Cyclopropenes and methylenecyclopropanes in 1,3-dipolar cycloaddition reactions

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The review considers the main results of the cycloaddition reactions involving cyclopropenes and methylenecyclopropanes, the compounds bearing strained three-membered rings and, respectively, endo- and exocyclic double bonds. The main attention is focused on the reactions of these compounds with 1,3-dipoles (nitrones, azomethine imines, azomethine ylides, carbonyl ylides, *etc*.), which gave complex heterocyclic systems with high regio- and stereoselectivity.

Key words: cyclopropenes, methylenecyclopropanes, dipolar cycloaddition, nitrones, azomethine ylides, azomethine imines, carbonyl ylides, diazo compounds.

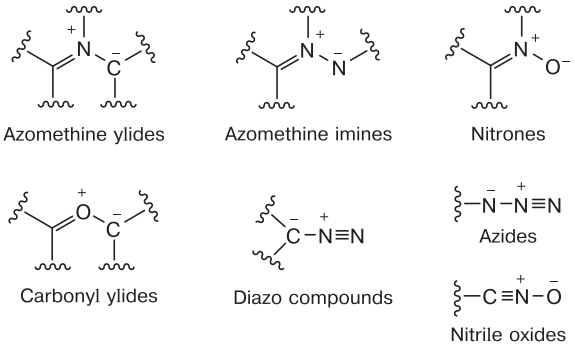
Introduction

Chemistry of small strained rings is one of the most rapidly developing fields of modern organic chemistry. Among natural and synthetic cyclopropane derivatives, the compounds exhibiting plant protection and pharmaceutical activities have been found.[1,2] Compounds containing strained three-membered rings are widely applied in synthetic organic chemistry. The high demand for three-membered carbocycles is due to their good availability, in particular *via* the carbene addition to unsaturated compounds, and possibility of selective three-membered ring opening with different reagents.[3—7] Donor-acceptor cyclopropanes are of special interest (see reviews[8—15]).

The present review is focused on the 1,3-dipolar cycloaddition reactions of cyclopropenes and methylenecyclopropanes that are highly strained three-membered ring-based compounds bearing endo- and exocyclic double bonds, respectively. The high strain energy of these compounds causes their high reactivity that allows their conversion to active species with unique structures (carbenes, 1,3-dipoles, ylides, *etc*.).

1,3-Dipolar cycloaddition is one on the most efficient approaches to construct five-membered heterocycles. A special interest is paid to the reactions of cyclopropene and methylenecyclopropane derivatives with 1,3-dipoles, *e.g.*, nitrones, nitrile oxides, azomethine ylides, azomethine imines, *etc*. These allyl-anion type and propargyl/allenyl type 1,3-dipoles are the most studied species in the dipolar cycloaddition reactions. They react with cyclopropenes and methylenecyclopropanes to give complex fused and spirocyclic heterocycles.

While chemistry of cyclopropane derivatives has already been extensively reviewed, compounds bearing a three-membered ring and a double bond receive much less attention. In the present review, we systematized the published data on the cycloaddition of cyclopropenes and methylenecyclopropanes to 1,3-dipoles resulting in heterocyclic compounds. In general, the literature coverage is limited to the last 20 years, although some earlier citations are included to refer to the initial discoveries and to show the peculiarities of the reactions.



1. Cyclopropenes

Despite cyclopropenes are highly strained structures (strain energy of cyclopropene is 54.5 kcal mol^{-1}),[16] they are rather readily available especially after discovery by D´yakonov and Komendantov of Cu^{I}-catalyzed addition of diazo compounds to triple bond that proceeded *via* Cu^{I}-carbene intermediates in 1956.[17] Due to their unique structure and high strain energy, cyclopropenes can be involved in different reactions, which are not typical for ordinary olefins. The most interesting of these transformations are the cycloaddition reactions.[18—23]

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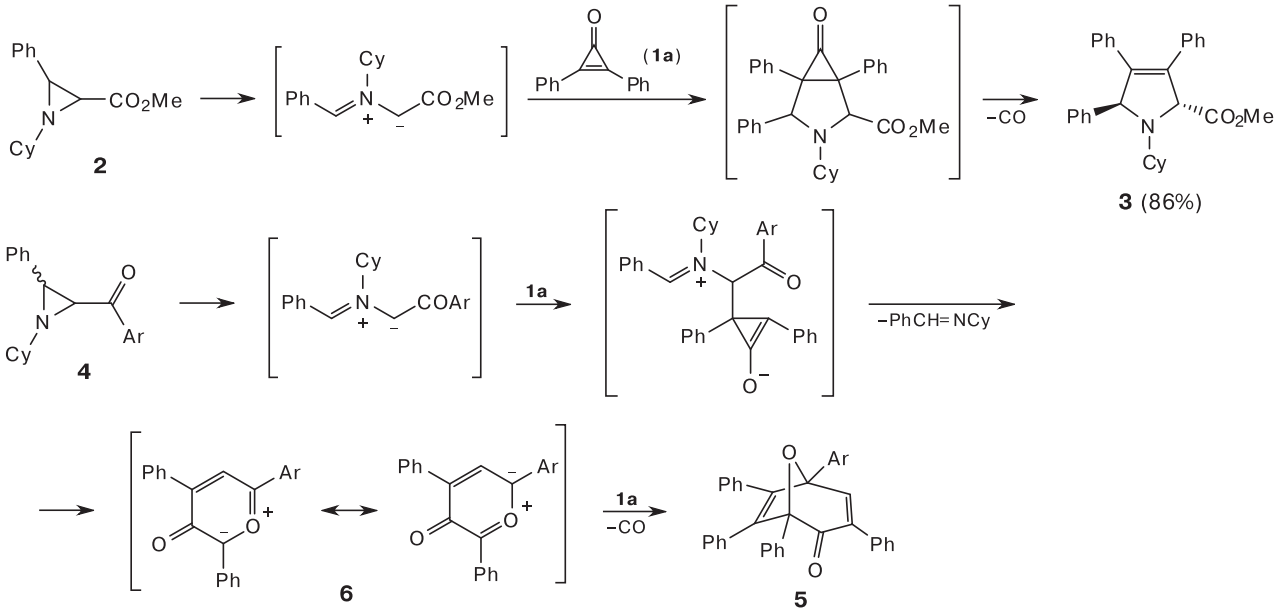
Scheme 1



Cy is cyclohexyl.

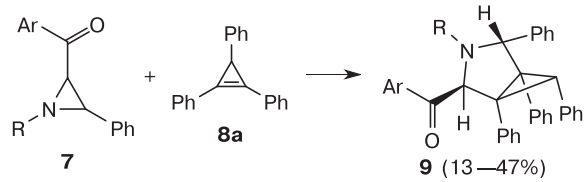
1.1. Reactions with azomethine ylides

1,3-Dipolar cycloaddition of azomethine ylides to unsaturated compounds gave nitrogen heterocycles, *viz.*, pyrrolidines.[24] In these reactions, cyclopropenes gave bicyclic 3-azabicyclo[3.1.0]hexanes. One of the first reactions of dipoles with cyclopropene derivatives is the reaction of azomethine ylides generated by thermal cleavage of 3-substituted aziridines with diphenylcyclopropenone **1a**.[25] The direction of this reaction depends on electronic and steric effects of the substituents in aziridine. Thus, heating of methyl 1-cyclohexyl-3-phenylaziridine-2-carboxylate **2** with compound **1a** in toluene afforded *trans*-3-pyrroline **3**[25]; while, the reaction of 3-aroylaziridines **4** with **1a** gave bicycles **5**[26] (Scheme 1). Apparently, in the first case the reaction proceeds as (3+2) cycloaddition of azomethine ylide generated by thermal ring opening of the aziridine to the C=C cyclopropene double bond to give bicyclic compound followed by decarbonylation;[25] whereas in the second case the six-membered ylide **6** is first generated that than reacted with the second molecule of compound **1a**.[26]

The reactions of azomethine ylide generated by thermal cleavage of 2-aroyl-1-methyl-3-phenylaziridines **7** with 1,2,3-triphenylcyclopropene (**8a**) produced bicycles **9** bearing 3-azabicyclo[3.1.0]hexane units (Scheme 2).[27]

In recent years, a great attention was paid to azomethine ylides generated *in situ* from carbonyl compounds and either α-amino acids or benzylamines that are readily react with compounds containing activated multiple bonds. High regio- and stereoselectivity of these reactions allow mild one-pot synthesis of complex heterocyclic systems bearing several chiral centers. The reactions of substituted cyclopropenes **8** with azomethine ylides generated from isatin **10** and either amino acid **11** or dipeptide glycylglycine **12** gave high yields of mainly single diastereomer of spirocycles **13** and **14** bearing the azabicyclo[3.1.0]hexane and oxoindole units[28] (Scheme 3). Stepakov and coworkers[28] rationalized the observed diastereoselectivity by the higher steric hindrance in the *exo* transition state than that in the *endo* transition state.

Scheme 2

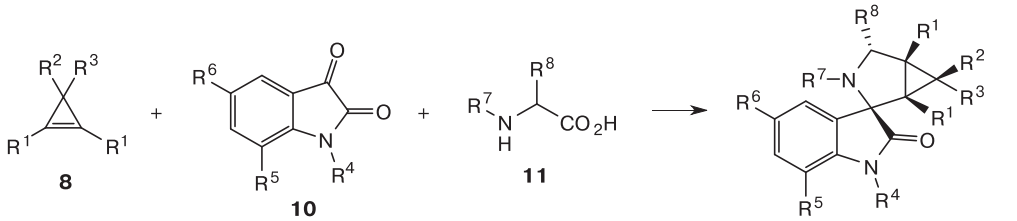


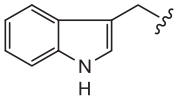
R = Me, *cyclo*-C_6H_{11}
Ar = Ph, 4-ClC_6H_4, 4-BrC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$

Reagents and conditions: toluene, reflux, 48 h.

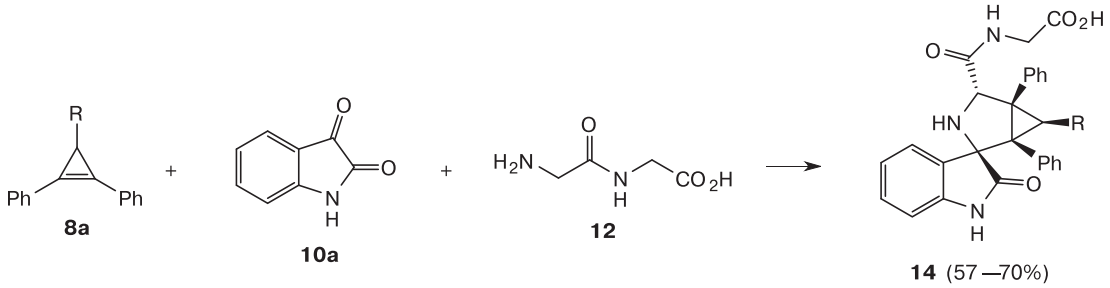
Compounds **15—17** bearing 3-azabicyclo[3.1.0]hexane moiety were synthesized by 1,3-dipolar cycloaddition of the substituted cyclopropenes **8** to azomethine ylides generated from amino acids **11** and the following activated carbonyl compounds: 11*H*-indeno[1,2-*b*][quinoxalin-11-one (**18**), derivatives of indolo[2,1-*b*]quinazoline-6,12-dione (triptanthrine) **19**, and ninhydrin **20** (Scheme 4).[29—31] Ninhydrin **20** reacted with sarcosine **11a** at room tem-

Scheme 3



8: R^1 = Me, Ph; R^2 = H, Ph; R^3 = H, Ph, CO_2Me, C(O)NHMe, CN
10: R^4 = H, Me, Bn; R^5 = H, Br; R^6 = H, Cl, Br, NO_2
11: R^7 = Me, R^8 = H (sarcosine), $R^7 + R^8 = (CH_2)_3$ (L-proline), R^7 = H, $R^8 = Pr^i$ (L-valine), CH(Me)CH_2Me (L-isoleucine), Bn (L-phenylalanine), 4-$HOC_6H_4CH_2$ (L-tyrosine), Ph (D,L-phenylglycine),  (L-tryptophan), *etc.*

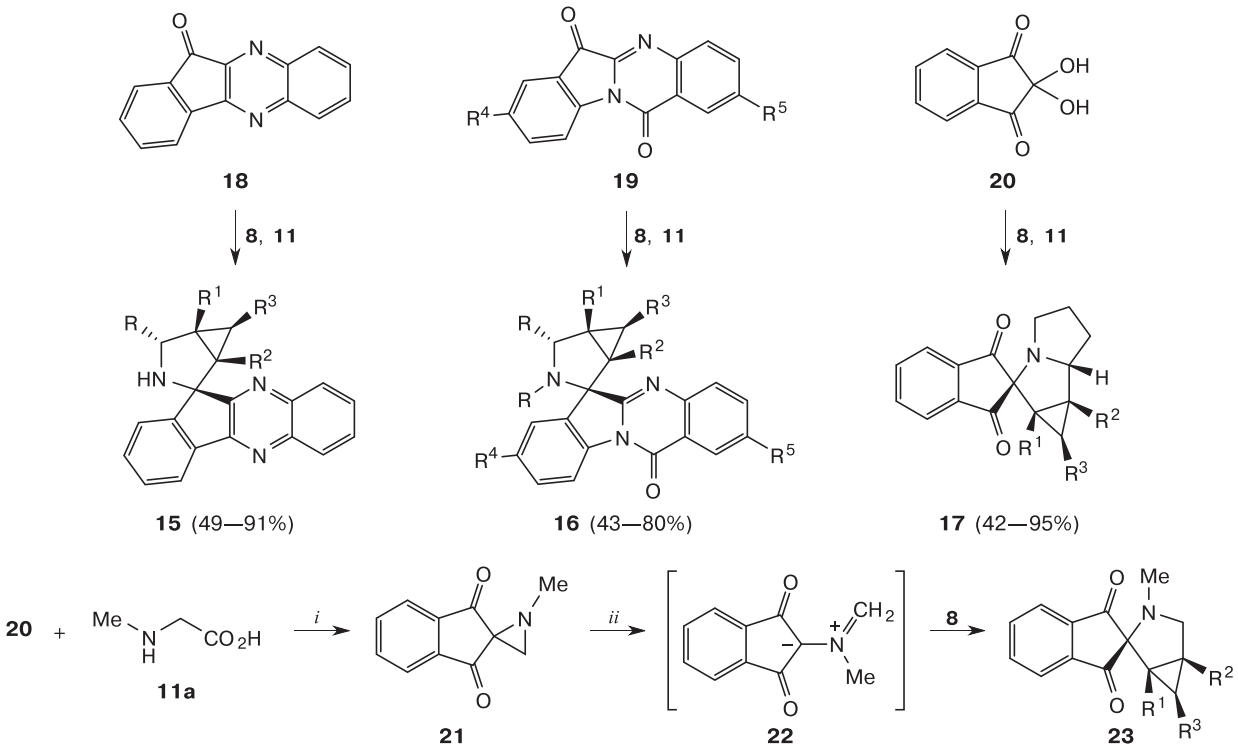
Reagents and conditions: MeOH (or PrOH), H_2O, reflux.



R = Ph, CO_2Me

Reagents and conditions: EtOH, H_2O, reflux.

Scheme 4

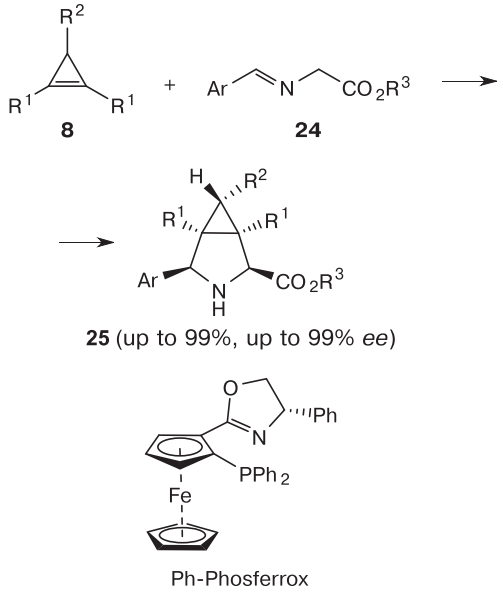


Conditions: *i*. MeOH, ~20 °C, 72 h; *ii*. MeOH, reflux.

perature to give 1-methylspiroaziridineindenedione **21** that served as the precursor for ylide **22**. The subsequent reaction of ylide **22** with cyclopropenes **8** afforded adducts **23**.[32] The reactions of sarcosine and ninhydrin with cyclopropene was also studied by DFT calculations.[32]

(3+2) Cycloaddition of azomethine ylides generated from imines **24** to prochiral trisubstituted cyclopropenes **8** catalyzed by chiral Cu^{I}/Ph-Phosferrox complex proceeded with excellent yields and enantioselectivities to give 3-azabicyclo[3.1.0]hexane derivatives **25** bearing five stereogenic centers[33] (Scheme 5).

Scheme 5

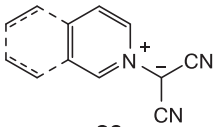


R^1 = Me, Ph; R^2 = Ph, CO_2R, CN, $CONMe_2$; R^3 = Me, Et, Bu^t

Reagents and conditions: $CuBF_4$ (5 mol.%), Ph-Phosferrox, Cs_2CO_3.

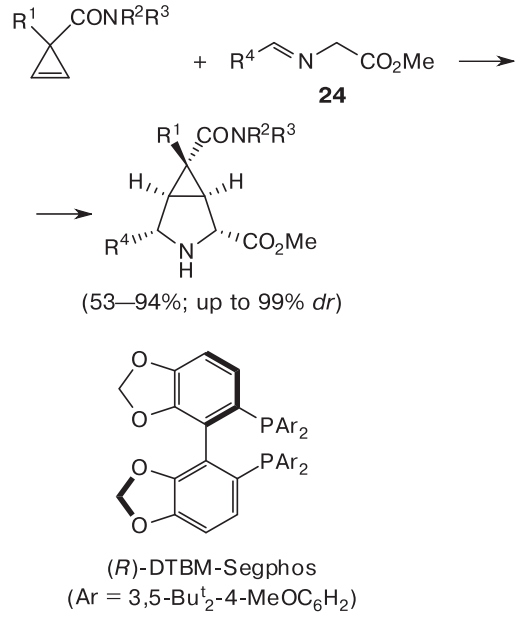
1,3-Dipolar cycloaddition of the same ylides to 1,1-disubstituted cyclopropenes catalyzed by chiral copper catalyst proceeded also with high yields and excellent dia- and enantioselectivities (Scheme 6)[34].

Dirhodium-catalyzed reactions of pyridinium and isoquinolinium dicyanomethylides **26** with enol diazoacetate **27a** gave simultaneously products of both (3+3) and (3+2) cycloadditions (Scheme 7).[35] Apparently, the intermediate metal carbene **28a** is in equilibrium with donor-acceptor cyclopropene **29a**. As a result, the reaction of azomethine ylide **26** with enol carbene **28a** gave (3+3) cycloaddition product **30**, while its reaction with cyclopropene **29a** afforded (3+2) cycloaddition adduct **31**. This assumption is supported by the fact that the reaction pathway depends on the catalyst loading and the



26

Scheme 6



Reagents and conditions: $Cu(MeCN)_4BF_4$ (10 mol.%), (*R*)-DTBM-Segphos (11 mol.%), K_2CO_3, CH_2Cl_2, ~20 °C.

observed enantioselectivity of the formation of adduct **31**. Thus, the catalyst-free reaction of azomethine ylide **26** with the preliminary synthesized cyclopropene **29a** proceeded as diastereoselective (3+2) cycloaddition to give product **31** in 76% yield.

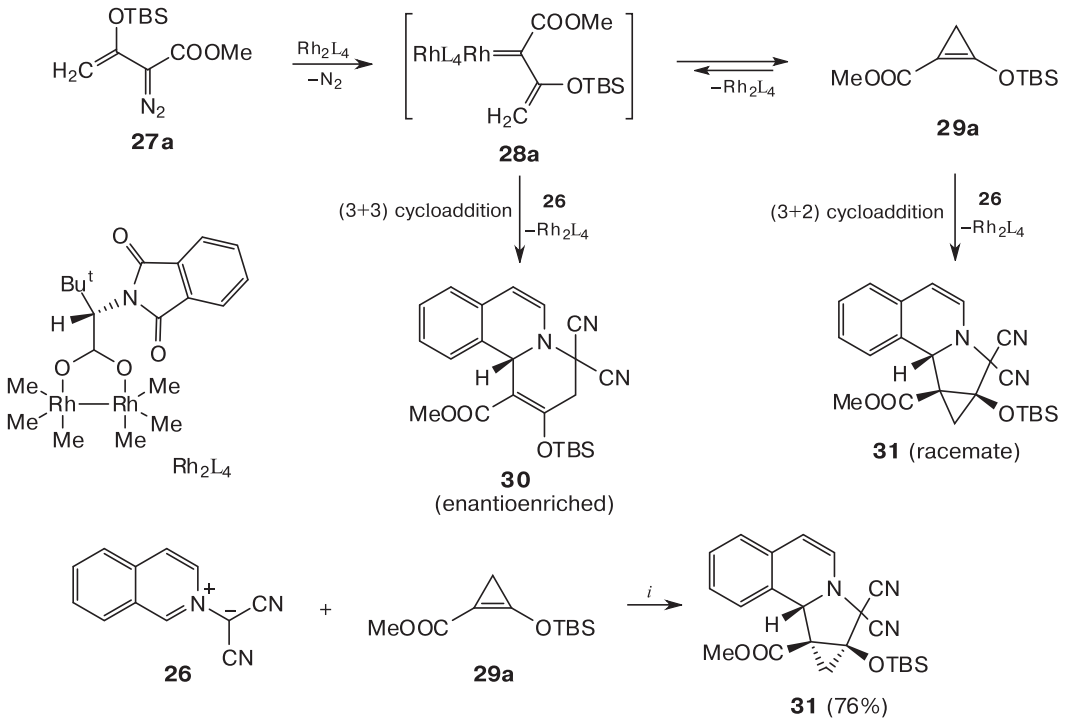
1.2. Reactions with nitrones

Nitrones are the most extensively studied dipoles. They are relatively available, convenient for storage, and valuable starting materials for the synthesis of wide variety of products, *e.g.*, isoxazolidines, that in turn could be transformed into β-amino acids, β-lactams, and 1,3-aminoalcohols.[36,37] Besides, nitrones show antioxidant activity and can be used in medicinal chemistry.[38]

Despite the fact that the first reaction between nitrones and cyclopropenes, namely, cycloaddition of nitrone **32a** to 1,3,3-trimethylcyclopropene to give 2-oxa-3-azabicyclo[3.1.0]hexane **33** in 96% yield (Scheme 8)[39], has been described in 1982, these reactions are still poorly studied.

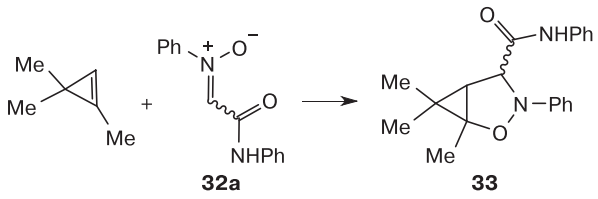
1,3-Dipolar cycloaddition of *C*-aryl-*N*-aryl(*N*-methyl) nitrones **34** to 3-substituted 1,2-diphenylcyclopropenes **8** afforded bicyclic adducts **35**, which further transformed successively to aziridines **36** and tetra(penta)arylpyrroles **37** or unsaturated ketones **38** (Scheme 9). Under thermolysis conditions, aziridines **36** slowly transformed to the corresponding pyrroles **37**. The orientation of cycloaddition is predetermined by the approach of nitrone from the least hindered face of cyclopropene. The nature of the

Scheme 7



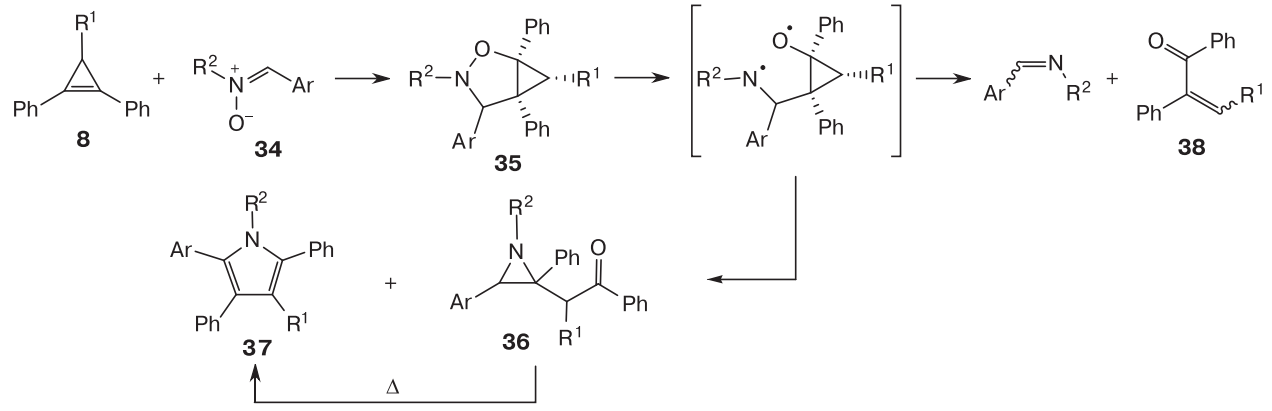
Conditions: *i*. toluene, ~20 °C, 3 h.

Scheme 8



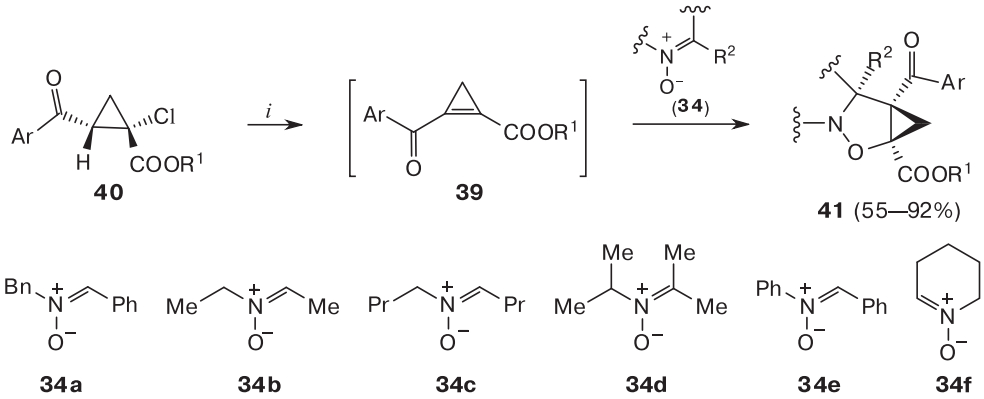
substituents in both nitrone and cyclopropene substantially affects both the reaction conditions required and the product yields. Thus, the reaction of *N*-methylnitrones (R^2 = Me) with cyclopropenes **8** bearing a 3-positioned hydrogen atom and alkyl groups (R^1 = H, Alk) furnished bicycles **35** that were stable under the reaction conditions. Heating of diarylnitrones (R^2 = Ph) with the same cyclopropenes led to the mixtures of aziridines **36** and tetraarylpyrroles **37**. Cyclopropenes bearing electron-withdrawing

Scheme 9



R^1 = H, Me, Ph, CO_2Me, CN; R^2 = Me, Ph; Ar = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, 2,4-$Cl_2C_6H_3$

Scheme 10



Reagents and conditions: *i*. Cs_2CO_3, THF, reflux.

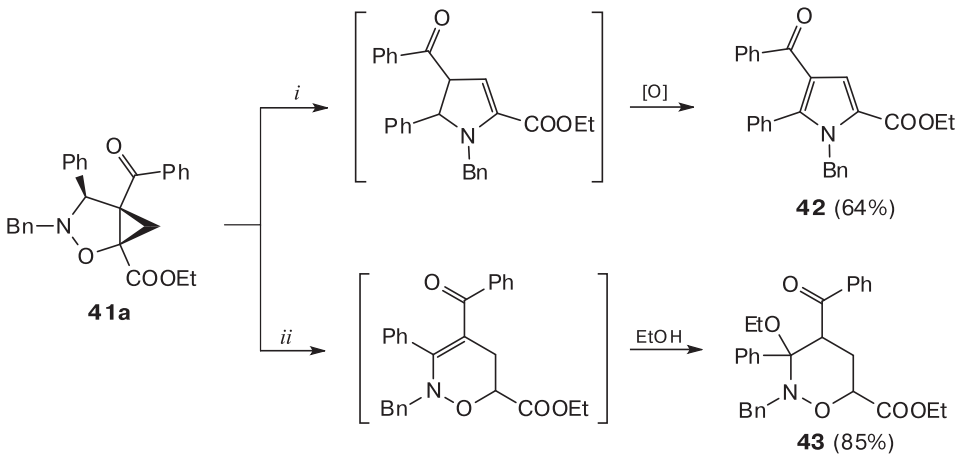
groups at position 3 required the higher temperature to react and afforded the complex mixtures, from which only pyrroles **37** and ketones **38** were isolated (see Scheme 9).[40]

The reaction of cyclopropenes **39** generated *in situ* from the corresponding cyclopropanes **40** under basic conditions with nitrones **34a—f** proceeded as (3+2) cycloaddition to give selectively 2-oxa-3-azabicyclo[3.1.0]hexanes **41** (Scheme 10).[41] This allowed Gong and coworkers to synthesize polysubstituted pyrroles **42** by treatment of compounds **41** with zinc in acetic acid and oxazines **43** by treatment of **41** with HCl·Py in EtOH (Scheme 11).[41]

The reaction of benzocyclopropene **44** with diphenylnitrone is the first reported[42] example of the formal (3+3) cycloaddition. Kagabu *at al*.[42] believed that the reaction occurred stepwise. Nucleophilic attack of nitrone **34e** enabled the three-membered ring opening to give ylide **45**, which underwent subsequent ring closure to afford oxazine **46** (Scheme 12).

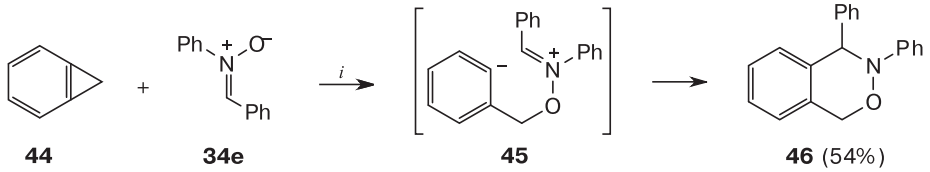
An efficient method for (3+3) annulation of nitrones and enol diazocarbonyl compounds **27** (enol diazoacetate (**27a**), enol diazoacetamide, enol diazosulfones, and enol diazoketones) was developed. Mild catalytic reactions of enoldi-

Scheme 11



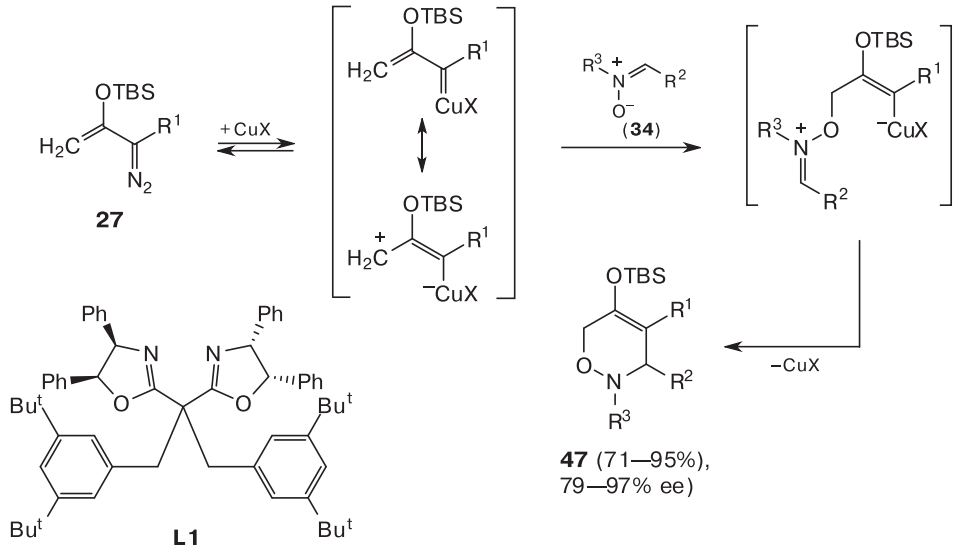
Reagents and conditions: *i*. Zn, AcOH, ~20 °C, air, 8 h; *ii*. HCl·Py, EtOH.

Scheme 12



Conditions: *i*. $CDCl_3$, 60 °C, 70 h.

Scheme 13



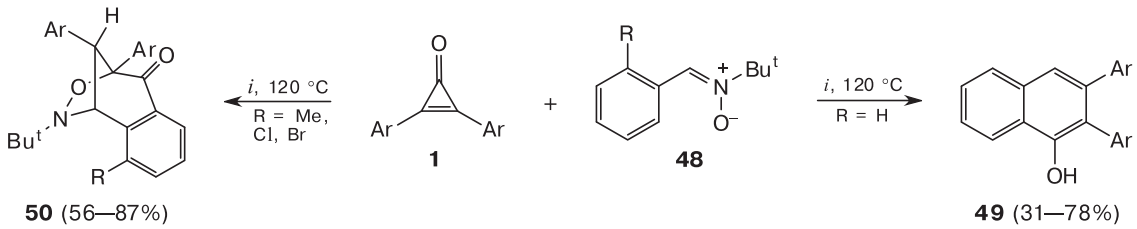
R^1 = COOMe, $C(O)NMe_2$, $C(O)NEt_2$, SO_2Ph, C(O)Ar

Conditions: CH_2Cl_2, 20 °C, 5 h.

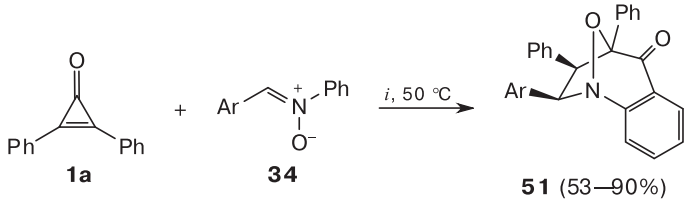
azo compounds and nitrones in the presence of Cu^I and Rh^{II} as the catalyst gave oxazines **47** in good yields.[43—45] The nature of the substituents in both enoldiazo compound and nitrone exerted no effect on the reaction outcome. Complex $Cu(MeCN)_4BF_4$ with chiral ligand **L1** provided excellent enantioselectivity in this reaction (Scheme 13).[46]

The outcome of the reactions between nitrones and cyclopropenes is strongly affected by the nature of the substituents in nitrone. Thus, diarylcyclopropenones **1** reacted with *N-tert*-butyl-*C*-phenylnitrone **48** (R = H) in the presence of the $\{RhCp \cdot Cl_2\}_2/AgSbF_6$ catalytic system at 100—120 °C to give 2,3-diaryl-1-naphthols **49** in good yields (Scheme 14).[47] Under the same conditions, the reaction of compound **1** with nitrones **48**, bearing the bulky substituents at the *ortho* position of the aromatic ring (R = Cl, Br, Me) afforded single isomers of bicyclic products **50** in 56—87% yields but not the corresponding 1-naphthols. The reaction of diphenylcyclopropenone **1a** with diarylnitrones **34** occurred even at 50 °C to give oxygen-bridged bicyclic products **51**. Apparently, compounds **51** are resulted from the reaction sequence involv-

Scheme 14



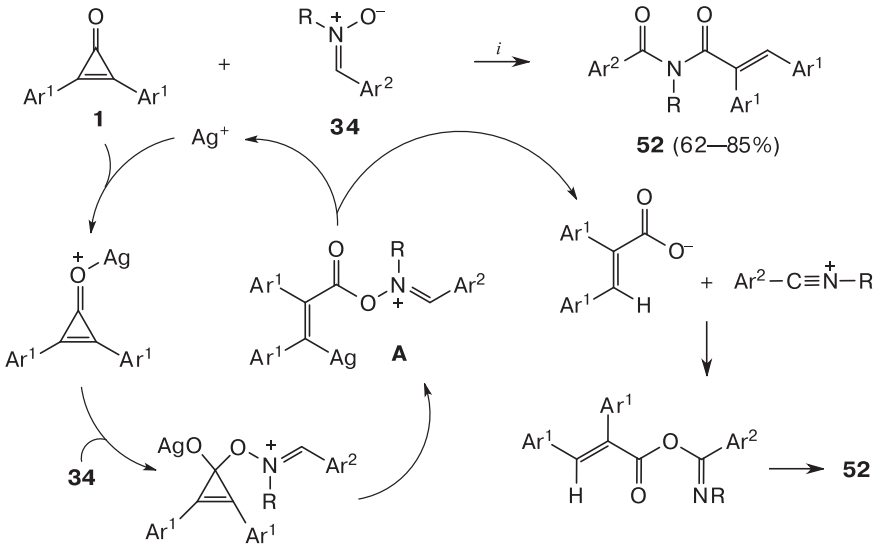
Ar = Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-MeC_6H_4



Ar = Ph, 4-ClC_6H_4, 4-BrC_6H_4, 2-ClC_6H_4, 3-$F_3CC_6H_4$, 4-$MeOC_6H_4$, 4-MeC_6H_4

Reagents and conditions: *i*. $[\{RhCp \cdot Cl_2\}_2]$, $AgSbF_6$, 4 Å molecular sieves, 1,2-dichloroethane.

Scheme 15



R = Me, Bn

Reagents and conditions: *i*. AgOTf (5 mol.%), 100 °C, 30 min.

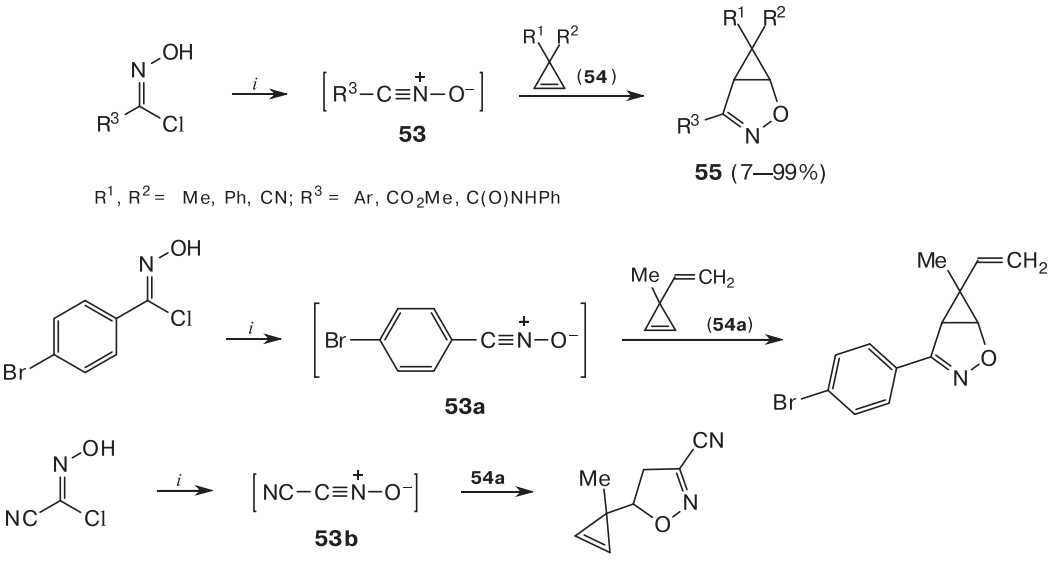
ing acylation of the nitrone and subsequent cycloaddition reaction (see Scheme 14).[47]

Ag^I-catalyzed reaction of cyclopropenones **1** with *N*-alkyl-*C*-arylnitrones **34** carried out at 100 °C gave imides **52**. The reaction is of high efficiency and regioselectivity. Sun and coworkers[48] assumed that the reaction proceeded *via* the key intermediate **A**. Intermediate **A** underwent sequential protonation and the N—O bond cleavage to deliver carboxylate anion and nitrilium ion. Nucleophilic addition of the anion and subsequent rearrangement gave the final imide **52** (Scheme 15). It is of note that no similar reaction occurred with *N*,*C*-diphenylnitrone **34e**.[48]

1.3. Reactions with nitrile oxides

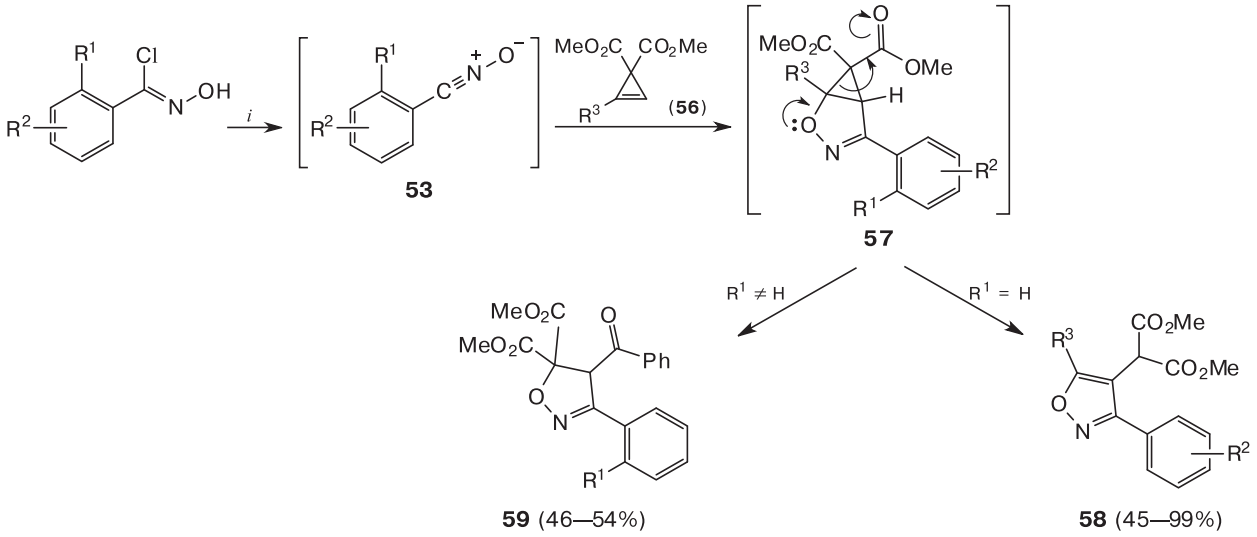
It was shown[49] that nitrile oxides **53** generated from chloro oximes bearing aromatic, methoxycarbonyl, and carbamoyl groups regioselectively reacted with 3,3-disubstituted cyclopropenes **54** to give stereoisomeric mixtures of substituted 2-oxa-3-azabicyclo[3.1.0]hex-3-enes **55** (Scheme 16). For instance, bromophenylnitrile oxide **53a** is added to the cyclic double bond of 3-methyl-3-vinylcyclopropene **54a**; while, more electrophilic cyanonitrile oxide **53b** reacted with **54a** mainly at the vinyl double bond (see Scheme 16).[49]

Scheme 16



Reagents and conditions: *i*. Et_3N, Et_2O.

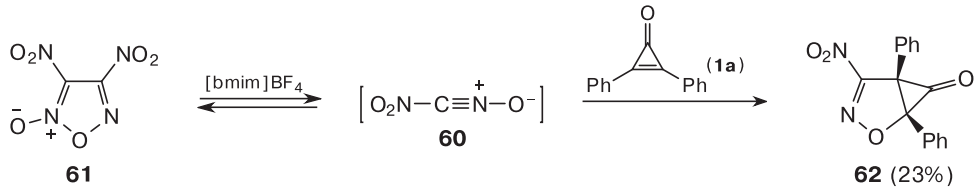
Scheme 17



R^1 = H, R^2 = H, 4-F, 4-Cl, 4-Me, 4-MeO, 3-Cl; R^1 = Cl, Br, R^2 = H
R^3 = H, Bu, Ph, 4-ClC_6H_4

Reagents and conditions: *i*. imidazole, CH_2Cl_2, ~20 °C.

Scheme 18

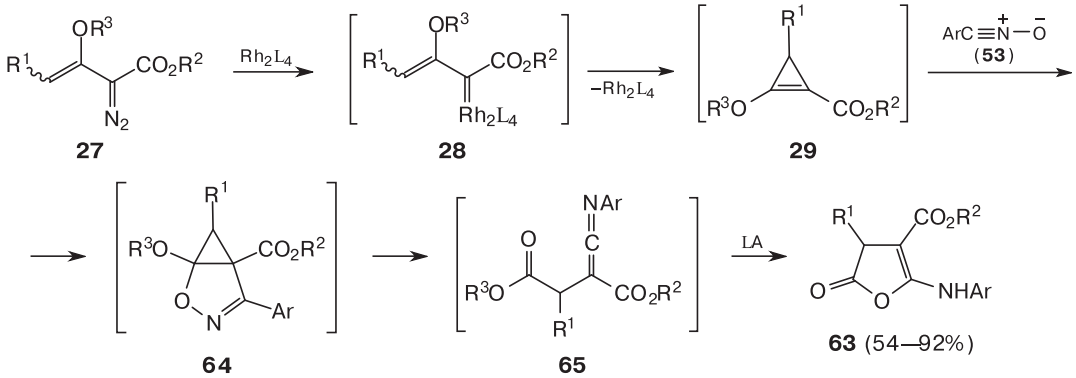


Cycloaddition of arylnitrile oxides **53** to methyl cyclopropene-1,1-dicarboxylates **56** afforded bicyclic intermediates **57** containing two geminal electron-withdrawing groups at the cyclopropene ring (Scheme 17).[50] The three-membered ring of these compounds readily underwent ring opening and the further reaction path depended on the substituents in the *ortho* position of the aromatic ring of the starting arylnitrile oxide **53**. When R^1 = H, the reaction gave isoxazoles **58**. In the case of $R^1 \neq H$, a competing reaction was realized and dihydroisoxazoles **59** were obtained as the main products (see Scheme 17).[50]

The reaction of nitroformonitrile oxide **60** generated from furoxan **61** with cyclopropenone **1a** promoted by ionic liquid [bmim]BF_4 afforded bicyclic adduct **62** in 23% yield (Scheme 18).[51]

Aromatic nitrile oxides **53** reacted with silyl-protected enol diazoacetates **27** similarly to nitrones. The Rh^{II}-catalyzed reactions of **53** with **27** gave 5-arylaminofuran-

Scheme 19



LA is Lewis acid.
R^1 = H, Me, Ph; R^2 = Me, Bn; R^3 = TBS, TIPS

2(3*H*)-ones **63** (Scheme 19).[52] Doyle and coworkers[52] assumed that the reaction proceeded *via* intermediate substituted cyclopropenes **29** that further underwent 1,3-dipolar cycloaddition to nitrile oxide **53** to afford 2-oxa-3-azabicyclo[3.1.0]hex-3-enes **64**. The three-membered ring opening of intermediates **64** gave rise to labile ketenimines **65**, which were converted to furan derivatives **63** by treatment with Lewis acids (see Scheme 19).

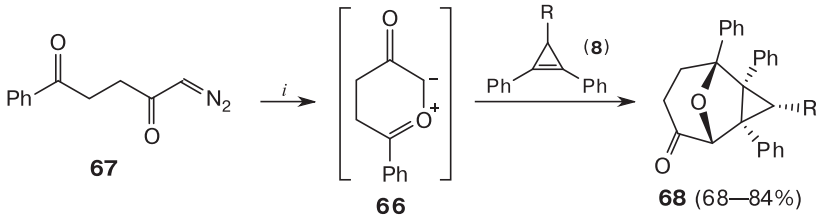
1.4. Reactions with carbonyl ylides

The most of carbonyl ylides are unstable highly reactive substances that are generated *in situ*. The general approach to carbonyl ylides is the reaction of free carbenes or metal carbenoids with the C=O group of the carbonyl compounds. The subsequent cycloaddition of carbonyl ylides to alkenes and alkynes gave five-membered oxygen heterocycles.[53]

Six-membered carbonyl ylide **66** generated from 5-diazo-1-phenylpentane-1,4-dione (**67**) in the presence of $Rh_2(OAc)_4$ stereoselectively reacted with 3-substituted 1,2-diphenylcyclopropenes **8** to give single isomers of 9-oxatricyclo[3.3.1.$0^{2,4}$]nonan-6-ones **68** (Scheme 20).[54] Cyclopropenes **8** bearing 3-positioned electron-withdrawing groups, methyl 2,3,3-triphenylcycloprop-1-ene-1-carboxylate, and 2,3,3-triphenylcycloprop-1-ene-1-carbonitrile are inert in this reaction.[54]

Carbonyl ylide **69** generated by catalytic decomposition of diazo compound **70** reacted with cyclopropenes **8** to give adducts **71** (Scheme 21).[55] The yields of products **71** strongly depend on the electronic effects of the substituents in the starting cyclopropene **8**. The electron-withdrawing groups at the position 3 of cyclopropene **8** (R = COOMe) reduces its reactivity, which is reflected in a decrease in the yield of product **71** to 5% (see Scheme 21). The reaction of five-membered cyclic carbonyl ylide **72** generated from diazo compound **73** with triphenylcyclopropene **8a** furnished adduct **74** in 72% yield (see Scheme 21). Both reactions selectively gave only *exo*-cycloadducts corresponding to *anti* orientation of addends in the transition state. This selectivity is due to the higher steric hindrance between the 3-positioned substituent of cyclopropene and carbonyl ylide for all other spatial orientations of the addends.[55]

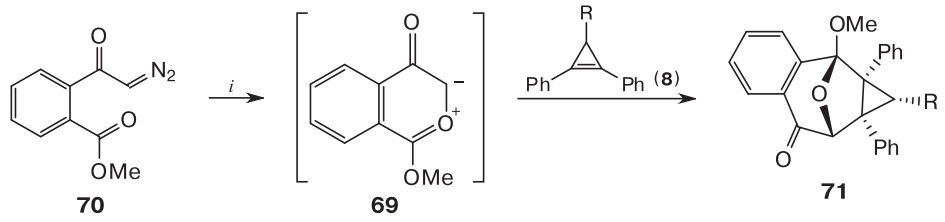
Scheme 20



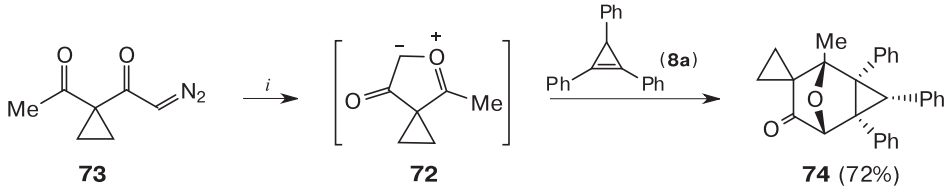
R = H, Me, CH=CH_2, (*Z*)-CH=CHPh, Ph

Reagents and conditions: *i*. $Rh_2(OAc)_4$, CH_2Cl_2, ~20 °C.

Scheme 21



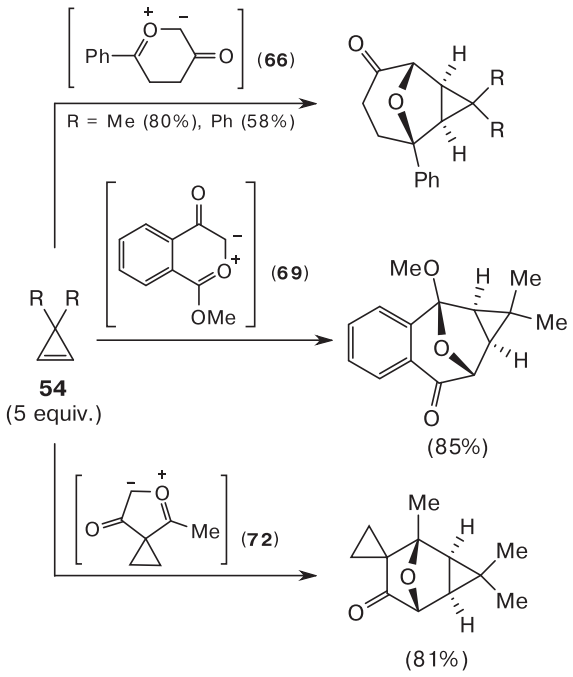
Reagents, conditions, and yields: *i*. $Rh_2(OAc)_4$, CH_2Cl_2, ~20 °C; R = H (92%), Me (76%), CH_2=CH (70%), Ph (67%), CO_2Me (5%).



Reagents: *i*. $Rh_2(OAc)_4$.

Carbonyl ylides **66**, **69**, and **72** reacted with 3,3-disubstituted cyclopropenes **54** to give good yields of the corresponding cycloadducts (Scheme 22).[55]

Scheme 22



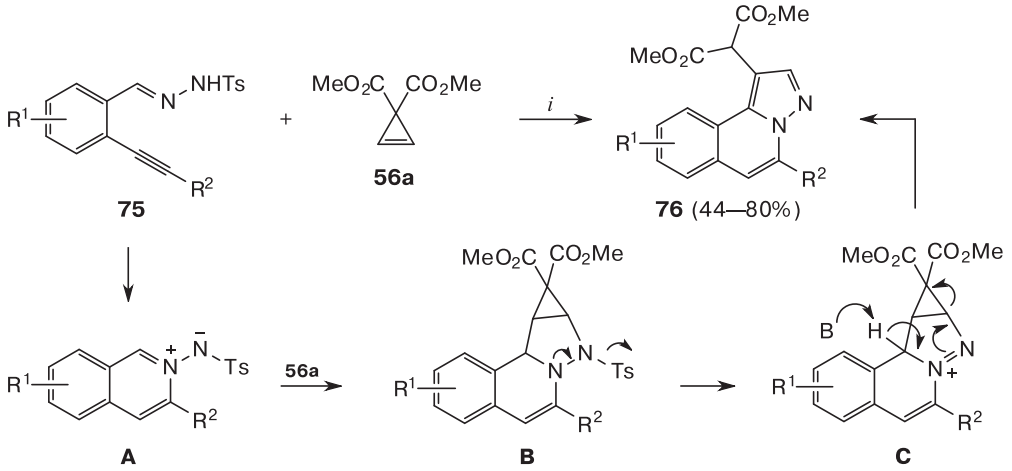
1.5. Reactions with azomethine imines

Azomethine imines are the dipoles of allyl-anionic type bearing the C=N—N fragment. Azomethine imines can be either unstable intermediates and should be generated *in situ* or stable and isolable compounds. The reactions of azomethine imines with olefins and alkynes follow mainly (3+2) cycloaddition pattern but the examples of (3+3)-, (4+3)-, and (3+2+2) cycloadditions are also known. Reviews[56,57] are focused on the 1,3-dipolar cycloaddition reactions of azomethine imines to alkenes and alkynes. The reactions of cyclopropenes with azomethine imines are scarcely studied. For instance, Yao *et al.*[58] reported the tandem reaction of *N*′-(2-alkynylbenzylidene)hydrazide **75** and cycloprop-2-ene-1,1-dicarboxylate **56a** co-catalyzed by Ag^I and Rh^I that resulted in pyrazolo[5,1-*a*]-isoquinolines **76** (Scheme 23). The authors[58] believed that the reaction proceeded *via* 6-*endo*-cyclization to give azomethine imine **A**, which further underwent (3+2) cycloaddition to cyclopropene **56a** to afford cyclic intermediate **B**. Removal of the tosyl group (Ts), three-membered ring opening, and subsequent aromatization gave rise to the final products **76** (See Scheme 23).[58]

Three-membered ring opening in 6-aryl-1,5-diazabicyclo[3.1.0]hexanes **77** through cleavage of the C—N ring bond either at heating[59] or under catalytic conditions ($BF_3 \cdot Et_2O$, ionic liquids)[60,61] gave unstable *N*,*N*-cyclic azomethine imines **78**, which can undergo cycloaddition to the multiple bonds. Thermolysis of 1,5-diazabicyclohexanes **77** in *p*-xylene at 140 °C in the presence of a twofold excess of cyclopropenones **1** led to tricyclic 4a,7b-diazacyclopenta[*cd*]inden-7-ones **79** (Scheme 24).[59,62] The authors assumed[59,62] that regioselective addition of azomethine imines **78** to cyclopropenone **1** initially gave adducts **80**. The three-membered ring opening, addition of the second molecule of cyclopropenone **1**, and extrusion of carbon monoxide resulted in the final products **79** (see Scheme 24).[59,62]

Reactions of diazabicyclohexanes **77** with diazo compounds **26** and donor-acceptor cyclopropenes **28** catalyzed

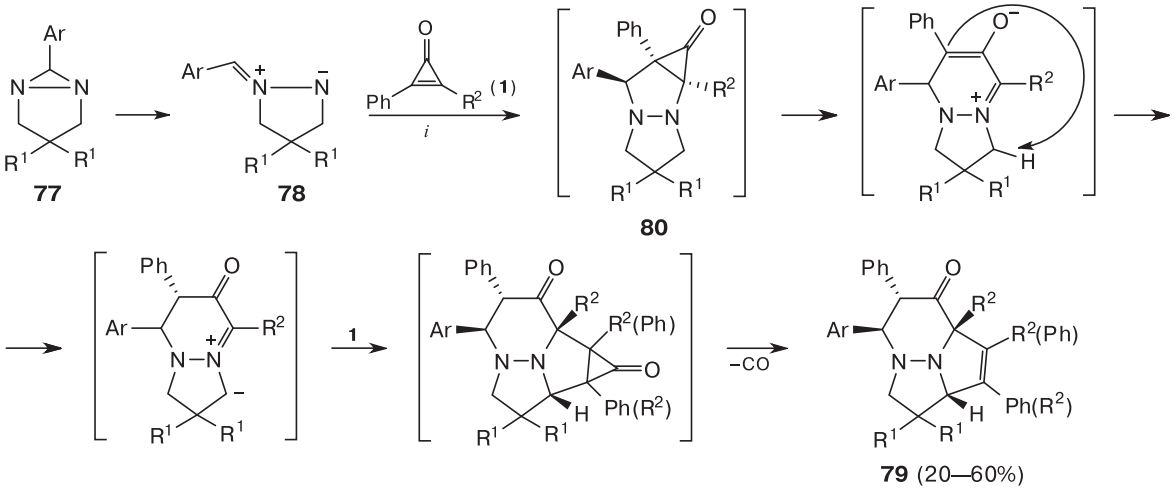
Scheme 23



B is base.

Reagents and conditions: *i*. AgOTf (10 mol.%), $RhCl(PPh_3)_3$ (10 mol.%), 1,4-dioxane, 60 °C.

Scheme 24

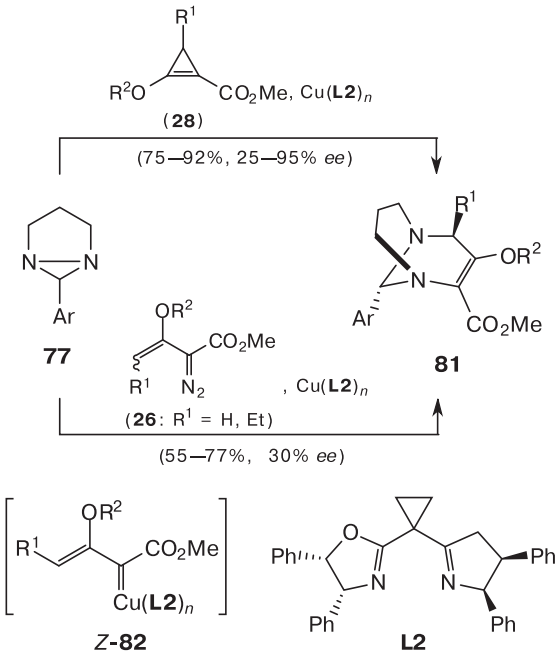


R^1 = H, Me; R^2 = Ph, Me, Pr^i

Conditions: *i*. *p*-xylene, reflux.

by the $Cu(MeCN)_4BF_4$/**L2** system proceeded as formal (3+3) cycloaddition to give bicyclic 1,5-diazabicyclo[3.3.1]-non-2-enes **81** in good yields (Scheme 25).[63] Zheng and Doyle[63] showed that both *E*- and *Z*-isomers of diazo compounds **26** underwent this cycloaddition. When the *E*/*Z*-mixtures of diazo compounds **26** were used, the enantioselectivity was generally lower than that achieved with cyclopropenes **28** (75—92% *ee*) except for sterically hindered isopropyl-substituted derivative (R^1 = Pr^i, R^2 = TBS; 25% *ee*). The authors rationalized this fact in terms of the formation of more reactive *Z*-isomer of the metallo-enolcarbenes (*Z*-**82**) upon catalytic ring opening of cyclopropenes **28** (see Scheme **25**).

Scheme 25



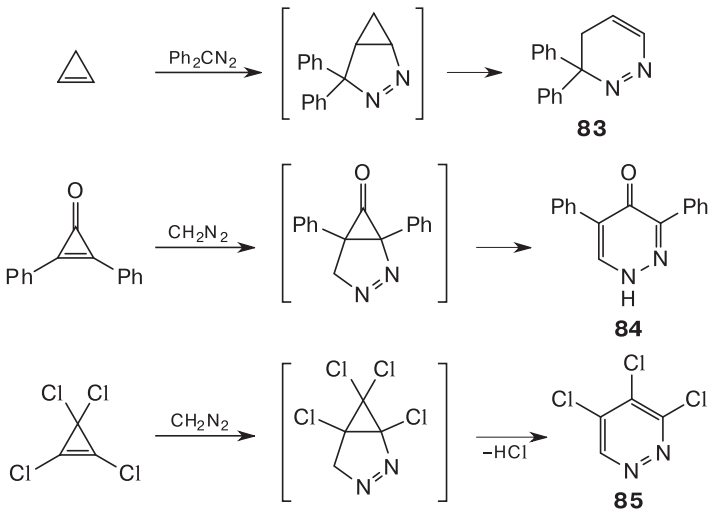
R^1 = H, Me, Et, Pr^i; R^2 = TBS, TIPS

1.6. Reactions with diazo compounds and other dipoles

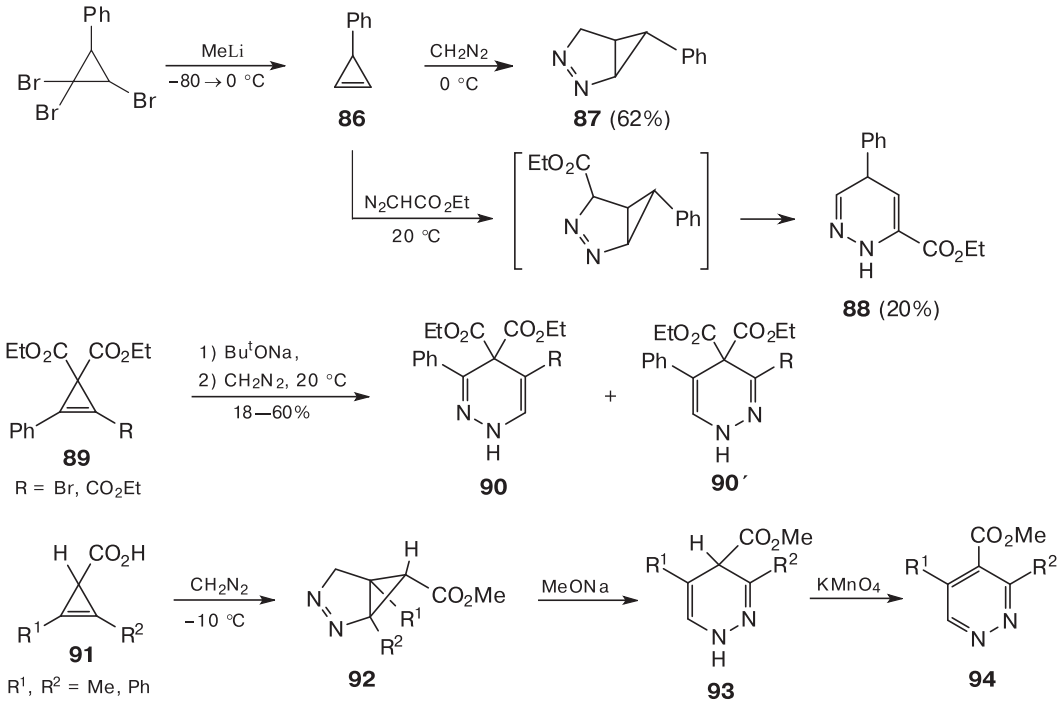
Reactions of cyclopropenes with diazomethane, diphenyldiazomethane, and diazoacetic ester proceeded *via* the three-membered ring opening in the initially formed adducts to result in the corresponding pyridazine derivatives.[64—68] Synthesis of compounds **83**[64], **84**,[65] and **85**[66] is exemplified in Scheme 26.

In some cases, the intermediate 2,3-diazabicyclo[3.1.0]-hex-2-enes can be isolated. In general, regioselectivity and possibility of further transformations of these bicycles depend on the substituent effects in the starting cyclopropenes and diazo compounds. The highest regioselectivity was achieved for cyclopropenes bearing the electron-withdrawing substituents at the double bond.[67—69] Thus, unstable 3-phenylcyclopropene **86** generated by treatment of 1,1,2-tribromo-3-phenylcyclopropane with methyllithium reacted with diazomethane to give bicyclic product **87**; while the reaction with ethyl diazoacetate was accompanied with intramolecular rearrangement and resulted in dihydropyridazine **88** (Scheme 27).[70] Ethyl cyclopropene-3,3-dicarboxylates **89** reacted with diazomethane in the presence of Bu^tONa at room temperature to afford the mixtures of regioisomeric pyridazines **90** and **90′**.[71] In contrast, the reaction of diazomethane with monocarb-

Scheme 26



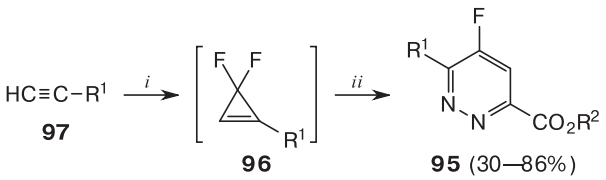
Scheme 27



oxylic acids **91** at 0 °C carried out in the dark gave bicyclic products **92**. Treatment of compounds **92** with bases and subsequent oxidation of the resulting dihydropyridazines **93** furnished pyridazine carboxylates **94** (see Scheme 27).[72,73]

Some reactions of diazo compounds with cyclopropenes were considered in reviews.[74—76] The main recent efforts were focused on the studies of dipolar cycloadditions of diazo compounds that involved *in situ* generation of dipoles or dipolarophiles. Thus, 5-fluoropyridazines **95** were synthesized by tandem (2+1) and (3+2) cycloadditions (Scheme 28).[77,78] Unstable 1-aryl-3,3-difluoro-

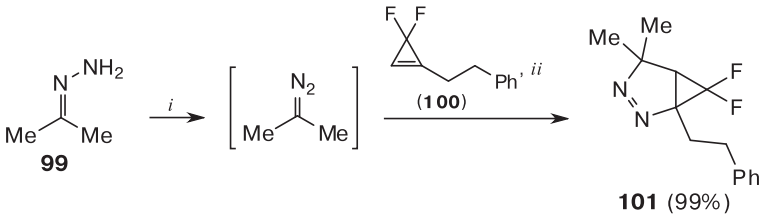
Scheme 28



R^1 = Ar, *cyclo*-C_6H_{11}; R^2 = Et, Bu^t, Bn

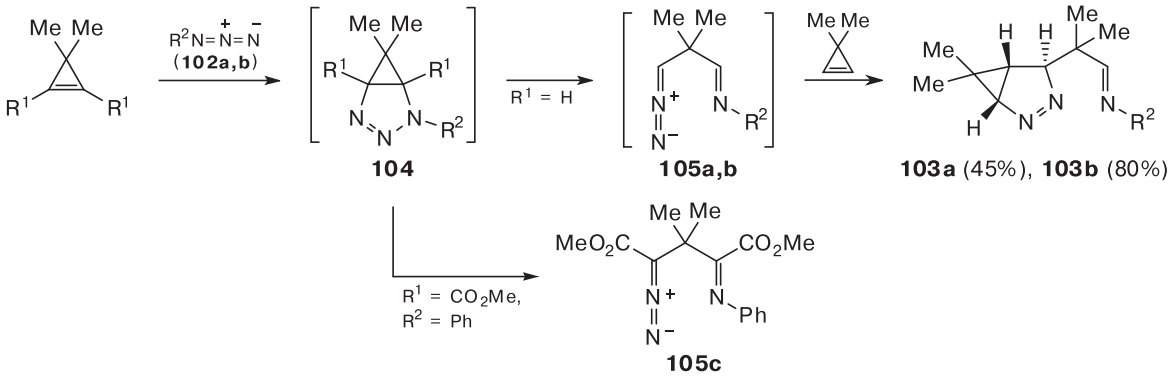
Reagents and conditions: *i.* $TMSCF_3$ (2—4 equiv.), NaI (2.2 equiv.), THF, 110 °C, 2 h; *ii.* $N_2CHCO_2R^2$ (**98**), Et_3N, DMF, ~20 °C.

Scheme 29



Reagents and conditions: *i*. Ag_2O, K_2CO_3, celite, –20 °C; *ii*. CH_2Cl_2, ~20 °C.

Scheme 30



R^1 = H, CO_2Me
R^2 = Ph (**a**), 4-$MeC_6H_4SO_2$ (**b**)

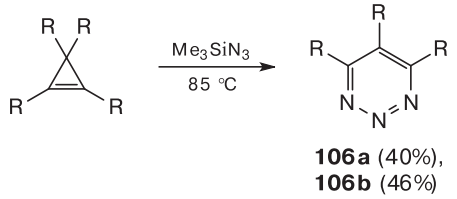
cyclopropenes **96** were prepared by the reaction of readily available acetylenes **97** with difluorocarbene generated from $TMSCF_3$. Crude compounds **96** were treated with diazo esters **98** in DMF in the presence of Et_3N at room temperature to give the corresponding 5-fluoropyridazines **95** in good yields (see Scheme 28).[77,78]

Charette and coworkers[79] generated non-stabilized alkyl diazo compounds by continuous flow oxidation of CH_2Cl_2 solutions of free aldehyde and ketone hydrazones on a column filled with Ag_2O- and K_2CO_3-supported celite. The obtained diazo compounds were subjected to the reactions with unsaturated compounds. This procedure was used for the reaction of acetone hydrazone **99** with 3,3-difluoro-1-(2-phenylethyl)cyclopropene **100** to obtain 2,3-diazabicyclo[3.1.0]hex-2-ene **101** in 99% yield (Scheme 29).[79]

The reaction of 3,3-dimethylcycloprop-1-ene with azides **102a,b** afforded pyrazolines **103a,b** (Scheme 30).[80,81] Aue and coworkers[80,81] assumed that this reaction first gave unstable intermediate triazabicyclo[3.1.0]hexenes **104** that transformed further to diazo compounds **105a,b**. Compounds **105a,b** reacted with the second molecule of cyclopropene to give pyrazolines **103a,b**. This mechanism is supported by the formation of diazo compound **105c** as the only product in the reaction of dimethylcycloprop-enedicarboxylate ($R^1 = CO_2Me$) with phenyl azide **102b** (^1H NMR data).[67]

Tetrachloro- and tetrabromocyclopropenes reacted with trimethylsilyl azide to give triazines **106a,b** (Scheme 31)[82,83]. The authors[82,83] believed that this reaction also proceeded *via* intermediates of the type **105**, which underwent cyclization to triazines **106**.

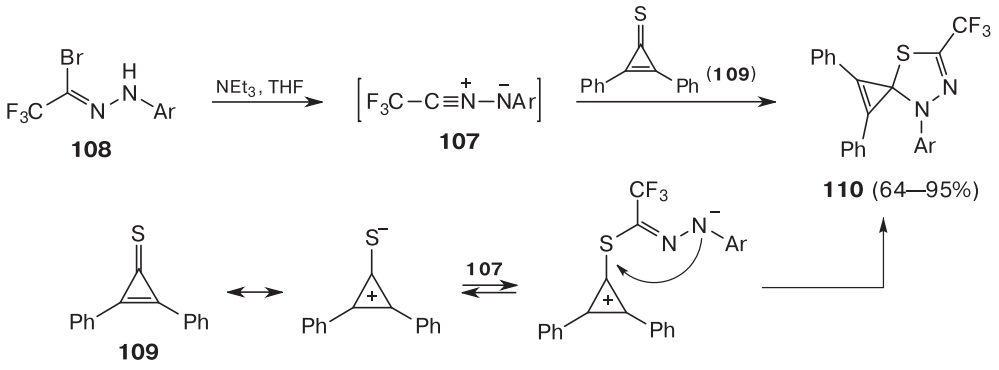
Scheme 31



R = Cl (**a**), Br (**b**)

It was shown[84] that *N*-aryl nitrile imines **107** generated *in situ* from 2,2,2-trifluoroacetohydrazonoyl bromides **108** were added to the C=S bond of diphenylcyclopropenethione **109** to give spirocyclic adducts **110** in high yields (Scheme 32). The authors[84] assumed that the reaction proceeds *via* a stepwise mechanism that involved initial

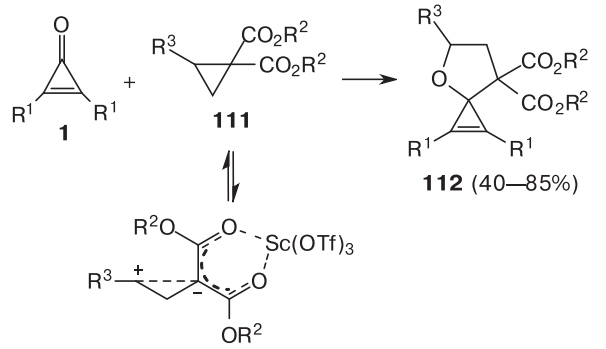
Scheme 32



nucleophilic attack of the sulfur atom onto the electrophilic atom of the dipole followed by ring closure resulting in the final product.[84]

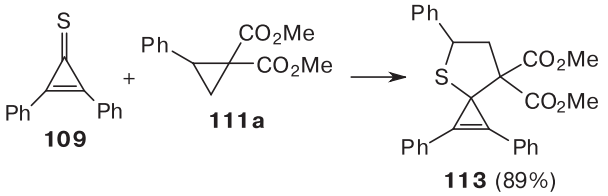
The C—C bond of the donor-acceptor cyclopropanes is highly polarized that facilitates their ring opening upon treatment with Lewis acids to give dipolar intermediates, which in turn can undergo cycloaddition reactions. Thus, the Lewis acid-promoted reactions of cyclopropenones **1** with compounds **111** gave spirocyclic 4-oxaspiro[2.4]hept-1-enes **112** in good yields (Scheme 33).[85,86] Density functional theory (DFT) calculations suggested that the (3+2) cycloadditions is more preferable than plausible (3+3) annulation leading to oxabicyclo[4.1.0]heptane derivatives.[85] Cyclopropenethione **109** reacted with 2-phenyl-1,1-dicarboxylate **111a** at the C=S bond to give spirocyclic product **113** in 89% yield (see Scheme 33).[86]

Scheme 33



R^1 = Et, Ph; R^2 = Me, Ph; R^3 = Ar

Reagents and conditions: $Sc(OTf)_3$, CH_2Cl_2, –20–80 °C.

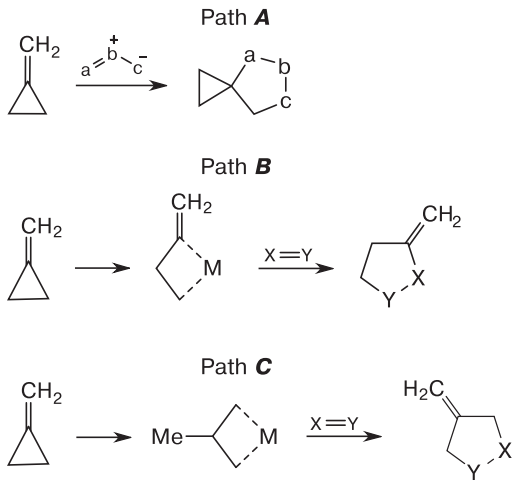


Reagents and conditions: $AlCl_3$, CH_2Cl_2, 25 °C.

2. Methylenecyclopropanes

Even though methylenecyclopropanes are highly strained molecules (41.7 kcal mol^{-1})[16], most of them are fairly stable and available compounds that prompted they wide application in organic synthesis.[87–95] The most typical reactions of alkylidenecyclopropanes are the cycloaddition reactions that can proceed in three different directions (Scheme 34).

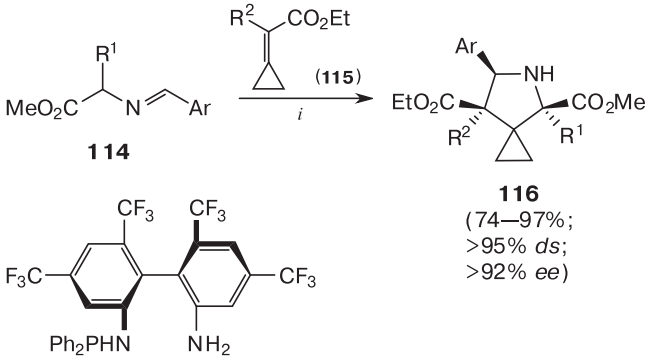
Scheme 34



Path ***A*** is the reactions involving the exocyclic double bond of methylenecyclopropanes that can be formally regarded as dipolarophile with dipoles, which resulted in spirocyclic products. Due to the high strain of the three-membered ring of the spirocycles, they can further undergo different transformations.

Paths ***B*** and ***C*** are catalytic reactions involving the cleavage of the cyclopropane ring at the C—C bond that is proximal or distal to the exocyclic double bond, respectively. The subsequent reactions of the intermediates formed with unsaturated compounds gave five-membered carbo- and heterocycles.

Scheme 35



R^1 = H, Alk; R^2 = Me, Et, Pr, Bn, Ph

Reagents and conditions: *i*. $CuBF_4$/**L3**, Et_3N, CH_2Cl_2.

2.1. Reactions with azomethine ylides

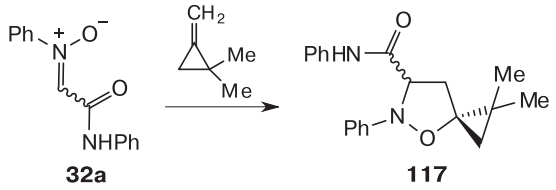
Compounds bearing the 5-azaspiro[2.4]heptane unit that constructed from methylenecyclopropanes and azomethine ylides being a constitutive part of numerous natural and synthetic biologically active substances are of great importance for medicinal chemistry. However, the data on the reactions resulting in formation of this unit are scarce. For instance, Wang and coworkers[96,97] described asymmetric 1,3-dipolar cycloaddition of azomethine ylides generated from methyl arylideneglycinate **114** to α-substituted ethyl 2-cyclopropylideneacetates **115** in the presence of chiral catalysts (*e.g.*, **L3**) and Et_3N in CH_2Cl_2 at room temperature to give 3-spirocyclopropanated pyrrolidines **116** in good yield and high dia- and enantioselectivity (Scheme 35).

2.2. Reactions with nitrones

Reactions of methylenecyclopropanes with nitrones are the most studied.[87,88,98] In contrast to other acyclic unsaturated compounds, methylenecyclopropanes are easily underwent cycloaddition reactions to nitrones. The first described example of the reaction of methylenecyclopropanes with nitrones is addition of *N*-phenyl-*C*-(*N*-phenylcarbamoyl)nitrone **32a** to 2,2-dimethyl-1-methylenecyclopropane.[39] Akhmanova *et al*.[39] isolated the only product to which structure of 5-spirocyclopropaneted isoxazolidine **117** was ascribed (Scheme 36).

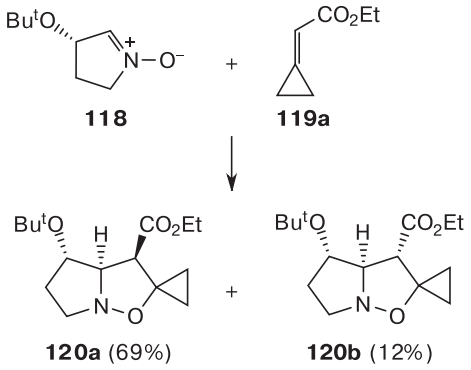
Cycloaddition of nitrones to methylenecyclopropanes gave mainly the mixtures of regioisomeric 5- and 4-spirocyclopropane isoxazolidines, the ratios of which depend on the nature of the substituents. When ketonitrones were used instead of aldonitrones, the content of 5-regioisomers increased. Reactions of nitrones with methylenecyclopropanes containing the alkyl and aryl substituents at the

Scheme 36



three-membered ring gave both 4- and 5-spirocyclopropane isoxazolidines.[98] Reactions of nitrones with methylenecyclopropanes bearing electron-withdrawing groups (Cl, COOR, CN) at the exocyclic carbon atom of the methylene group are more selective. Thus, the reaction of nitrone **118** with methylenecyclopropane **119a** selectively afforded 5-spirocyclopropane isoxazolidines **120** (Scheme 37).[99]

Scheme 37

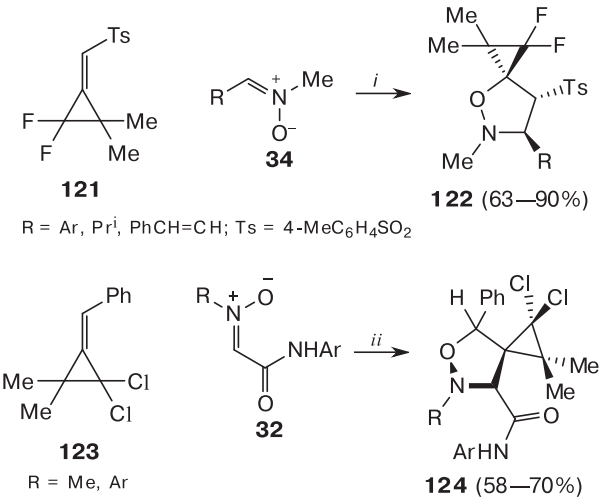


Conditions: toluene, 30 °C.

Methylenecyclopropane **121** bearing the fluorine atoms at the three-membered ring reacted with *N*-methyl-*C*-

(alkyl,aryl)nitrones **34** to give 5-spirocyclopropane isoxazolidines **122**;[100] while the reaction of methylenecyclopropane **123** containing Ph-group at the exocyclic double bond with *N*-alkyl(aryl)-*C*-carbamoyl nitrones **32** selectively afforded 4-spiro isomers **124** (Scheme 38).[101]

Scheme 38



Conditions: *i*. petroleum ether, 50 °C, 12 h; *ii*. toluene, 110 °C.

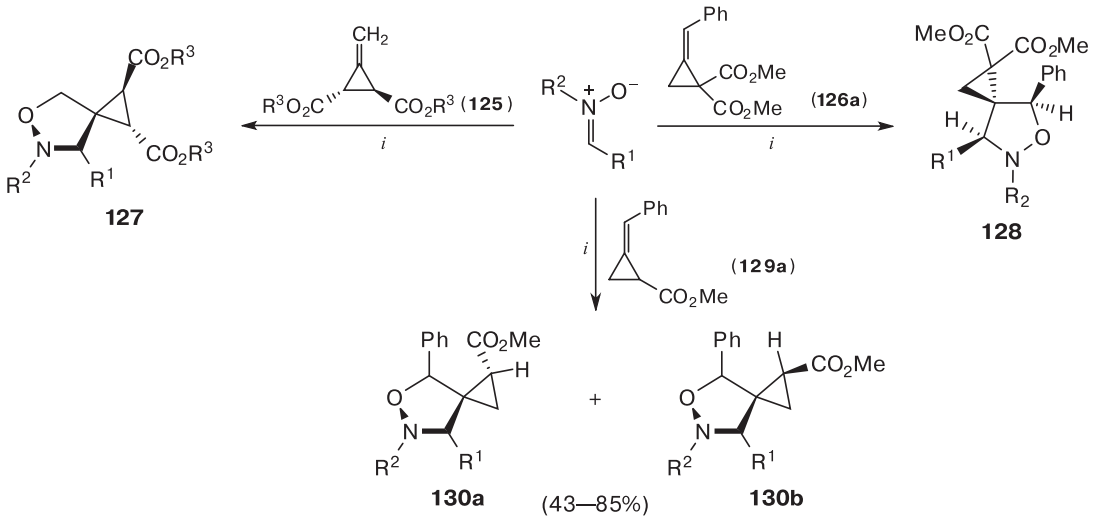
C-Aryl and *C*-carbamoyl nitrones reacted with 3-methylenecyclopropan-1,2-dicarboxylate **125** bearing the electron-withdrawing groups at the three-membered ring and with 2-benzylidenecyclopropane-1,1-dicarboxylate **126a** to give the corresponding 4-spirocyclopropane isoxazolidines **127** and **128** (Scheme 39).[102—105] In both cases, the reaction produces only one diastereomer in up to 90% yield. At the same time, the reactions of nitrones with 2-benzylidenecyclopropane-1-carboxylate **129a** bearing one electron-withdrawing group at the ring resulted in diastereomeric 4-spirocyclopropane isoxazolidines **130a,b**. The ratios of diastereomers **130a** and **130b** depend on the substituents in nitrone being **130a** : **130b** ≈ 1 : 1 for *C*,*N*-diaryl nitrones and 4 : 1 for *C*-carbamoyl nitrones; while *N*-methylnitrones gave exclusively isomers **130a** (see Scheme 39).[106]

Reactions of benzylidenecyclopropane **131a** with *C*,*N*-diaryl and *N*-aryl-*C*-carbamoyl nitrones proceeded regio- and stereoselectively to give single isomer of 4-spirocyclopropane isoxazolidines. In contrast, the regioselectivity is retained in the reactions involving *N*-phenyl-*C*-cyclopropane nitrone bearing the electron-releasing cyclopropyl ring and *N*-methyl-*C*-aryl nitrones but two diastereomeric isoxazolidines were obtained (Scheme 40).[107] Density functional calculations indicated that concerted mechanism of the formation of *cis* isomer is more preferable.[107]

Reaction of *N*-aryl-*C*-carbamoyl nitrones **32** with methylenecyclopropanes **132** and **133** bearing the aromatic substituent at the three-membered ring and an ester group afforded 4-spiroisoxazolidines **134** and **135** (as a 1 : 1 mixture of two diastereomers) (Scheme 41).[108] Molchanov and coworkers[108] rationalized the formation of products **134** in the reaction between compounds **32** and **133** in terms of thermal isomerization of the starting compound **133** to **132**.

Thermal transformations of 5-spirocyclopropane isoxazolidines. Reactions of methylenecyclopropanes with nitrones became of great interest because the products of

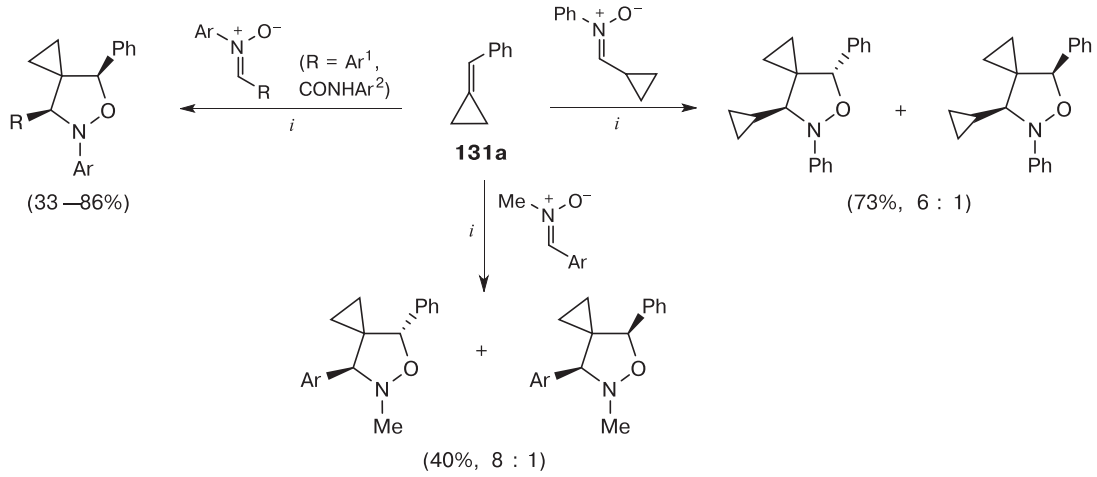
Scheme 39



R^1 = Ar, CONHPh; R^2 = Me, Ar

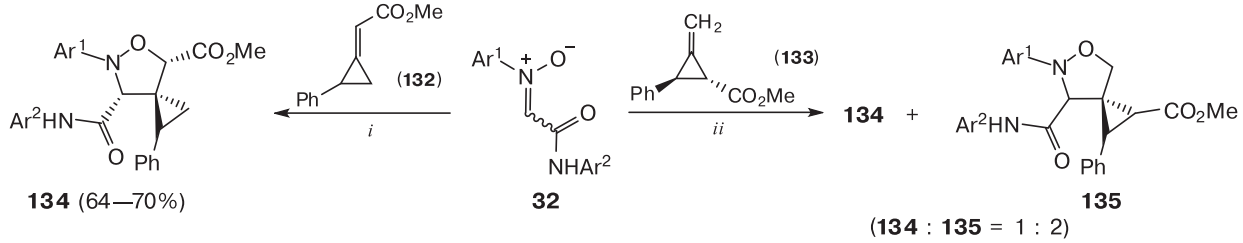
Conditions: *i*. toluene, 110 °C.

Scheme 40



Conditions: *i*. toluene, 110 °C.

Scheme 41



Conditions: *i*. toluene, 110 °C, 1 h; *ii*. CH_2Cl_2, ~20 °C, 25 days.

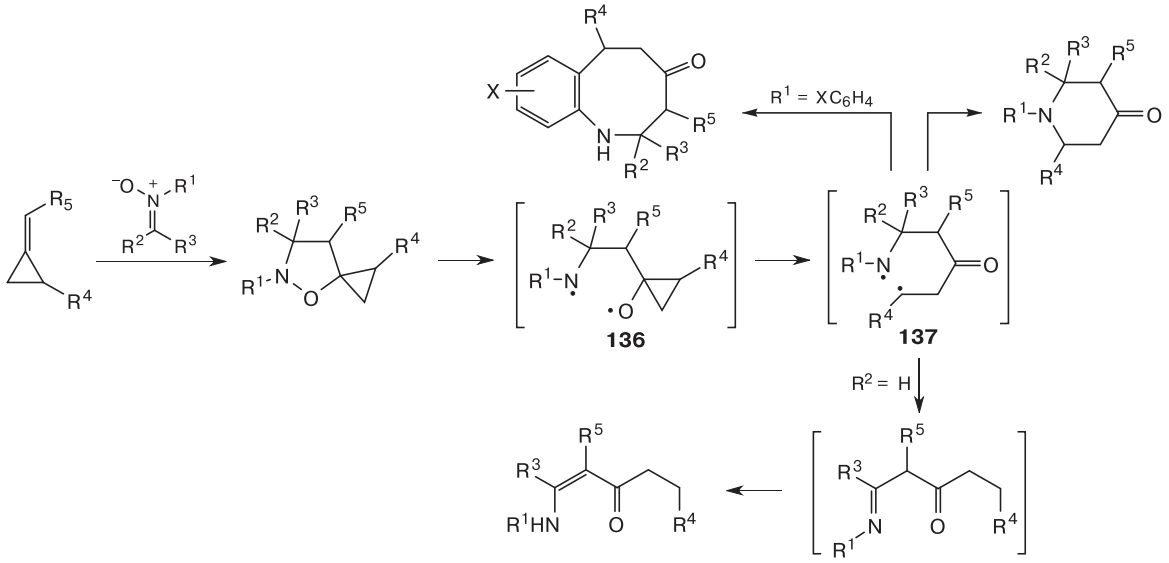
this reaction, 5-spirocyclopropane isoxazolidines, are readily underwent the Brandi—Guarna rearrangement that involved the cleavage of the relatively weak N—O bond proximal to three-membered ring followed by cyclopropane ring cleavage.[109,110] Depending on the nature of the substituents in nitrone and methylenecyclopropane, the reaction can produce either tetrahydropyrid-4-ones or enaminones. In the case of *N*-aryl-substituted nitrones, benzo-fused systems are formed. According to the plausible reaction mechanism suggested by Cordero and coworkers,[111] the reaction is initiated by a homolytic cleavage of the N—O bond to give biradical **136** followed by the cleavage of the C—C bond of the spiro-fused cyclopropane. Cyclization and H-shift in biradical **137** resulted in the final products (Scheme 42). Density functional calculations of the isomerization of 5-spirocyclopropane isoxazolidines confirmed the suggested methanism.[112—114]

Reaction of bicyclopropylidene **138** with cyclic nitrone **139a** afforded 4,5-bis(spirocyclopropane)isoxazolidine **140**, which underwent isomerization under the reaction conditions to give spiro(cyclopropanepyrido[2,1-*a*]isoquinolin-2-one) **141** as the main product and small amount of tricyclic isomer **142** (Scheme 43).[115] Reaction of enantiopure pyrrolidine *N*-oxide **143** with compound **138** gave predominantly indolizinone **144** arising from thermal isomerization of adduct **145** (see Scheme 43).[115]

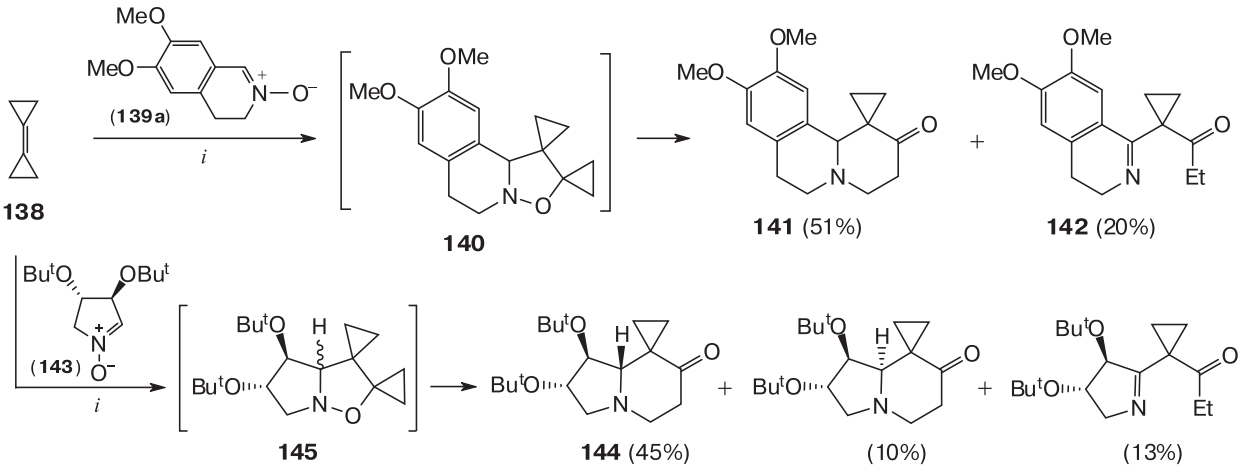
Temperature required for isomerization to occur is strictly dependent on the substituents in nitrone. Non-isomerized product can be isolated by carrying out the reaction at low temperatures. Thus, isoxazolidine **146** was synthesized in 84% yield by reacting compound **138** with nitrone **147** at 20 °C. However, when this reaction was carried out at 40 °C only isomerization product **148** was isolated in 45% yield. Reactions of compound **138** with nitrones **149** and **143** led to non-isomerized isoxazolidines **150** and **151** (Scheme 44).[116,117]

Feist´s ester **125a** reacted with ketonitrones **152** in toluene at 110 °C to give 5-spirocyclopropane isoxazolidines **153**. Under the reaction conditions, intermediate **153** underwent the Brandi—Guarna rearrangement resulting in a mixture of azeto[1,2-*a*]quinolines **154** and tetrahydropyridines **155** (Scheme 45).[118] Molchanov and coworkers[118] assumed that azetoquinolines **154** are resulted from the *trans*-annular cyclization of the corresponding

Scheme 42



Scheme 43



Conditions: *i*. xylene, 125 °C.

benzazocinones **156**. Azeto[1,2-*a*]quinolines **154** are oxidized with air oxygen upon the prolonged heating or upon treatment with DDQ to give 2-vinylquinolines **157** *via* the four-membered ring cleavage (see Scheme 45).[119]

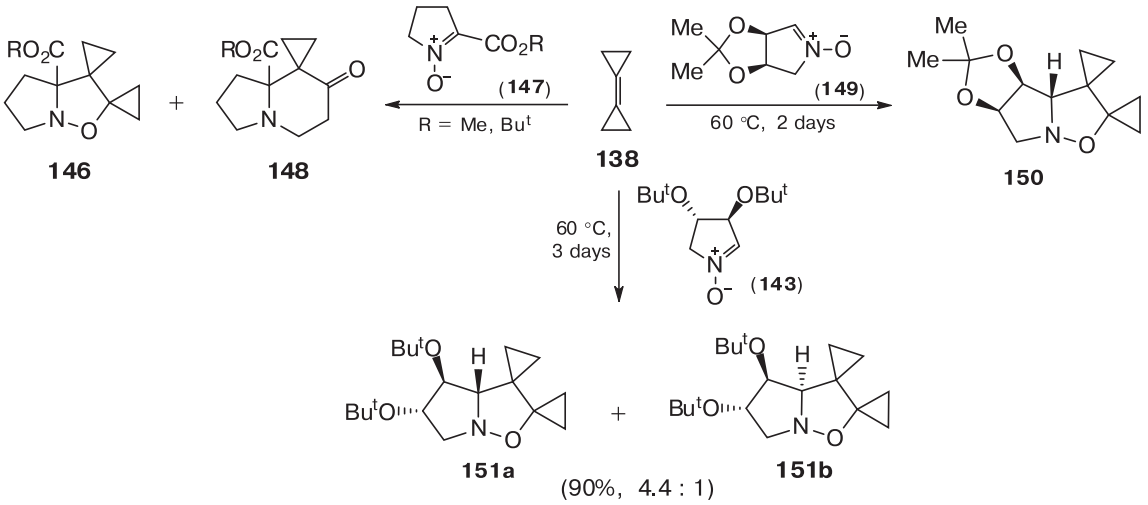
Dipolar addition of cyclic aldonitrones **34f** and **139** to Feist´s ester **125a** led to the mixtures of diastereomeric 5-spirocyclopropane isoxazolidines **158** and **159** (Scheme 46).[120] Both diastereomers of compound **159** underwent thermally induced rearrangement in xylene at 140 °C to afford pyrido[2,1-*a*]isoquinoline **160** and bicyclic enaminone **161** (see Scheme 46).[120]

Addition of ketonitrones **152** to methylenecyclopropane **126a** resulted in thermally unstable 5-spirocyclopropane isoxazolidines **162**. A series of subsequent transformations of compounds **162** gave rise to pyrrolo[1,2-*a*]-quinolinones **163** (Scheme 47).[118]

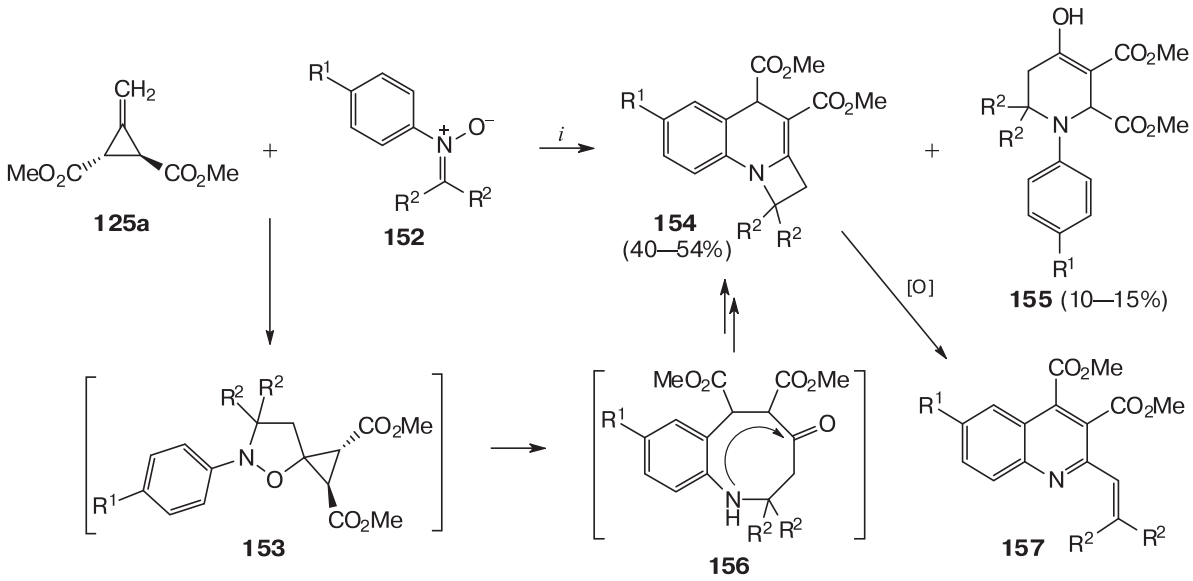
Thermal rearrangement of 5-spirocyclopropane isoxazolidines **164** derived from fluorenone *N*-arylnitrones **165** and methylenecyclopropanes **166** gave piperidinoles **167** in low yields (Scheme 48).[121] Substituted piperidin-4-ones **168** can be prepared in high yields by reduction of the ester group of compounds **164** followed by thermal rearrangement of the resulting hydroxymethyl derivatives **169** (see Scheme 48).[121]

Bis(methylene)cyclopropane **170** bearing two exocyclic double bonds is regioselectively added to the less substituted double bond of *C*,*N*-diaryl nitrones **34**. Thermal rearrangement of the initially formed adducts afforded

Scheme 44



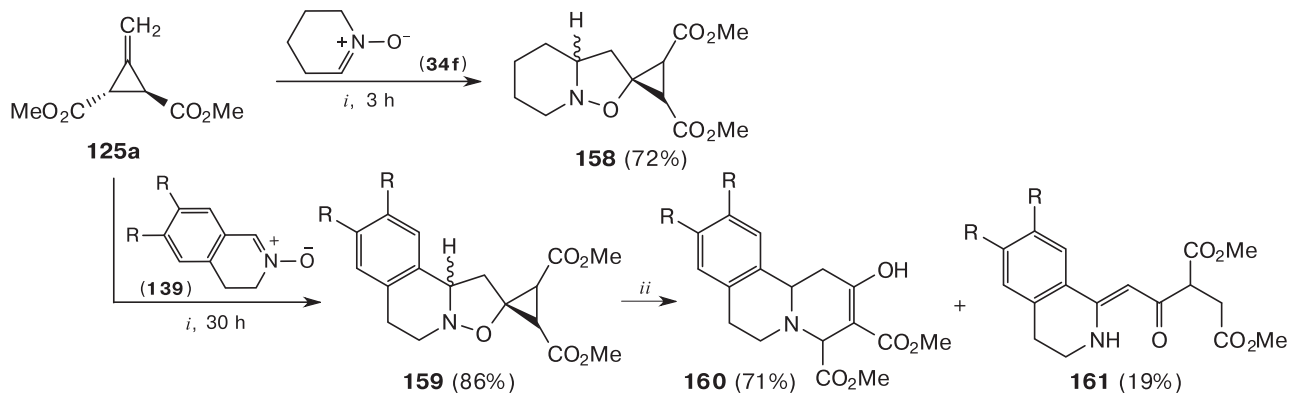
Scheme 45



R^1 = Me, OMe, Cl; R^2 = Ph, CO_2Me

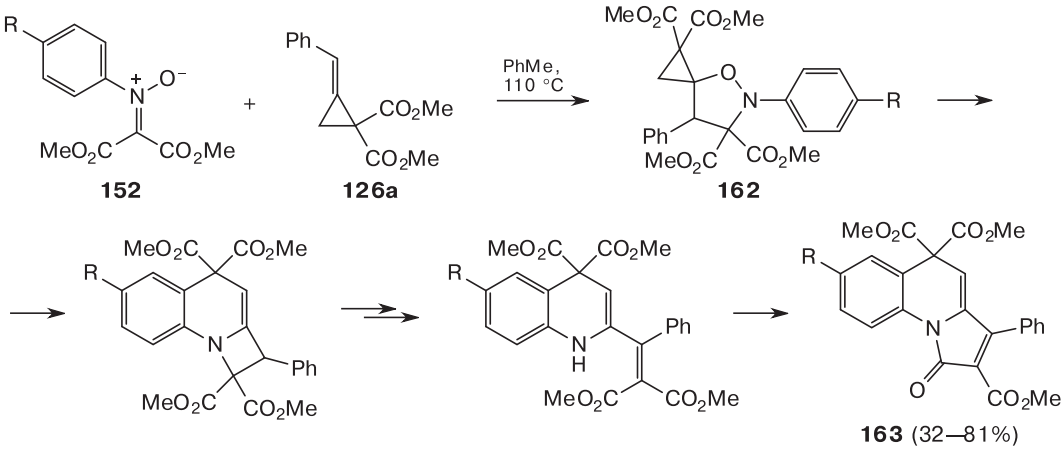
Conditions: *i*. toluene, 110 °C, 66—77 h.

Scheme 46

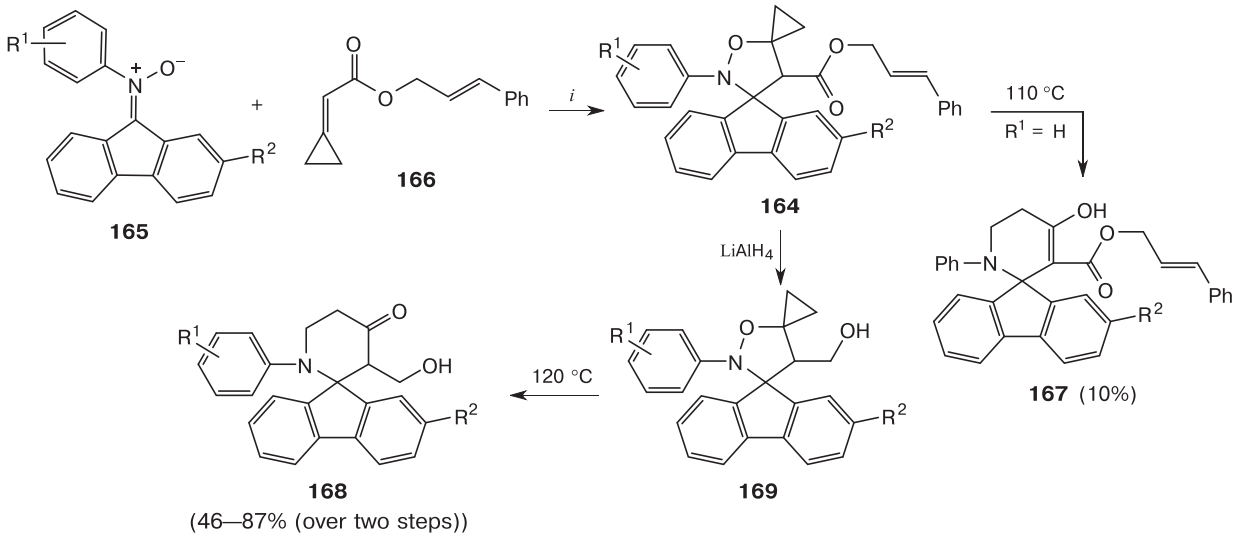


Conditions: *i*. benzene, 80 °C; *ii*. xylene, 140 °C.

Scheme 47



Scheme 48

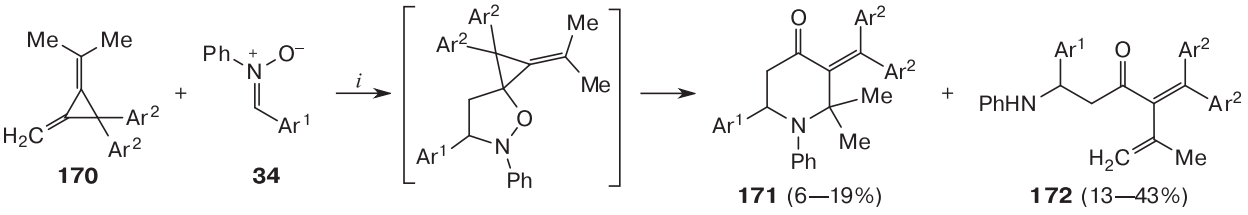


Conditions: *i*. 1,2-dichloroethane, 25 °C.

pyridinones **171** and open-chain dienes **172** in low yields (Scheme 49).[122]

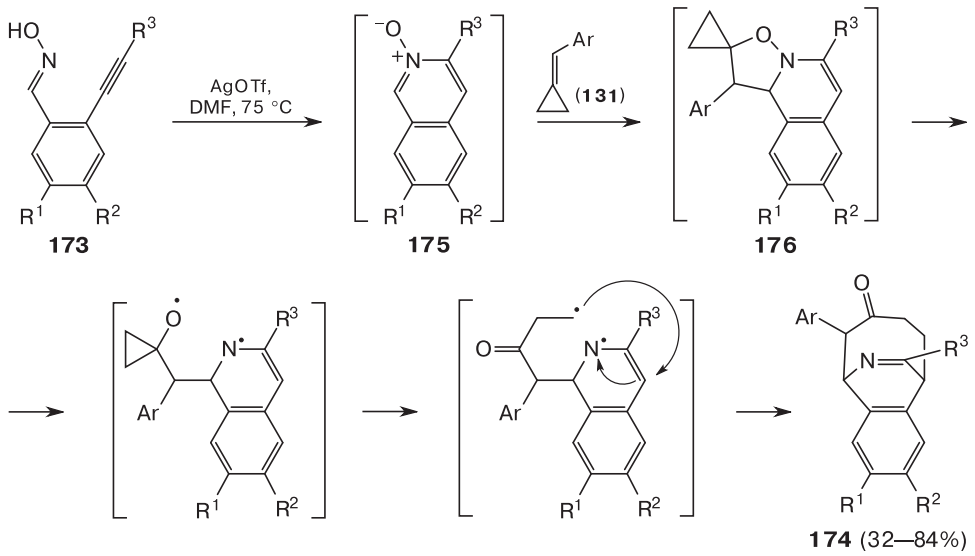
The AgOTf-catalyzed reaction of 2-alkynylbenzaldoximes **173** with arylmethylenecyclopropanes **131** at 75 °C gave benzo-7-azabicyclo[4.2.2]dec-7-en-4-ones **174** in good yields (Scheme 50).[123] Wu and coworkers[123] assumed that the reaction involved Ag^{I}-catalyzed 6-*endo* cyclization of benzaldoximes **173** to isoquinoline *N*-oxides **175** followed by 1,3-dipolar cycloaddition of **175** to methylenecyclopropane **131** to give 5-spirocyclopropane isoxazolidines **176**. Subsequent homolytic cleavage of the N—O bond of compounds **176** and

Scheme 49



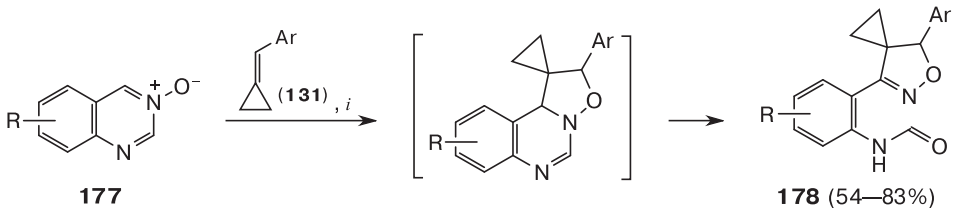
Conditions: *i*. benzene, 80 °C.

Scheme 50



R^1, R^2 = H, Me, F, Cl; R^3 = Ar

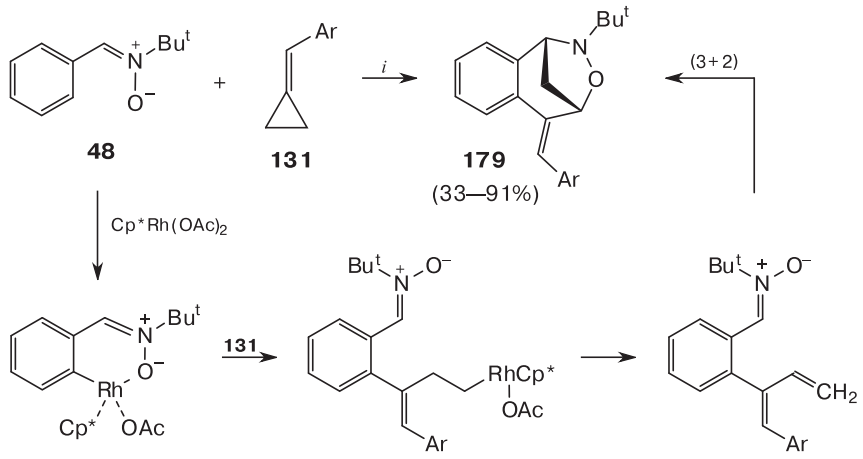
Scheme 51



R = H, Me, MeO, Cl

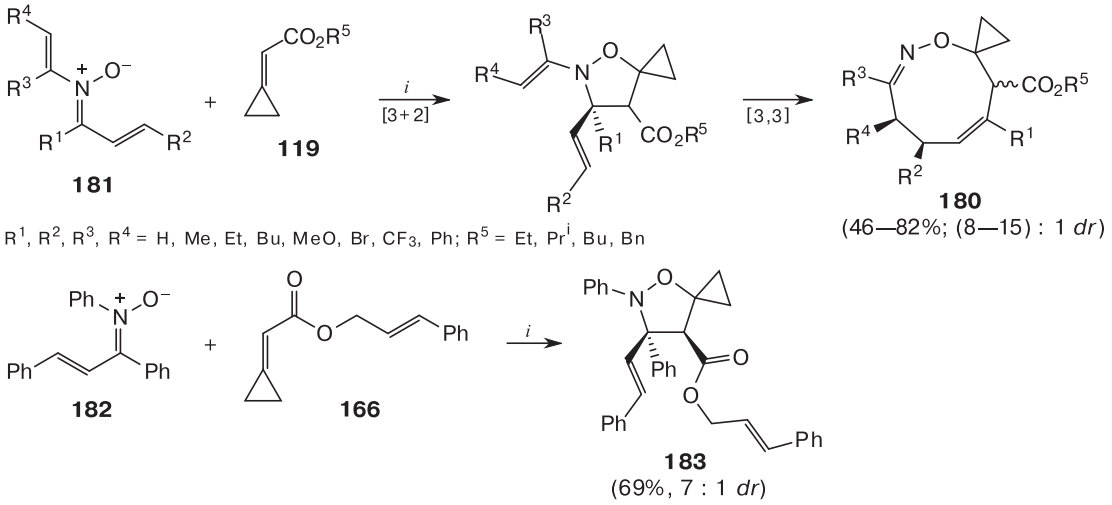
Reagents and conditions: *i*. $CuCl_2$ (5 mol.%), H_2O, 1,4-dioxane, 80 °C.

Scheme 52



Reagents and conditions: *i*. $[Cp^*Rh(OAc)_2]$/AgOAc, CF_3CH_2OH, 40 °C.

Scheme 53



Reagents and conditions: *i*. $Yb(OTf)_3$, ~20 °C, $MeOBu^t$.

intramolecular radical addition provided products **174** (Scheme 50).[123]

The Cu^{II}-catalyzed three-component reaction involving quinolizine 3-oxide **177**, methylenecyclopropane **131**, and a water molecule led to *N*-[2-(5-oxa-6-azaspiro[2.4]-hept-6-en-7-yl)phenyl]formamides **178** in good yields (Scheme 51).[124]

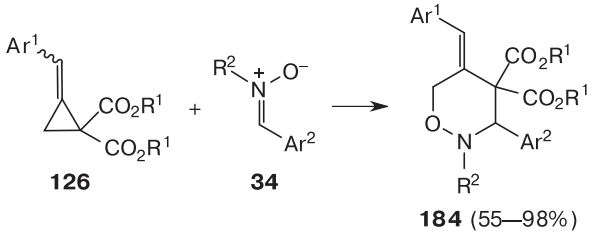
Rhodium-catalyzed reaction of *N-tert*-butyl-*C*-phenyl nitrone **48** and arylmethylenecyclopropanes **131** in the presence of AgOAc in trifluoroethanol at 40 °C resulted in tricyclic products **179** in 33—91% yields (Scheme 52).[125] Li and coworkers[125] suggested that the reaction is finalized by intramolecular (3+2) cycloaddition (see Scheme 52).[125]

Nine-membered nitrogen heterocycles **180** bearing three stereocenters were synthesized by the $Yb(OTf)_3$-catalyzed formal (7+2) cycloaddition of *N*-vinyl-α,β-unsaturated nitrones **181** to methylenecyclopropanes **119** (Scheme 53).[126] The plausible mechanism suggested by Mo and coworkers[126] involved (3+2) cycloaddition of nitrone to the double bond and the subsequent [3,3]-rearrangement. The reaction proceeded with high diastereoselectivity and gave products **180** in good yields.[126] In contrast, the reaction of *N*-aryl nitrones **182** with methylenecyclopropanes **166** carried out under the same conditions gave exclusively (3+2) cycloaddition products **183** (see Scheme 53).[126]

2.3. (3+3) Cycloaddition

Except the reactions involving the exocyclic double bond, methylenecyclopropane similarly to donor-acceptor cyclopropanes can undergo dipolar cycloaddition with three-membered ring opening. These reactions require catalysis with Lewis acids and follow formal (3+3) cycloaddition mechanism. Thus, the $Yb(OTf)_3$-catalyzed reaction of methylenecyclopropane dicarboxylate **126** with *C*-aryl-*N*-aryl(methyl)nitrones **34** gave rise to 5-methylene-1,2-oxazines **184** that are resulted from the cyclopropane ring opening at the C(1)—C(3) bond and subsequent addition of nitrone (Scheme 54).[127]

Scheme 54



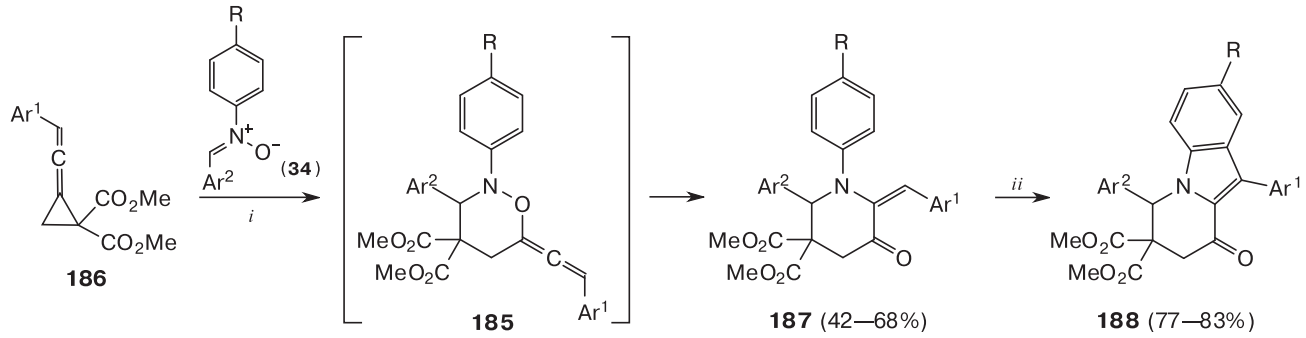
Reagents and conditions: $Yb(OTf)_3$, THF, 40 °C.

Oxazines **185** derived by the reaction of nitrones **34** with vinylidenecyclopropane dicarboxylates **186** are unstable and under the reaction conditions rearranged to piperidines **187**. Product **187** in the presence of HOTf underwent a ring closure to give indole derivatives **188**, which Wu and Shi[128] defined as a new synthetic approach to indoles (Scheme 55).

2.4. Reactions with nitrile oxides, carbonyl ylides and azomethine imines

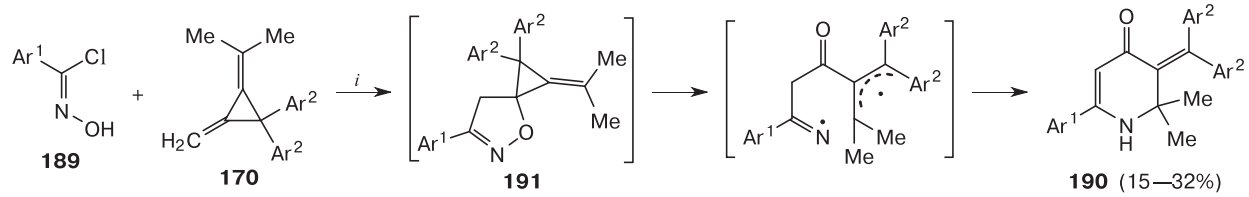
Nitrile oxides reacted with methylenecyclopropanes to give either 4- or 5-spirocyclopropane isoxazolines, which similarly to isoxazolidines are prone to thermal

Scheme 55



Reagents and conditions: *i*. $Yb(OTf)_3$, toluene, ~20 °C, *ii*. TfOH, CH_2Cl_2, 0—20 °C.

Scheme 56



Reagents and conditions: *i*. benzene, 60 °C.

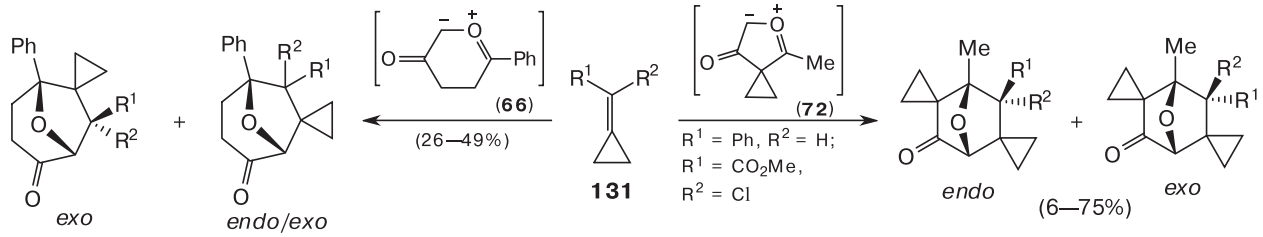
rearrangements leading to dihydropyridin-4-ones.[111] Reaction of nitrile oxides generated from hydroxymoyl chlorides **189** with bis(methylene)cyclopropanes **170** gave dihydropyridines **190** in moderate yields (Scheme 56).[122] Stepakov and coworkers[122] assumed that the reaction proceeded *via* cycloaddition of nitrile oxide to the unsubstituted double bond followed by rearrangement of the intermediate 5-spirocyclopropane isoxazoline **191** to the final adduct **190** (see Scheme 56).

Reaction of six-membered (**66**) and five-membered (**72**) carbonyl ylides generated by catalytic decomposition of the corresponding diazo compounds (see Schemes 20 and 21) with methylenecyclopropanes **131** bearing substituents at the double bond was not selective and gave mixtures of several possible isomers (Scheme 57).[129] It should be noted that the reactions involving methylenecyclopropane **131b** bearing an electron-withdrawing ester moiety and a chlorine atom at the double bound ($R^1 = CO_2Me$, $R^2 = Cl$) were most selective and gave the highest product yields.

Reactions of carbonyl ylides **66**, **69**, and **72** with bicyclopropylidene **138** led to cycloadducts **192—194** in the yields from low to moderate (Scheme 58).[129]

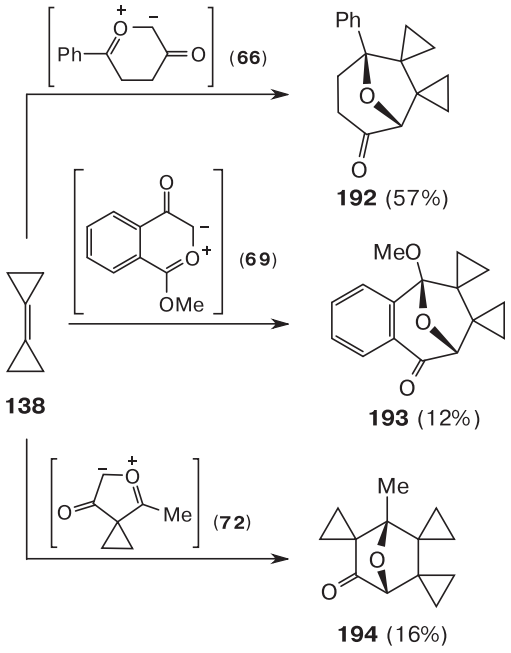
Rhodium-catalyzed cycloaddition of stable azomethine imines **195** to methylenecyclopropanes **131** carried out under conditions similar to those used for their reactions with nitrones **48** (see Scheme 52) afforded [3.2.1]tricyclic compounds **196** in 45—82% yields (Scheme 59).[125]

Scheme 57

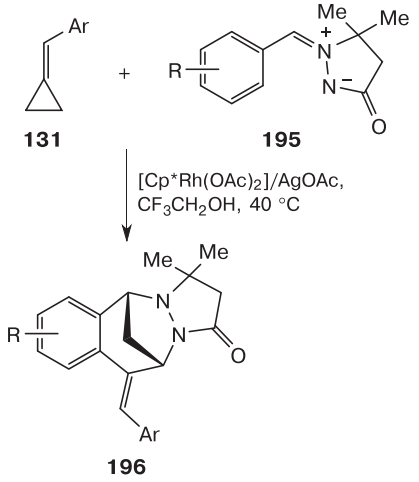


R^1 = Ph, C_7H_{15}, CO_2Me, Br; R^2 = H, Cl

Scheme 58



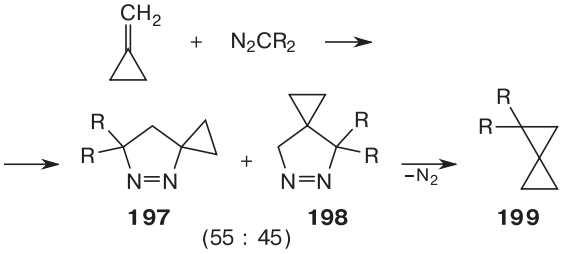
Scheme 59



2.5. Reactions with diazo compounds and other dipoles

Dipolar cycloaddition of diazo compounds to methylenecyclopropanes was well studied. Regioselectivity of these reactions strictly depend on the nature of the substituents at the three-membered ring and in the diazo compound. For instance, the reaction of methylenecyclopropane with diazomethane proceeded with low selectivity to give 1-pyrazolines **197** and **198**, thermal decomposition of which led to release of nitrogen and formation of spiropentane **199** (Scheme 60).[130]

Scheme 60



R = H, D

Reaction of 2,2-difluoromethylenecyclopropane **200** with diazomethane also led to the mixtures of regioisomeric 1-pyrazolines **201** and **202**, while the reaction with diphenyldiazomethane gave rise exclusively to pyrazoline **201** (Scheme 61).[131] Similar alteration of selectivity was observed in the reactions of methyl 2-chloro-2-cyclopropylideneacetate **131b** with diazomethane, dimethyl-, and diphenyldiazomethane resulting in regioisomeric cycloadducts **204** and **205** (see Scheme 61).[132]

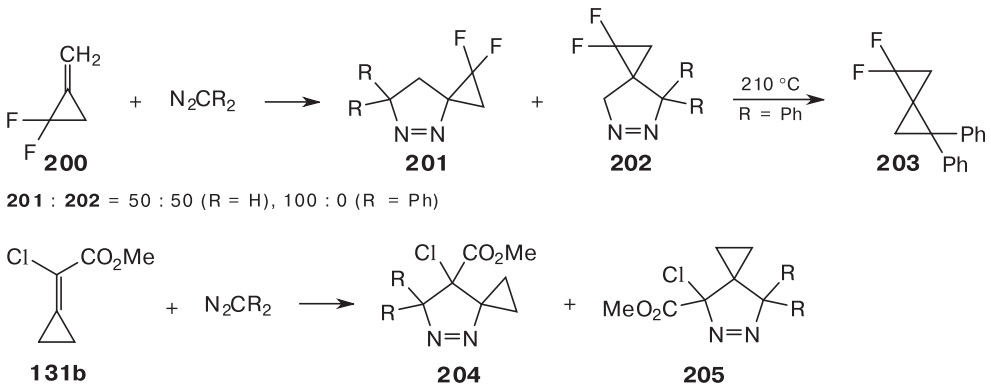
Diazocyclopropane **206** generated from *N*-(cyclopropylidenemethyl)-*N*-nitrosourea **207** reacted with methylenecyclopropane to give a mixture of pyrazoline **208** and tricycloheptane **209**.[133] Reactions of diazomethane with ring fused alkylidenecyclopropanes **210** regioselectively afforded pyrazolines **211**. Thermal decomposition of compounds **211** gave no spiropentane derivatives but resulted in ring expansion giving rise to methylenecyclobutanes **212** (Scheme 62).[134]

Reaction of methylenecyclopropane **213** bearing two electron-withdrawing ester groups at the three-membered ring with diazomethane selectively afforded dihydropyrazole **214**. Ring opening of compound **214** accompanied by elimination of bromide anion and subsequent aromatization gave rise to pyrazole **215** in 45% yield (Scheme 63).[71]

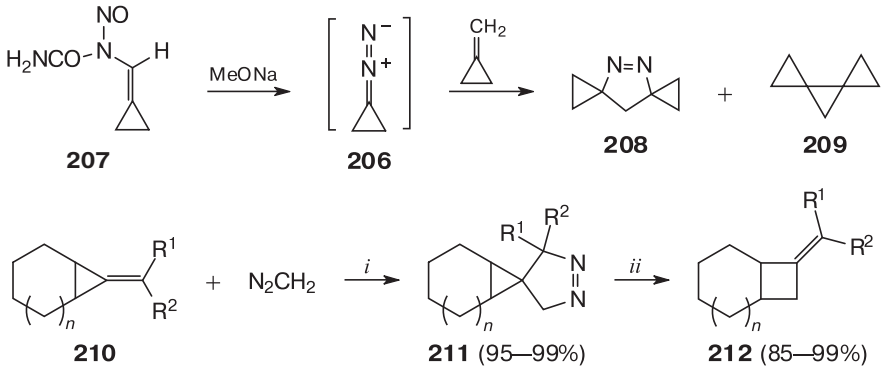
Vinylidenecyclopropanes **186** reacted with diazo compounds **216** generated *in situ* from the corresponding aldehydes and tosylhydrazide to afford pyrazoles **217** and **218** (Scheme 64).[135] Regioselectivity of this reaction depends on the nature of the substituents R^1 at the cyclopropane double bond. When R^1 is an aromatic substituent or benzyl group, the reaction selectively provided pyrazoles **218** in 10—88% yields. When R^1 = H, the mixtures of pyrazol-5-yl- (**217**) and pyrazol-4-ylcyclopropanes (**218**) were obtained in the yields of 25—30% and 47—53%, respectively. Wu and Shi[135] assumed that compounds **218** were formed *via* generation of diazo compound, isomerization of vinylidenecyclopropane to acetylene derivative, (3+2) cycloaddition, and tautomerization (see Scheme 64).

Reactions of other diazo compounds with methylenecyclopropanes are poorly studied. For example, reaction of diazo ketones **219** with *N*-(2-cyclopropylidenemethylphenyl)phosphanimines **220** gave good yields of quinolines **221** (Scheme 65).[136] Zhao *at al.*[136] believed that the reac-

Scheme 61



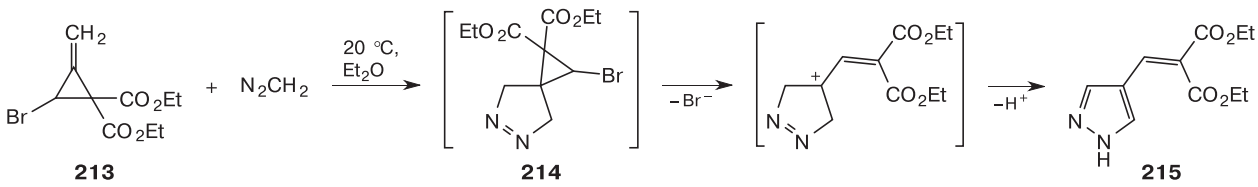
Scheme 62



$R^1 = R^2$ = Alk; *n* = 1, 2

Reagents and conditions: *i*. diethyl ether, ~20 °C, 3 days; *ii*. *o*-xylene, 130 °C, 30 min.

Scheme 63



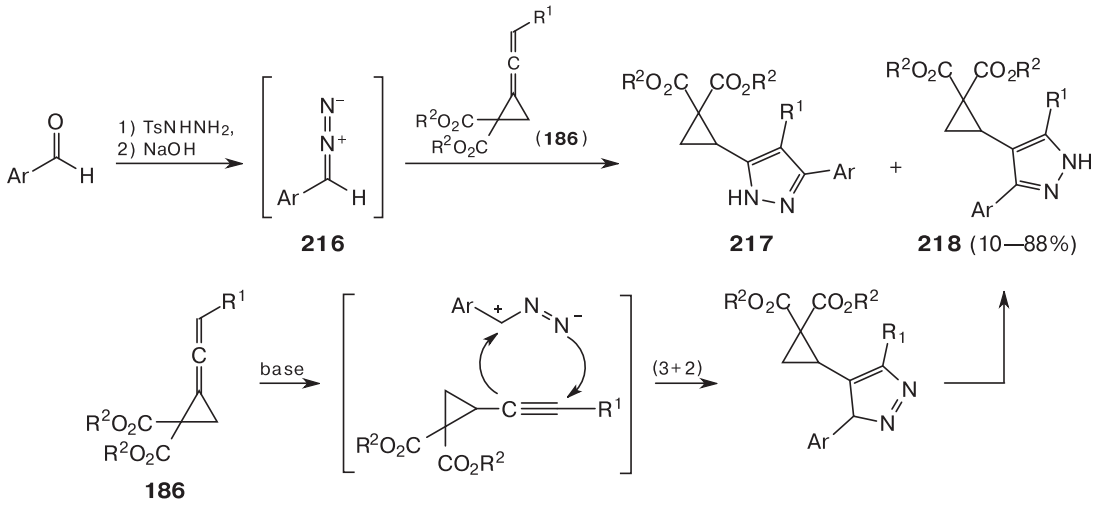
tion involved the Wolf rearrangement of α-diazo ketones **219** to ketenes **222**, the aza-Wittig reaction of the latter at the C=P bond of phosphane imines **220** to give imines **223**, and subsequent intramolecular cyclization to afford the final products **221** (see Scheme 65).[136]

Reaction of methylenecyclopropanes **131** with phenyl azide gave triazolines **224** in 70% yield. Under photolytic conditions, compounds **224** liberated nitrogen to form 1-phenylazaspiropentanes **225** in 90% yield (Scheme 66).[137,138] Other regioselectivity was observed in the reaction of phenyl azide with methylenecyclopropanes **125a** and **226a,b** bearing the ester groups at the carbon atoms of the three-membered ring. In this case, the final products are triazoles **227** resulting from the three-membered ring opening of the intermediate adducts **228** (see Scheme 66).[139]

Reaction of cyclopropylidenetetrazole **229** with methyl azide gave rise to spirocyclic derivative **230** in 30% yield (Scheme 67).[140]

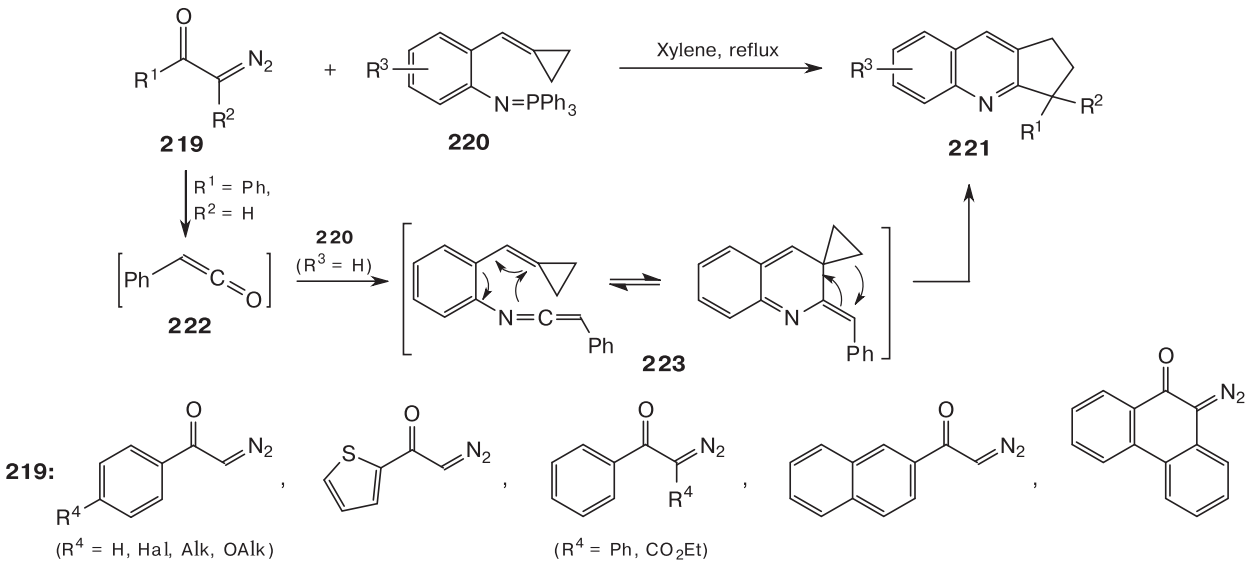
Reaction of nitrile ylide **231** generated from *N*-(4-nitrobenzyl)benzimidoyl chloride **232** with methylenecyclopropane **131b** exclusively afforded pyrrole **233** in 41%

Scheme 64

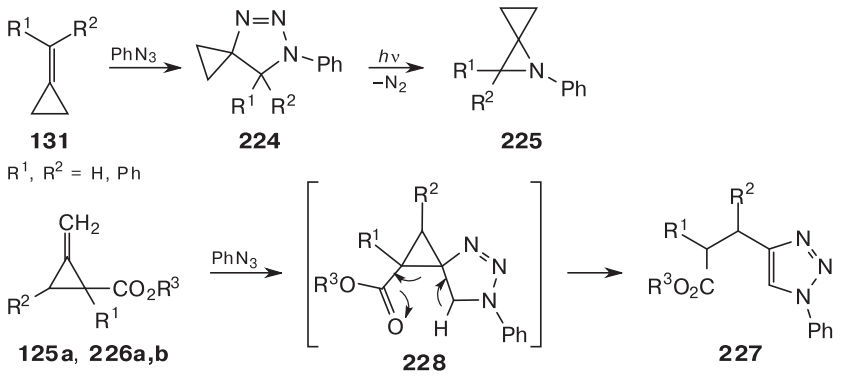


R^1 = H, Bn, Ar; R^2 = Me, Bn

Scheme 65

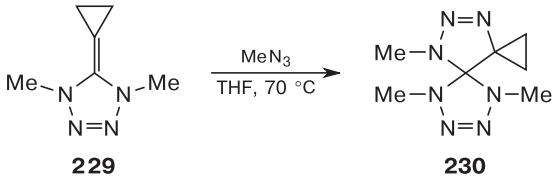


Scheme 66



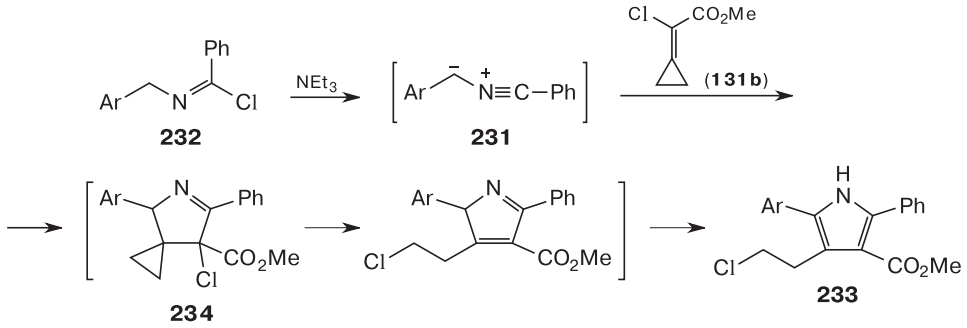
R^1 = H, R^2 = CO_2Me, R^3 = Me (**125a**);
R^1 = R^2 = H, R^3 = Et (**226a**); R^1 = Me, R^2 = H, R^3 = Et (**226b**)

Scheme 67



229 **230**

Scheme 68



232 **231** **234** **233**

Ar = 4-$NO_2C_6H_4$

isolated yield (Scheme 68).[132] The plausible reaction mechanism suggested by de Meijere and coworkers[132] involved cyclopropylcarbinyl-homoallyl rearrangement of the initially formed adduct **234** and subsequent 1,2-hydride shift that led to product **233**.

Conclusions

The data reviewed herein indicated that an essential progress in studies and synthetic application of the reactivity of the compounds bearing strained three-membered ring was archived during last two decades. Combination of cyclopropyl ring and the multiple bond in one molecule significantly expands the synthetic application of these compounds in rational organic synthesis. Dipolar cycloaddition reactions that occur in a single step *via* the concerted mechanism are mainly characterized by high regio- and stereoselectivity and allow synthesis of complex heterocyclic structures with predetermined configuration. High strain energy of these compounds promoted such reactions but, in some cases, often led to tandem transformations thus significantly expanding the synthetic potential of the reaction. These reactions were used to synthesize a wide variety of heterocyclic compounds bearing pyrrolidine, tetrahydrofuran, aziridine, oxazine, isoxazoline, pyridine, isoquinoline and some other units that are formed fused and spirocyclic systems. Nevertheless, numerous promising applications of small rings are still poorly explored. For instance, the reactions of cyclopropenes and methylenecyclopropanes with many dipoles are studied insufficiently or even scarce. Moreover, there is little research on catalytic methods for dipole generation and application of metal complex catalysts and organocatalysts in the synthesis of chiral compounds. Multicomponent reactions that allow synthesis of the target products without isolation of the intermediates are also of great promise.

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The authors declare no competing interests.

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