
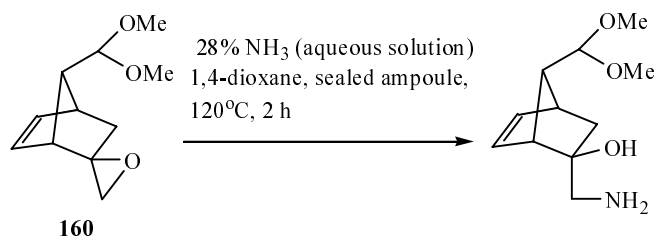
VII. REACTION CONDITIONS. ACHIRAL AND CHIRAL CATALYSTS

Reactions of epoxy derivatives with amines are usually carried out in alcoholic solutions (in methanol or isopropyl alcohol). However, even more reactive spiro-oxiranes, e.g., compounds **160** having a terminal epoxy moiety, require severe conditions for the aminolysis to
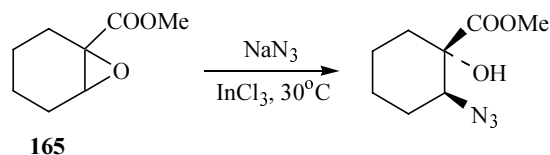
Scheme 55.

Scheme 56.

**162**   **163**   **164**

Scheme 57.

165

occur [141] (Scheme 54). The process may be accelerated using special solvents or catalysts. Das *et al*. [142] recently proposed fluorinated alcohols as solvents which possess an enhanced ability to form hydrogen bonds thus activating the oxirane fragment for nucleophilic attack [142]. These solvents ensure ready reactions of

Scheme 58.

2, *n* = 4

$(i\text{-PrO})_2\text{AlOCOCF}_3$
CH_3CN

Scheme 59.

2, *n* = 4

NRR' = NEt$_2$, NHPh, NHCH$_2$Ph,

epoxycyclohexane with aromatic amines on heating for 2.5–4.0 h under reflux; the yields of the corresponding amino alcohols attain 84–90%. A classical procedure, according to which an epoxy derivative is heated with excess amine, is hardly suitable for reactions with expensive weakly nucleophilic and sterically hindered amines, though it was successfully applied to reactions with sulfamic acid salts [143]. Charrada *et al*. [144] found that fluoroalkyloxiranes **161** react with aqueous ammonia under mild conditions to give exclusively difluoroalkyl-containing amino diols (Scheme 55).

In 1999, Frinquelli *et al*. [145] proposed a convenient procedure for the azidolysis of alicyclic epoxy derivatives with sodium azide in aqueous solution. The fraction of diol as by-product increases to 30% at low pH values; by contrast, at pH 4.2–9.5 and especially in the presence of salts as catalysts, the yield of the target azido alcohol becomes almost quantitative. The regioselectivity in reactions with unsymmetrical epoxy derivatives also depends on the acidity of the medium. In fact, the ratio of products **163** and **164** resulting from α- and β-attack on compound **162** is 35 : 65 and 84 : 14, respectively, at pH 9.5 and 4.2 [145] (Scheme 56). The azidolyss of α,β-epoxycarboxylic acids and their esters **165** in water is also characterized by high regio- and stereoselectivity, and the corresponding α-azido-β-hydroxycarboxylic acids (esters) are obtained in high yields [146, 147] (Scheme 57). These reactions in aqueous solution occur more readily than in organic solvents (MeCN, CH$_2$Cl$_2$, THF, Et$_2$O). Lithium azide was also used for the introduction of an azido group [148].
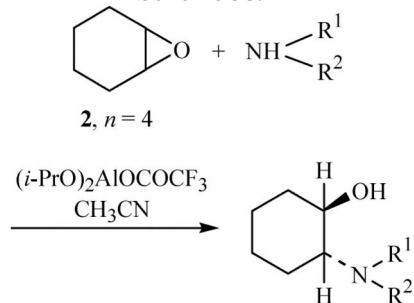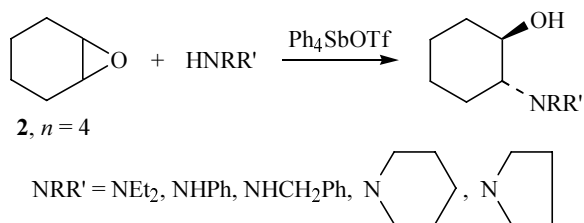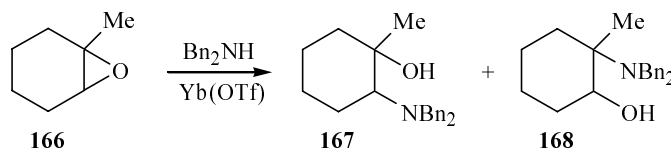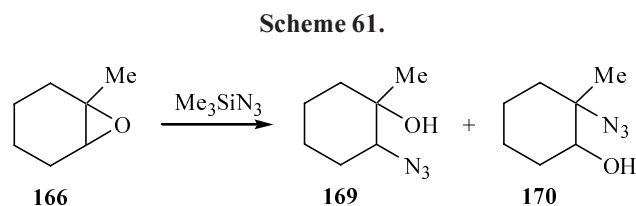
Some reactions of alicyclic epoxy derivatives with amines and azides successfully occur in the presence of

Scheme 60.

166   **167**   **168**

Scheme 61.

166   **169**   **170**

catalysts, such as aluminum oxide [149, 150], montmoril-lonite [151], and cyclodextrins in aqueous solution. These catalysts ensured mild reaction conditions and high yields of β-amino alcohols. Like most other methods, this procedure is characterized by *trans*-stereoselectivity in the oxirane ring opening in the epoxycyclohexane and epoxycyclopentane series [152]. Catalytic transformations of epoxy groups grafted to solid polymeric support were also reported [153]. Some reactions were carried out over zeolites [154, 155] and silica gel [14]. Epoxy derivatives were activated with the use of aluminum and titanium compounds [156, 157].

Extensive studies were performed on the effect of Lewis acids, namely boron trifluoride–ether complex [155], magnesium bromide [11], cobalt(II) salts [158], aluminum chloride [159], and copper nitrate [160], on the oxirane ring opening. The latter two catalysts showed excelent results in reactions of 2,3-epoxycarboxylic acids with sodium azide [159, 160]. The use of cerium(IV) derivatives [21, 161], indium chloride [162], and thallium pentachloride [163] as catalysts was reported. The presence of 10 mol % of thallium pentachloride ensured ready reaction of epoxycycloalkanes with aromatic amines in methylene chloride at room temperature [163]. Indium chloride, aluminum halides, and tin chloride turned out to be the most efficient catalysts for the above discussed reactions of epoxycyclohexanes with sodium azide in aqueous medium [145–147]. Emziane *et al*. [164, 165] described highly regioselective opening of the oxirane ring with trimethylsilyl azide in the presence of aluminum tris(isopropoxide). Diisopropoxyaluminum trifluoroacetate was proposed as catalyst for aminolysis of epoxycyclohexane **2** [166] (Scheme 58). The catalytic activity of copper and tin trifluoromethanesulfonates [167], as well as of tetraphenylstibonium trifluoromethanesulfonate [168] (Scheme 59), was studied. The latter catalyst makes it possible to carry out aminolysis in a homogeneous medium which facilitates monitoring of the reaction progress. Tetraphenylstibonium halides were also tested as catalysts in the above reaction: tetraphenylstibonium iodide was found to be the most effective. Two possible reaction mechanisms were discussed. The first of these involves coordination of the catalyst at the oxirane oxygen atom, followed by nucleophilic attack by an amine on the

spatially more accessible carbon atom. According to the second mechanism, the catalyst reacts with an amine to afford antimony(V) derivative (Ph_4SbNR_2).

Lanthanide tris(trifluoromethanesulfonates), such as $Yb(OTf)_3$, $Nd(OTf)_3$, and $Gd(OTf)_3$, are quite efficient catalysts in the aminolysis of alicyclic epoxy derivatives [70, 169]: Epoxycyclohexane reacted with alkylamines in methylene chloride and acetonitrile to give 90–98% of the corresponding oxirane ring opening products. Meguro *et al*. [170] proposed a procedure for the aminolysis of epoxy derivatives in the presence of ytterbium tris(trifluoromethanesulfonate) under elevated pressure. However, this procedure has no appreciable advantages as compared to the catalytic synthesis under atmospheric pressure. Reactions of epoxycyclohexane with a large number of amines were studied [$PhCH_2NH_2$, $(PhCH_2)_2NH$, $PhNH_2$, *i*-$PrNH_2$, pyrrolidine]; the poorest yields were obtained with isopropylamine. The reaction of 1,2-epoxy-1-methylcyclohexane (**166**) with dibenzylamine in the presence of $Yb(OTf)_3$ gave regioisomeric adducts **167** and **168** at a ratio of 90 : 10 [170] (Scheme 60).

Zirconium, hafnium, and ytterbium trifluoromethanesulfonates also catalyze azidolysis of epoxy derivatives; apart from sodium axide, 1,1,3,3-tetramethylguanidinium azide and trimethylsilyl azide were used as nucleophiles [171, 172]. Some of these reactions were carried out in the presence of quaternary ammonium salts ($Bu_4NF \cdot 3H_2O$, $Bu_4NCl \cdot H_2O$, Bu_4NBr, Bu_4NI, etc.) [172]. Poor regioselectivity was observed in the reaction with 1,2-epoxy-1-methylcyclohexane (**166**): the yields of isomers **169** and **170** were 43 and 34%, respectively [171] (Scheme 61). Highly stereoselective synthesis of b-amino alcohols was effected via reaction of oxiranes with anilines using Co(II) chloride as catalyst [82]. Epoxy alcohols readily reacted with amines in the presence of titanium alkoxides [173]. Crotti *et al*. [174–176] revealed catalytic effect of a series of other salts, e.g., lithium perchlorate, magnesium perchlorate, zinc perchlorate, and ammonium chloride, on the aminolysis and azidolysis of epoxy derivatives. Analogous sodium and calcium salts showed no catalytic effect.

In the last decade, much attention was given to reactions of amines with optically active epoxy derivatives [177, 178]; however, the use of optically inactive substrates and chiral catalysts seems to be more advantageous [179–182]. Enantioselective desymmetrization of achiral substrates (epoxy derivatives among them) is an exceptionally fruitful concept in the development of asymmetric synthesis, as follows from some recent reviews

Enantioselective opening of the oxirane ring in *meso*-epoxy derivatives with trimethylsilyl azide in the presence of chromium complex **67** (M = CrCl) [179]

Compd. no.	**2**, *n* = 4	**2**, *n* = 3	**54b**	**147**	**13c**	**1** (R = R'= Me)
Reaction time, h	18	28	18	16	46	30
Yield, %	80	80	80	80	72	65
Optical yield, %	88	94	98	95	81	82

[75, 183, 184]. The review by Hodgson *et al*. [183] considers both enantioselective deprotonation during the synthesis of optically active allyl alcohols and some aspects of enantioselective addition to achiral epoxy compounds of oxygen-, sulfur-, nitrogen-, halogen-, and carbon-centered nucleophiles. Nitrogen-containing ligands for asymmetric homo- and heterogeneous catalysis were discussed in [184], and an attempt to establish the mechanism of catalytic desymmetrization of epoxy derivatives by the action of metal-complex catalysts was made in [75]. The reaction of epoxycyclohexane with trimethylsilyl azide was used as an example to demonstrate specific utility of chromium and cobalt complexes. The most interesting results in the field of asymmetric azidolysis of epoxy derivatives were reported in [179, 185, 186] where catalytic properties of chromium complexes **67** (M = CrCl) were studied. This catalyst was used to effect asymmetric opening of the oxirane ring in 4,5-epoxycyclohexene (**113c**) [187] and 3,4-epoxycyclopentanone (**54b**) [188]. Chromium complexes catalyzed enantioselective opening of the oxirane ring in the azidolysis of epoxycyclohexane. Analogous aluminum, titanium, and manganese complexes also catalyzed the same reactiont, but only racemic products were obtained. Some results are collected in table.

Song *et al*. [186] recently showed that enantioselective opening of the oxirane ring in the presence of chromium complexes is favored by addition of pure ionic liquids **172** (X = PF_6, SbF_6, BF_4, OTf), e.g., 1-butyl-3-methylimidazolium salts. Desymmetrization of alicyclic

172
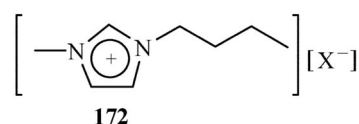
epoxy derivatives with amines and azides is carried out in the presence of bivalent metal tartrates (Zn, Cu, Mn, Sn, Cd, Co, Fe, Mg). In the reaction of epoxycyclohexane with aniline, ee (enantiomeric excess) value attains 52% [in the presence of zinc(II) tartrate], and it is equal to 40% for the reaction of the same epoxy derivative with trimethylsilyl azide in the presence of copper(II) tartrate [181]. Chiral zirconium alkoxides also showed a good catalytic activity in this reaction; the corresponding (*S,S*)-stereoisomers were mainly obtained [189]. In the latter case, chiral titanium complexes with bulky tartrate molecules, e.g., (+)-*tert*-butyltartrate and related structures, were more efficient [190].

In 1998, Asao *et al*. [191] described a new dinuclear titanium complex **173**. The high catalytic activity of this complex predermined its successful application in reactions of epoxy derivatives and carbonyl compounds, as compared to other systems. For example, complex **173**

Scheme 62.

173 **113a**
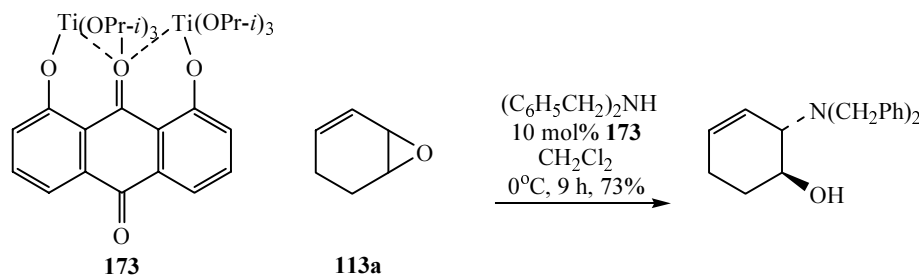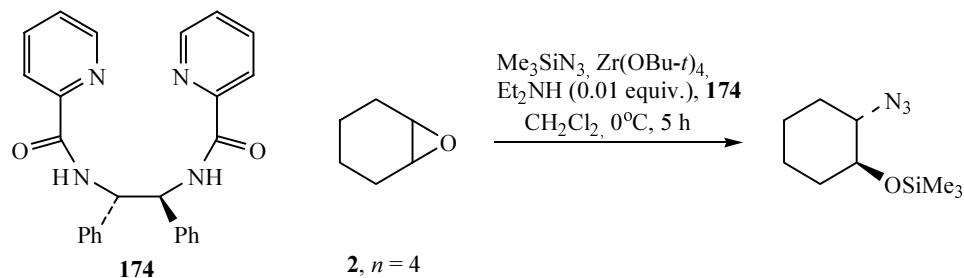
Scheme 63.

Scheme 64.
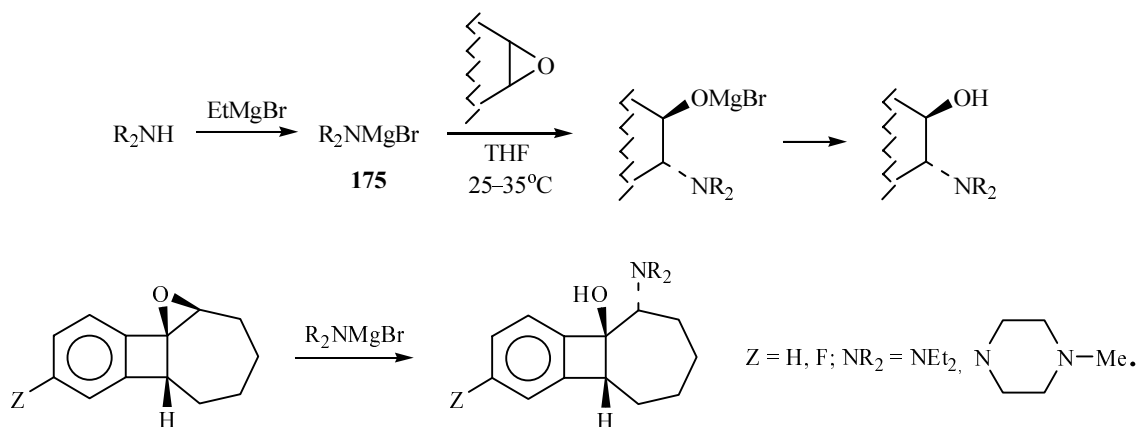
effectively catalyzed aminolysis of epoxycyclohexene **113a** (Scheme 62). Cleavage of the simplest oxiranes with diethylamine, catalyzed by Lewis acids, was reported in [180]. The maximal enantioselectivity exceeded 55% (EtAlCl$_2$). Apart from chiral aluminum complexes, zirconium and titanium derivatives showed a good catalytic activity. Desymmetrization of *meso*-epoxy derivatives via enantioselective addition of nucleophiles in the presence of zirconium catalysts based on tris(2-hydroxypropyl)-amine as ligand was described in [76] (see Section III). The catalyst favors addition of trialkylsilyl azides to oxiranes with an ee value of up to 90%. Zirconium complexes with bisamide **174** were used to catalyze azidolysis of epoxycyclohexane [183, 192] (Scheme 63).

VIII. REAGENT ACTIVATION IN THE AMINOLYSIS OF EPOXY DERIVATIVES

Transformation of amines into the corresponding metal amides **175** is desirable to effect reactions of cyclic epoxy derivatives which are sensitive to drastic conditions [193, 194]. Epoxycyclohexane, epoxycycloheptane, and more complex structures reacted in such a way with bulky nucleophiles: isopropylamine, *tert*-butylamine, diethylamine, etc. (Scheme 64). On the other hand, metal amides (in particular, lithium amides) are capable of ab-

stracting a proton from the α-position with respect to the epoxy moiety, thus giving rise to formation of substituted allyl alcohols in considerable amounts. Amides derived from other metals (e.g., antimony and lead) react preferentially at the most substituted carbon atom. Such reagents are referred to as pseudoacidic metal amides [193, 195, 196]. Yamada *et al*. [197] proposed a new lead reagent, benzylamino(tributyl)plumbane (**176**), for regioselective cleavage of oxirane ring. Compound **176** reacted with unsymmetrically substituted oxiranes according to the Krasusky rule. The reaction with 1,2-epoxy-1-methylcyclohexane (**166**) is characterized by a fairly high regioselectivity [193] (Scheme 65).
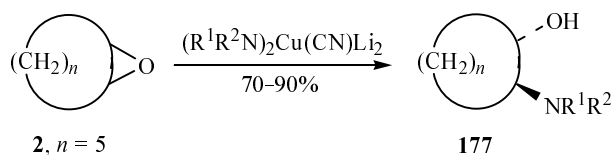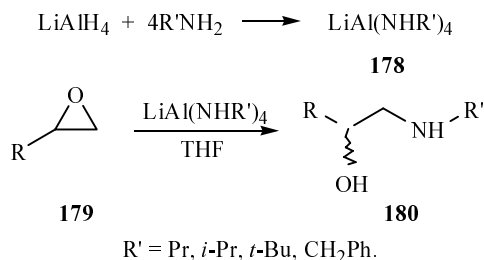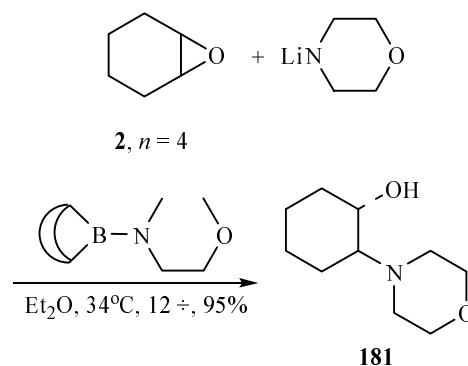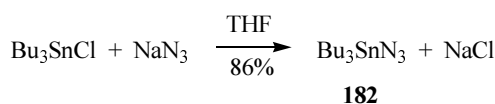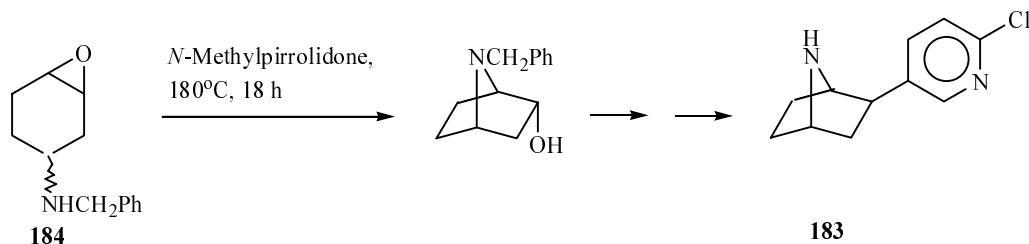
Scheme 65.
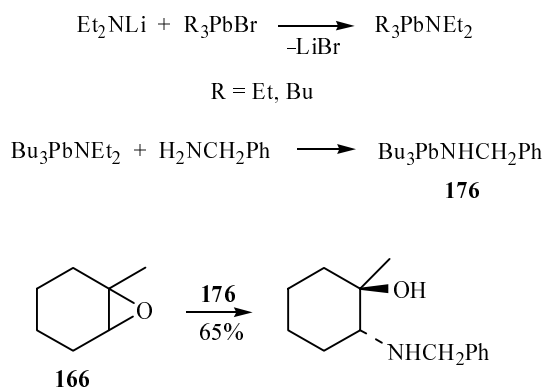
In 1990s, new reagents derived from aluminum, boron, and copper compounds were proposed for aminolysis of oxiranes [179, 198, 199]. The aminolysis of epoxycyclohexane **2** (*n* = 4) and epoxycycloheptane **2** (*n* = 5) was effected with the use of reagents having an amidocuprate structure (R^1, R^2 = Et, $PhCH_2$, Ph, H); as a result, amino alcohols **177** (*n* = 4, 5) were obtained [179] (Scheme 66). Aluminum-containing reagents **178** were synthesized on the basis of lithium aluminum hydride [198]. They ensured high yield (70–100%) and regioselectivity (95–100%) in the aminolysis of monosubstituted oxiranes **179** to amino alcohols **180** [198] (Scheme 67). Aminoboranes generated *in situ* from 9-borabicyclononane and the corresponding amine should be regarded as catalysts rather than reagents in reactions of epoxy derivatives with lithium amides. These catalysts completely suppress side formation of allyl alcohols [199] (Scheme 68). Amino alcohol **181** was synthesized in such a way with almost quantitative yield. It was also found that even 9-bromo-9-borabicyclononane, which is added to the reaction mixture while performing aminolysis, possesses a catalytic activity [199].

The addition of an azido group can also be effected with the aid of heteroelement-containing compounds, among which trimethylsilyl azide and recently proposed tributylstannyl azide (**182**) [200] (Scheme 69) are used most widely. The new reagent is more efficient than its silicon-containing analog. The reactions of epoxycyclohexane with trimethylsilyl azide and compound **182** take, respectively, 336 and 0.4 h in the absence of a solvent and 50 and 3 h in DMF.

IX. INTRAMOLECULAR CYCLIZATIONS ACCOMPANYING REACTIONS OF EPOXY COMPOUNDS WITH NITROGEN-CONTAINING NUCLEOPHILES

Some reactions of epoxy derivatives with nitrogen-containing nucleophiles are accompanied by heterocyclizations. Among these, especially interesting is the synthesis of natural alkaloid epibatidine (**183**) [201] (Scheme

Scheme 66.

2, *n* = 5   **177**

Scheme 67.

$$LiAlH_4 + 4R'NH_2 \longrightarrow LiAl(NHR')_4$$

178

179   **180**

R' = Pr, *i*-Pr, *t*-Bu, CH_2Ph.

Scheme 68.

2, *n* = 4

Et_2O, 34°C, 12 ÷, 95%

181

Scheme 69.

$$Bu_3SnCl + NaN_3 \xrightarrow[86\%]{THF} Bu_3SnN_3 + NaCl$$

182

Scheme 70.

184   **183**

Scheme 71.

185   186a   186b

Scheme 72.

187   189   188   190

Scheme 73.

191   192   193

Scheme 74.

194   195   196

Scheme 75.

197   198   199

Scheme 76.

200   201   202

Scheme 77.

203 **204**

Scheme 78.

(1) NH$_4$OH, 140°C
(2) NaH

LiAlH$_4$

205 **206** **207**

Scheme 79.

H$_2$NNMe$_2$, EtOAc

MgSO$_4$, EtCOOH
–40°C → –25°C

208 **209** **210**
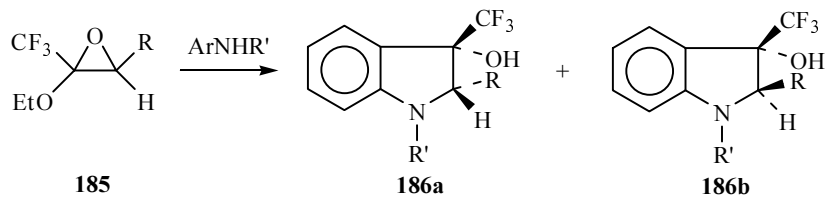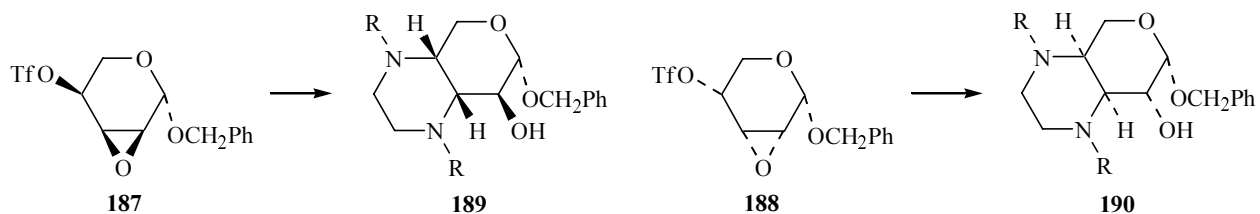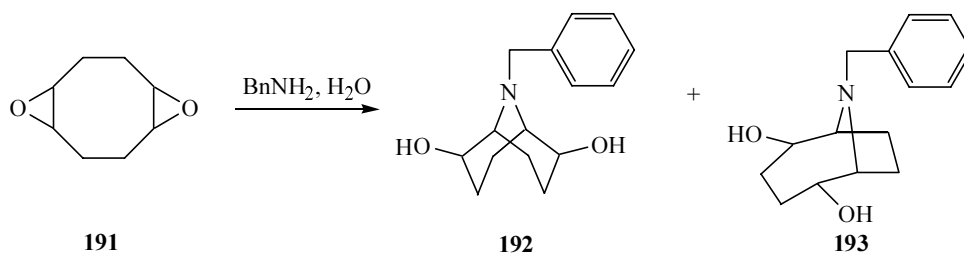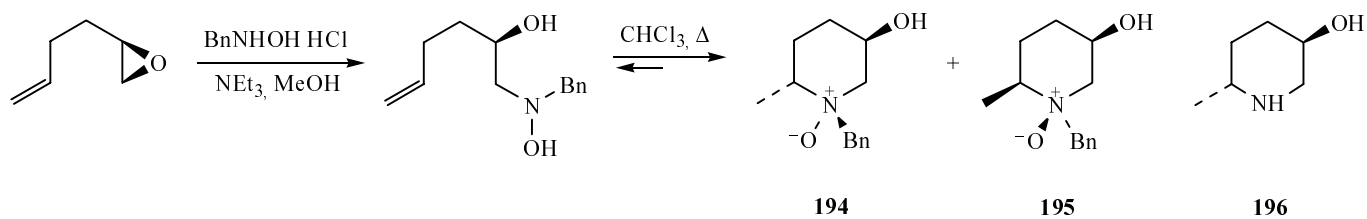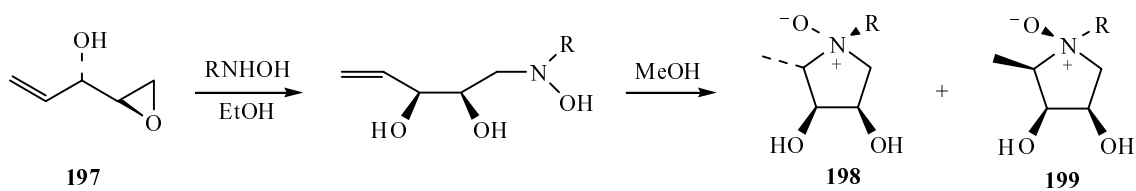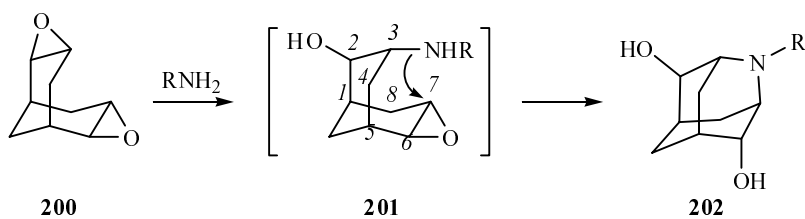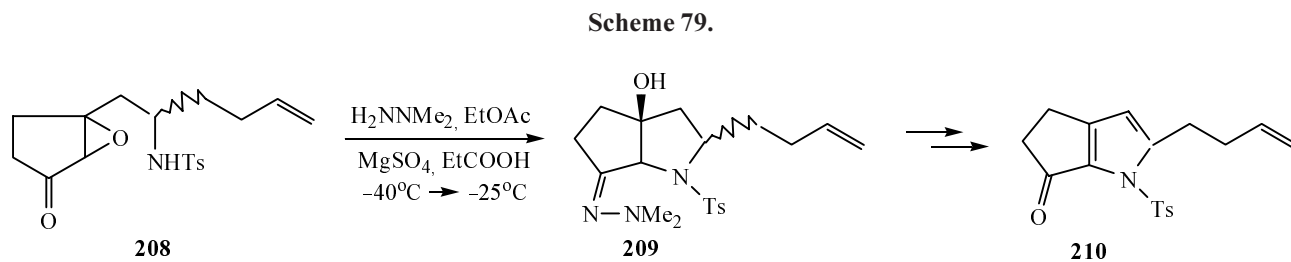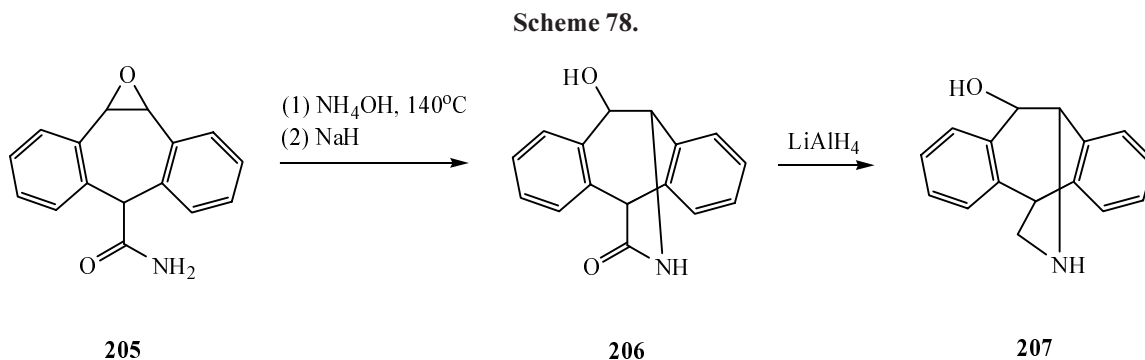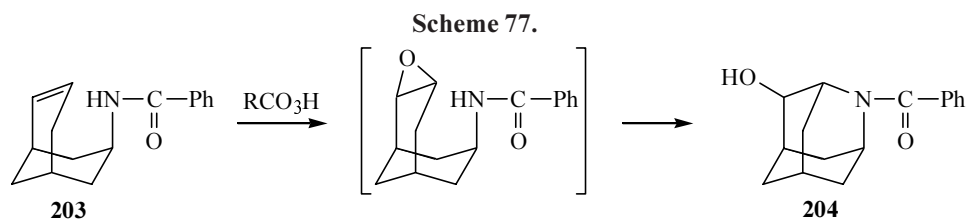
70). This compound is stronger than morphine in analgetic effect by a factor of 200. It was prepared in the enantiopure form by cyclization of aminoepoxycyclohexane **184**. Alicyclic epoxy esters **185** (R = Ph, PhCH$_2$CH$_2$) react with aromatic amines to give stereoisomeric dihydroindoles **186a** and **186b** [202] (Scheme 71). Abdel-Jalil *et al*. [203] reported on the stereospecific synthesis of chiral tetrasubstituted piperazines **189** and **190** (R = H, Me, Et, Ph, PhCH$_2$) in high yield from epoxytetrahydropyrans **187** and **188**, respectively, and *N,N'*-disubstituted ethylenediamines [203] (Scheme 72). The above examples indicate that nitrogen-containing

systems with a five- or six-membered heterocyclic fragment are usually prepared from products of oxirane ring opening with nitrogen-containing nucleophiles [204]. In 2000, Michel and Rassat [205] performed an elegant synthesis of *N*-benzyl-9-azabicyclo[3.3.1]nonane-2,6-diol (**192**) via aminolysis of 1,2 : 5,6-diepoxycyclooctane (**191**) and developed a procedure for separation of product **192** from its isomer **193** (Scheme 73). At the same time, O'Nail *et al*. [206, 207] described the synthesis of chiral functionally substituted piperidines and pyrrolidines via the reverse Coupe cyclization. The ratio of stereoisomers **194** and **195** depends on the solvent. The more polar

Scheme 80.

RNHNH$_2$

211 **212**
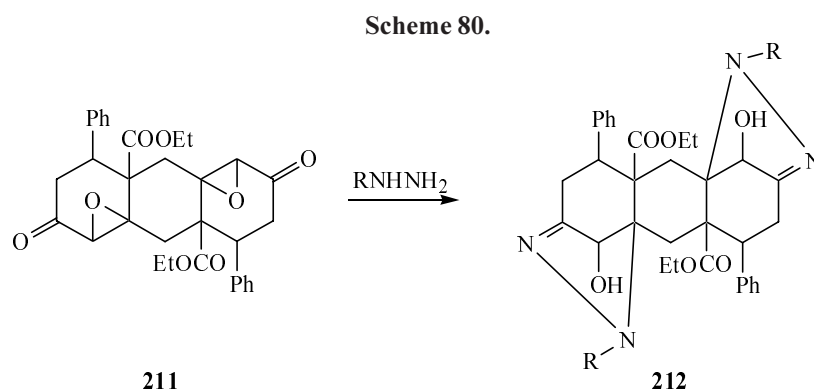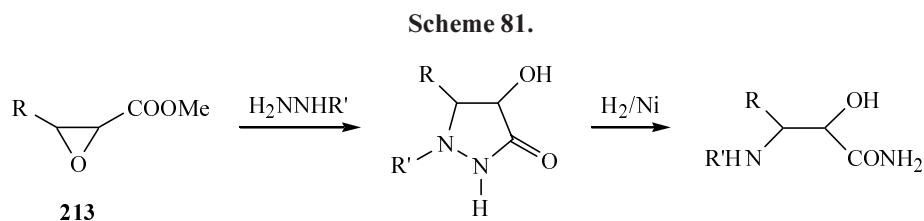
Scheme 81.

N-oxide **194** was quantitatively reduced to piperidine **196** (Scheme 74).

  N-Hydroxypyrrolidinediols **198** and **199** were synthesized on the basis of optically active (2*R*,2*S*)-1,2-epoxy-4-penten-3-ol (**197**) (Scheme 75). The isomer ratio **198** : **199** ranges from 80 : 90 to 10 : 20 (R = H, Me, Bzl, Ph) [208]. Spontaneous transannular cyclization leading to azaadamantane derivatives **202** occured in the aminolysis of diepoxy derivative **200** (Scheme 76). Favorable mutual arrangement of the epoxy fragments in the substrate makes the nitrogen atom and C^7 in intermediate **201** spatially close (~1.5 E) [209]. Analogous derivative **204** was obtained by oxidation of substituted bicyclo[3.3.1]nonene **203** with *m*-chloroperoxybenzoic acid [210] (Scheme 77).

  A number of reactions were reported, where the cyclization involves a nitrogen atom attached to electron-withdrawing groups. In particular, transannular reaction with the product of ammonolysis of compound **205** was studied. Reduction of the resulting amide **206** afforded new cage-like amine **207** [211] (Scheme 78). Epoxy derivatives were used as starting compounds in the synthesis of 3-aminoazetidines; however, the use of aziridines for this purpose is more convenient [212]. Analogous heterocyclizations of oxiranes with participation of nitrogen are extensively studied in the series of epoxy compounds derived from acyclic systems [213, 214]. Kim and Fuchs [215] succeeded in effecting cyclization of δ-*p*-tolylsulfonylamino-α,β-epoxy ketone **208** with *N,N*-dimethylhydrazine to obtain β-hydroxydimethyl-hydrazone **209** containing a pyrrolidine ring (Scheme 79). Compound **209** was then converted into substituted pyrrole **210**.

  Polycyclic systems **212** (R = H, Ph) were synthesized from diepoxy derivative **211** (Scheme 80). As in the reaction with 208, in the first stage hydrazine reacts at the carbonyl rather than epoxy group [216]. Likewise, hydrazine reacts first with the ester group in oxirane **213** [217] (Scheme 81). Epoxycycloalkanols were transformed into heterocyclic systems containing oxygen and boron [218] and oxygen and nitrogen atoms. Among the latter, the most accessible are oxazolidines and oxazolidinones. They are readily prepared by reactions of monosubsti-

Scheme 82.

Scheme 83.
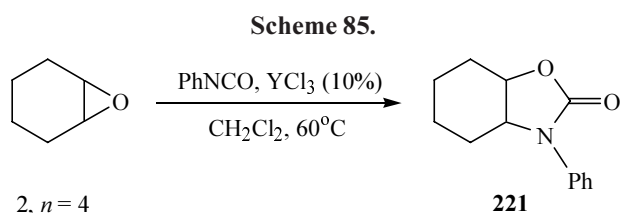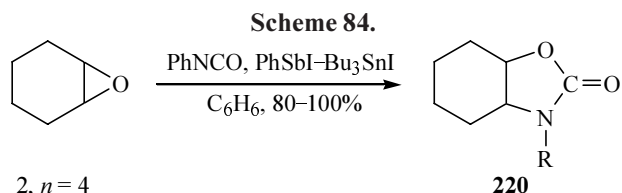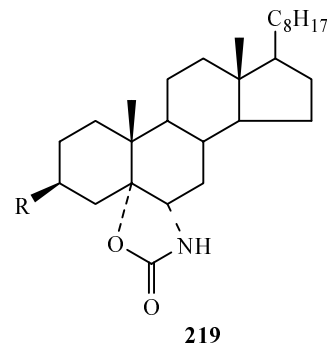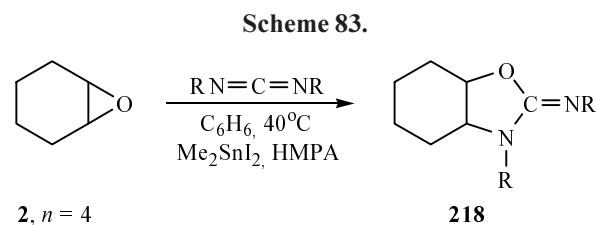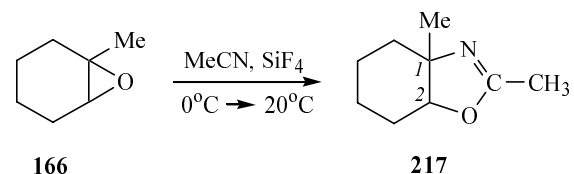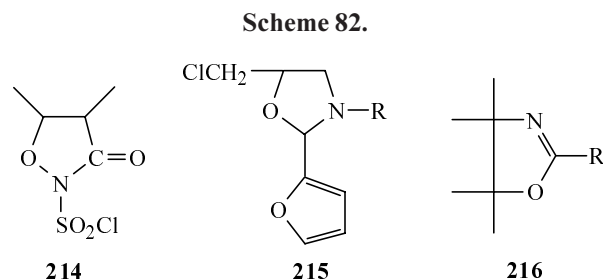
Scheme 84.

Scheme 85.

Scheme 86.
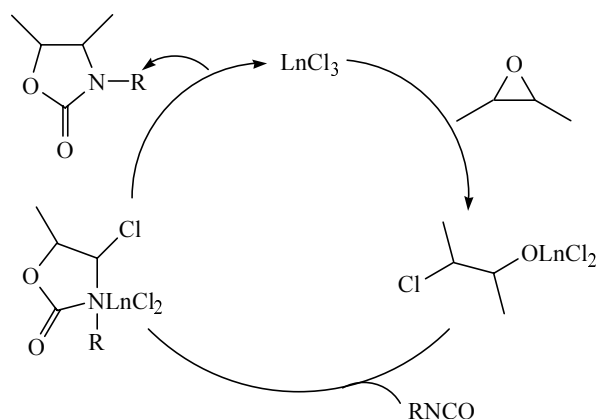
tuted oxiranes with isocyanates. Later on, reactions of oxiranes with chlorosulfonyl isocyanate [219, 220], Schiff bases [221], and nitriles [222] were reported. The corresponding products (compounds **214–216**) are quite promising from the viewpoint of synthesis of biologically active compounds. The reactions of 1,2-epoxy-1-methylcyclohexane (**166**) and epoxycyclododecane **2** ($n = 8$) with acetonitrile afforded 30–40% of the respective dihydrooxazoles. The reaction is regioselective: 4,5-dihydrooxazole **217** is formed exclusively [222] (Scheme 82). Tetrahydrooxazole derivatives **218** (R = Bu, Ph, C_6H_{11}) were synthesized by reaction of epoxycyclohexane with carbodiimides [223] (Scheme 83). Oh *et al.* [224] recently reported on the synthesis of oxazolidines using a polymeric support. Oxazolidin-2-ones **219** were obtained from 5,6-epoxycholestanes and glycine in DMF in the presence of ammonium chloride as catalyst [225]. Alternative routes to oxazolidin-2-ones were also developed; examples are reactions of aminooxiranes with carbon dioxide [226] and functionalization of β-amino alcohols which are readily available via aminolysis of oxiranes [227].

Reactions of monosubstituted oxiranes with isocyanates are catalyzed by Pd(0) complexes [228], as well as by organohalogen compounds of antimony or tin [229]. However, these catalysts were insufficiently active in reactions with less reactive disubstituted oxiranes, including epoxycyclohexane and epoxycyclopentane. These reactions were successfully accomplished in 1986, using a combination of tetraphenylstibonium iodide and tributylstannyl iodide as catalyst. As a result, compounds **220** (R = Ph, p-ClC$_6$H$_4$, *p*-MeC$_6$H$_4$, *i*-Pr) were obtained [229] (Scheme 84). This fact is very interesting, taking into account that each of the above catalysts taken separately does not ensure even a 20% yield of the product. Addition of tin, zinc, aluminum, or copper iodide as the second component increases the yield of oxazolidines to 50%. The activity of the second component decreases in the following series Bu$_3$SnI > Bu$_2$SnI$_2$ >> SnI$_2$ and ZnI$_2$ > AlI$_3$.

Qian and Zhu [230] successfully used lanthanide metal halides to catalyze reactions of monosubstituted oxiranes with isocyanates; however, only 32% of product **221** was obtained from epoxycyclohexane and phenyl isocyanate in the presence of YCl$_3$, and the reaction time was as long as 48 h (Scheme 85; in the case of epichlorohydrin, 99% and 3 h, respectively) [230]. The catalytic cycle for the cycloaddition reaction is shown in Scheme 86.

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