

**1,3-DIPOLAR CYCLOADDITIONS TO CYCLOPROPENES:
CONVENIENT WAY FOR THE SYNTHESIS OF HETEROCYCLIC SYSTEMS**

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Abstract. *A range of selective and synthetically useful transformations that utilize such a class of strained cyclic compounds as cyclopropene and its various derivatives in the construction of heterocyclic systems were described. Both classical 1,3-dipolar [3+2]-cycloaddition reactions to cyclopropene double bond and formal [3+3]-cycloaddition reactions were considered.*

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1. Introduction

Heterocyclic compounds account for more than half of all known organic compounds including some of the most important compounds for humans. Therefore this class of compounds constantly attracts the special attention of chemists developing and improving selective synthesis methods that provide access to a huge variety of structural and functional characteristic features of these compounds.

The purpose of this review is to summarize and analyze methods that utilize such a class of strained cyclic compounds as cyclopropene and its various derivatives to produce heterocyclic systems by means of 1,3-dipolar (cyclo)addition reactions ([3+2]- and formal [3+3]-cycloadditions). Their use in the synthesis of heterocyclic compounds is currently experiencing new spurt and, thus, it seems relevant to reflect the current state. Special attention will be paid at newly arised asymmetric formal [3+3]-cycloaddition reactions of stable 1,3-dipoles to cyclopropenes that themselves act as 1,3-dipole source.

Although cyclopropenes are known for more than 100 years, it was not until about 1970 that the exploration of the cyclopropene chemistry really began. In fact the utility of such building blocks for organic synthesis has been recognized only in recent years. All cyclopropene derivatives, including unsubstituted cyclopropene, are highly strained molecules, but the stability of many of them is sufficient for their use in synthetic purposes (both in pure form and as intermediates). The development of methods for the synthesis of heterocyclic compounds using these substrates is essentially based on the use of reactive reagents containing one or more heteroatoms. At the same time, the presence of a strained cyclopropane fragment in the product can lead to further rearrangements of the formed (hetero)cyclic framework. Meanwhile, the high energy contained in these compounds gives a huge potential for their application in organic syntheses, which has only been partially disclosed in recent decades.^{1,2}

The huge potential in the formation of all molecular diversity, the possibility of obtaining different (poly) spiro and fused heterocyclic frameworks with wide variability in the introduction of different functional groups into the resulting framework, is realized by a variety of possible combinations of substrates or their intermediates (Figure 1). It is worth noting that in many cases, reactions involving such unstable intermediates are the only possible approaches to the synthesis of complex polycyclic compounds with a wide range of pharmacological activity.

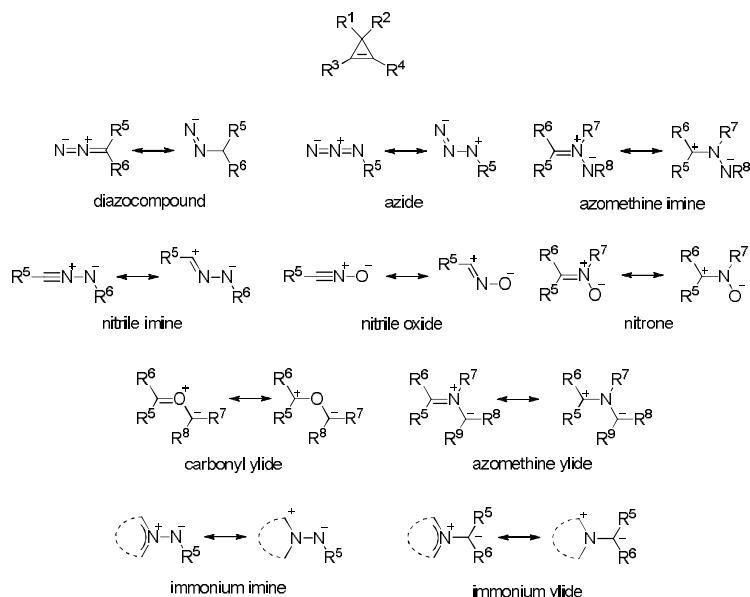


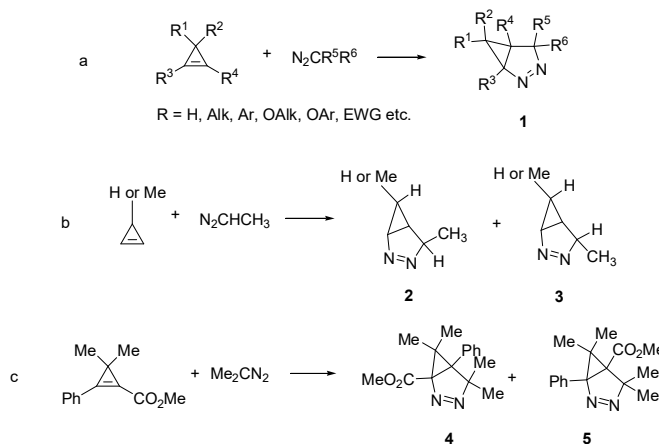
Figure 1. Structures of cyclopropenes and 1,3-dipoles.

2. Diazocompounds

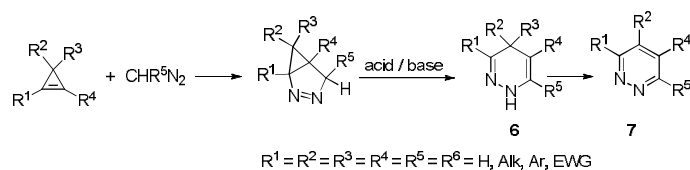
Diazoalkanes and related compounds readily undergo dipolar cycloaddition to cyclopropenes leading initially to pyrazolines. These are the most studied reactions of 1,3-dipolar cycloadditions to cyclopropenes. Therefore we will give here short common overview and some interesting applications. Historically the first examples of reaction of cyclopropene with diazocompounds were described by Wilberg and Bartley in 1960. They have found that interaction of cyclopropene with diphenyldiazomethane or ethyl diazoacetate proceeds readily to give 1:1 addition compounds³. Since that a large pull of cycloaddition reactions was described and used for synthesis of various carbo-⁴⁻⁶ and heterocyclic compounds.⁴⁻²⁵ While reactions of symmetrically substituted cyclopropenes^{3,7-9,16,17} or diazo compound lead to sole addition product **1** (Scheme 1, a), using unsymmetrically substituted compounds can lead either to epimeric mixture^{7-9,10} **2** and **3** (in case of diazocompounds, Scheme 1, b) or structural isomers^{9,10} **4** and **5** (for cyclopropenes, Scheme 1, c). Diazoalkane addition to cyclopropenes having electron-withdrawing substituents at the double bond generally occurs faster and leads to the regioselectivity predicted on electronic or frontier orbital grounds (still minor amounts of the regioisomers are isolated in some cases).^{5,11-15}

For instance, diphenyldiazomethane reacts with both cyclopropene or 1-methylcyclopropene to produce bicyclic pyrazolines, that can be further transformed by irradiation to corresponding 2,2-diphenylbicyclo[1.1.0]butanes.⁴ 1,3-Dipolar cycloaddition of 3-diazo-1-propene to 3,3-dimethylcyclopropene at -50 °C furnishes 6,6-dimethyl-4-vinyl-2,3-diazabicyclo[3.1.0]hex-2-ene as sole *exo*-isomer.⁸

However sometimes the primary formed pyrazoline cycloadducts are very sensitive to acid or base and undergo rearrangement under reaction condition or during working up/purification step and a number of reports indicate that the products are in fact dihydropyridazines^{5,7,15} **6** or pyridazines¹² **7** (Scheme 2).

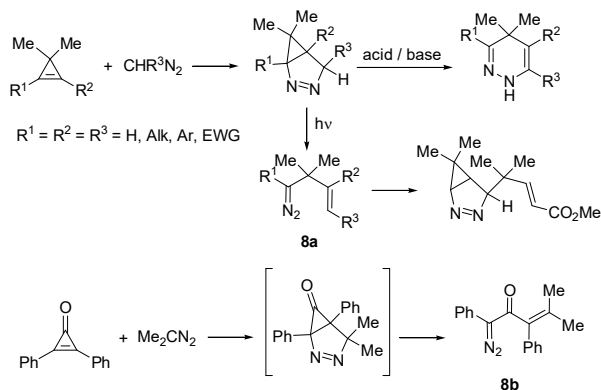


Scheme 1. Pyrazoline formation by cycloaddition of cyclopropenes with diazocompounds.



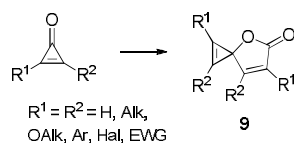
Scheme 2. Pyridazine formation by cycloaddition of cyclopropenes with diazocompounds.

A further complication is the retro conversion of primary formed pyrazolines to diazocompounds **8a** that can be brought about in many cases either by heat or by light, coupled to the secondary decomposition of these diazospecies (Scheme 3).⁵ Sometimes primary formed product is not stable enough due to arising additional tension and transform to new diazocompound under reaction condition **8b** (Scheme 3). On the other hand, pyrazolines can be converted on brief heating or on photolysis at low temperature to yellow solutions of diazocompounds, which can survive for a few hours at room temperature.⁸ Such obtained new diazospecies can be further used for the construction of heterocyclic rings by trapping with the excess of starting material or with other reactive dipolarophiles.⁷



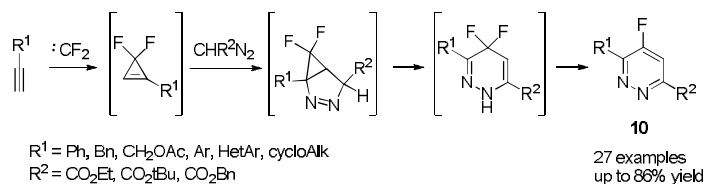
Scheme 3. Retro conversion of primary formed pyrazolines with formation of new diazospecies.

It should be noted that cyclopropenones themselves undergo thermal dimerization to yield spiroactones **9** (Scheme 4).¹⁸ This is a formal 1,3-dipolar cycloaddition between the cyclopropene single bond of one molecule and the carbonyl group of another molecule, that can occur by the nature of cyclopropenones, since they have both polarized and strained characters.



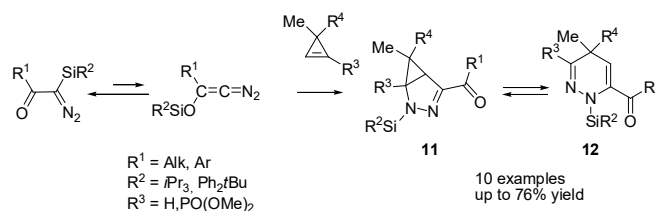
Scheme 4. Spiroactone formation by thermal dimerization of cyclopropenones.

An easy access to 5-fluoropyridazines **10** by [2+1]/[3+2]-cycloadditions between terminal alkynes, difluorocarbene and diazo compounds was reported by Tran.¹⁹ A wide range of 5-fluoropyridazine derivatives was synthesized from readily available starting materials without necessitating of any intermediates isolation (Scheme 5).



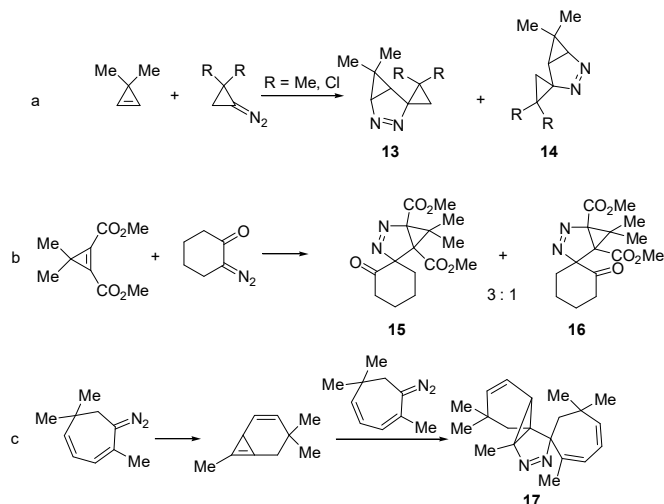
Scheme 5. Fluoropyridazines formation by cycloadditions between terminal alkynes, difluorocarbene and diazo compounds.

An interesting cycloaddition of diazosilanes to cyclopropenes was described by Muschauer and Maas.²⁰ They have found that in solutions, in most cases, formed 2-silyl-2,3-diazabicyclo[3.1.0]hex-3-enes **11** and 1-silyl-1,4-dihydropyridazines **12** are in temperature- and solvent-dependent equilibrium, while in the absence of solvent, either a liquid mixture of these two products or only one of the two structural isomers was obtained (Scheme 6). At the same time, bearing an electron-withdrawing group at the double bond cyclopropene produce only the 1-silyl-1,4-dihydropyridazines **12**.



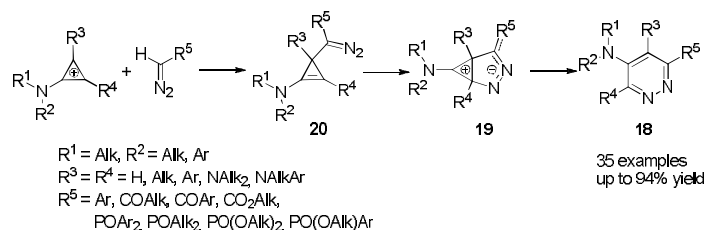
Scheme 6. Cycloaddition of diazosilanes to cyclopropenes.

Using cyclic diazo-derivatives is a simple route to fused polycyclic compounds. For instance, spiro 2,3-diazabicyclo[3.1.0]hex-2-ene-4,1'-cyclopropanes **13** and **14** are readily available *via* reaction of corresponding cyclopropenes with cyclic diazo compound (Scheme 7, a).²¹ Cyclic diazoketones (such as 2-diazocyclohexanone) react with cyclopropene derivatives leading to 2'-oxo-2,3-diazaspiro[bicyclo[3.1.0]hex-2-ene-4,1'-cyclohexane scaffold **15** and **16** (Scheme 7, b).²² Also non-classical dimerization of tosylhydrazone derivative of eucarvone leading to fused polycycle **17** was described by Baumann et al. The key step in this process is dipolar cycloaddition of corresponding diazo compound to transient cyclopropene (Scheme 7, c).²³



Scheme 7. Synthesis of spirofused polycycles.

An interesting way to mono-, di- and triaminopyridazine derivatives **18** *via* reaction of aminocyclopropenyl cation with various diazomethane derivatives was described by Heydt et al. While the formation of the cation **19** could be explained as a 1,3-dipolar cycloaddition, complete reaction mechanism was interpreted in terms of an initial electrophilic substitution of the diazoalkane with formation of corresponding cyclopropene derivative **20**, which undergo [1,5]-cyclization to form zwitterion **19** followed by valence bond isomerization to the pyridazine derivatives **18** (Scheme 8).^{24,25}

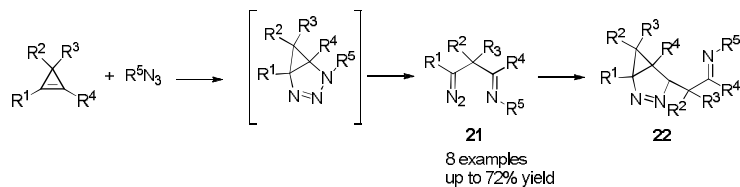


Scheme 8. Aminopyridazine formation *via* reaction of cyclopropenyl cation with various diazocompounds.

3. Azides

There are several examples for cycloaddition of cyclopropenes to azides.^{7,11,13,26} All of them are accompanied by rearrangement of an initially formed dipolar cycloadduct (reverse 1,3-dipolar addition) to give diazocompound **21**. The latter can react with the excess of cyclopropene to afford 2:1 adduct (**22**) with the large substituent at C-4 in the less hindered exo position (Scheme 9). But more often these formed diazocompounds can be isolated.

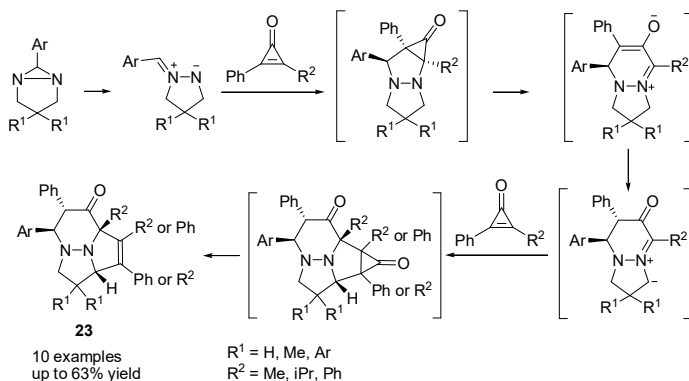
Recently the ability of cyclopropenes to form adducts with azides was investigated regarding their possible use in the study of biological processes *in vivo*, since azide and tetrazine cycloadditions have become central reactions in the rapidly developing field of cellular component labeling with bioorthogonal reactions.²⁷⁻²⁹ However, it was found that studied cyclopropene derivatives (1-methyl-, 1,3-dimethyl- and 3,3-dimethylcyclopropene) show high rates of reaction with tetrazines. Still there is an example of utilizing of methylcyclopropenes and organic azides in tandem for cellular metabolic labeling.²⁸



Scheme 9. Addition of azides to cyclopropenes.

4. Azomethine imines

There are rare examples of azomethine imines cycloaddition to cyclopropenes. However it was described formation of fused tricyclic system with diazacyclopenta[*cd*]indene framework **23** as a result of unusual successive cycloaddition of two cyclopropenone molecules to azomethine imine generated by thermally induced ring opening of diaziridine fragment of 6-aryl-substituted diazabicyclohexanes (Scheme 10).^{30,31}



Scheme 10. Construction of 4a,7a-diazacyclopenta[*cd*]inden-7-one framework by reaction of cyclopropenones with 1,5-diazabicyclo[3.1.0]hexanes.

The first step of cycloaddition proceeds fully regioselectively, leading to the adduct with vicinal arrangement of the aryl groups. Subsequent ring expansion of formed during first step cycloadduct gives azomethine ylide which is stabilized *via* addition of second cyclopropenone molecule followed by carbon monoxide extrusion. Regioselectivity of this step is proposed to be determined by spatial interactions between substituents in the cyclopropenone molecule and trimethylene bridge of the diazabicyclohexane (Figure 2). In all the cases approach of second cyclopropenone molecule to intermediate azomethine ylide should give rise to spatial interactions between substituent in cyclopropenone molecule and one of methyl group in trimethylene bridge. Such reaction of 2-methyl-3-phenylcyclopropenone with 3,3-dimethyl substituted 6-aryl-1,5-diazabicyclo[3.1.0]hexanes lead to sole regioisomer (with vicinal arrangement of the methyl groups), while mixture of two regioisomers are formed without these methyl groups at 3 position. Using of 2-isopropyl-3-phenylcyclopropenone result in sole isomer formation with vicinal arrangement of isopropyl and phenyl groups.

Another example that could be formally considered as azomethine imine cycloaddition is a base-promoted reaction between acylhydrazones and cyclopropenes, *in situ* generated from 2-aryl-substituted alkyl 1-chlorocyclopropanecarboxylates (Scheme 11).³² Authors noticed that this protocol is transition-metal free and apparently different from classic 1,3-dipolar cycloaddition reaction catalyzed by Lewis or Brønsted acid. They reported two step mechanism included addition of nitrogen anion of starting hydrazine to *in situ* generated cyclopropene followed by cyclization reaction. However used for cyclopropene generation base, CsCO_3 , might also act as a rather weak catalyst that *via* coordination with imine nitrogen could lead the

azomethine imine formation (analogously to well-known metal-catalyzed dipolar cycloaddition). Also they reported quick aromatization reaction of formed pyrazolidines **24** to pyrrole **25** derivatives.

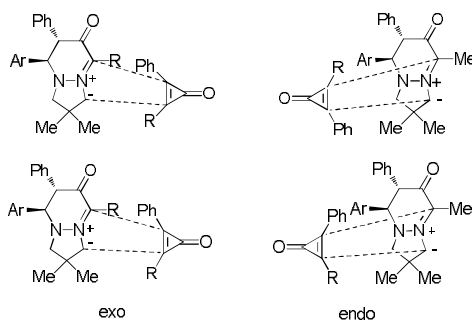
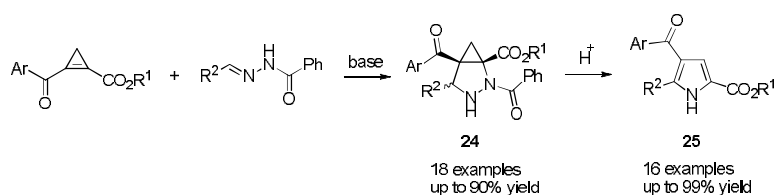


Figure 2. Possible *exo* and *endo*-approaches of second cyclopropanone molecule to intermediate azomethine ylide.



Scheme 11. Formation of bicyclic pyrazolidines *via* tandem reaction of acylhydrazones and alkyl 2-aryl-1-chlorocyclopropanecarboxylates and aromatization of formed pyrazolidines to pyrroles.

5. Nitrile imines

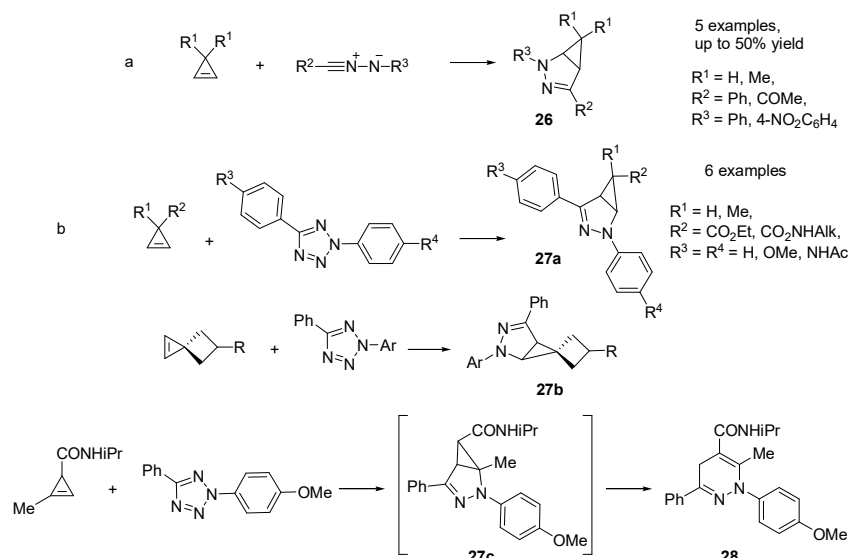
Generated from either hydrazone chlorides^{20,33} (Scheme 12, a) or tetrazoles³⁴⁻³⁸ (Scheme 12, b) nitrile imines readily undergo 1,3-dipolar cycloadditions to cyclopropenes leading to pyrazole derivatives **26** and **27a-c**. It was however found during seeking good bioorthogonal chemical reporters that primary formed from 1,3-disubstituted cyclopropane (*N*-isopropyl-2-methylcycloprop-2-enecarboxamide) and nitrile imine pyrazole derivative **27c** was unstable and undergo rearrangement to corresponding dihydropyridazine **28**.

High reaction rate of photogenerated from tetrazole nitrile imines have found implementation in studying of bioorthogonal transformations. It was found that 1,3- and 3,3-disubstituted as well as spirocyclic cyclopropenes have distinct reactivity towards commonly used tetrazines and nitrile imines (1,3-disubstituted cyclopropenes are all more reactive towards tetrazines, while latter react rapidly with nitrile imines). Moreover, nitrile imine generation in this case could proceed in the presence of tetrazine with no observable side reactivity that make it possible to use them in tandem for biomolecule labelling. Indeed, ability to selectively modify isomeric cyclopropenes, and therefore ultimately target them to discrete biomolecules, will facilitate multicomponent imaging studies *in vitro* and in live cells.³⁴⁻³⁸

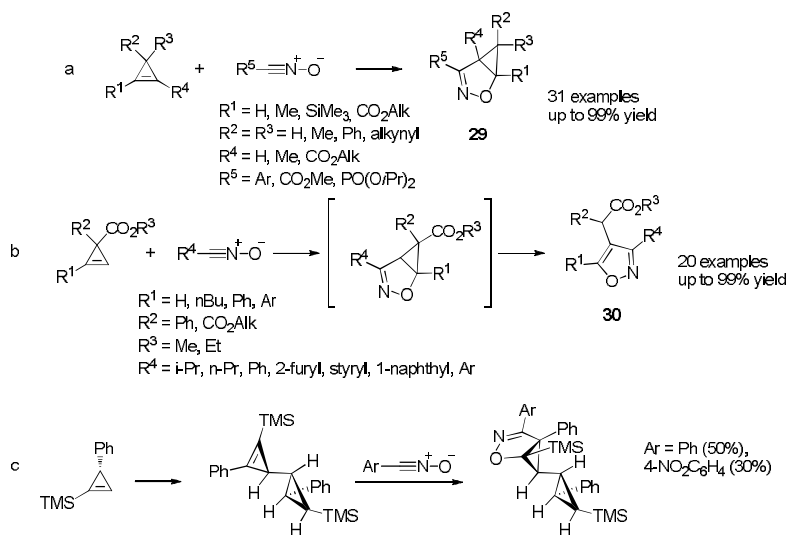
6. Nitrile oxides

Nitrile oxides were found readily undergo 1,3-dipolar cycloadditions to cyclopropenes yielding isoxazolines **29** and isoxazoles **30**. Cycloadditions of unactivated cyclopropenes lead to incorporated into 2-oxa-3-azabicyclo[3.1.0]hex-2-ene scaffold isoxazolines **29** (Scheme 13, a).^{16,17,33,39,40} Phosphorylnitrile oxide could also be utilized for synthesis of phosphorus-containing bicyclic isoxazolines **29**, as it was found by Pavlov et al.⁴¹ The reaction of symmetrically substituted cyclopropenes proceed smoothly leading to one isomer, while unsymmetrically substituted derivatives could form two stereoisomeric products which are easily separated by preparative chromatography. It was found by Wang et al. that deactivated cyclopropenes undergo appropriate cycloaddition followed by opening of cyclopropane ring with formation of isoxazole

derivatives **30** (Scheme 13, b).⁴² Nitrile oxide cycloaddition reaction was described also for 1-trimethylsilyl-3-phenylcyclopropene dimerization product (Scheme 13, c).⁴³



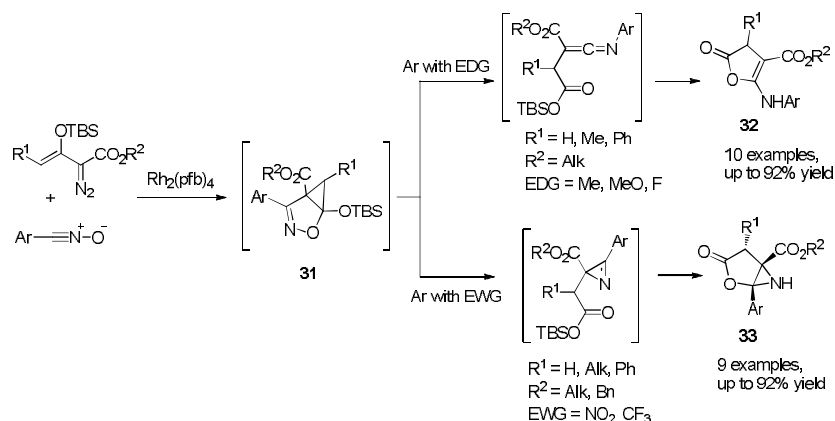
Scheme 12. Pyrazole formation by cycloaddition of nitrile imines to cyclopropenes.



Scheme 13. Cycloaddition reactions of nitrile oxides with cyclopropenes.

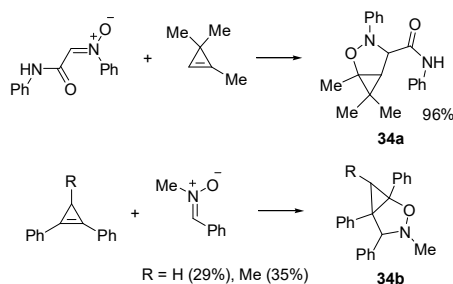
Unexpected nitrile oxide substituent dependence on the reaction course was found for dirhodium catalyzed reactions of silyl-protected enol diazoacetates with nitrile oxides.^{44,45} Corresponding primary formed *via* dipolar cycloaddition of *in situ* generated donor-acceptor cyclopropenes and nitrile oxides isoxazolines **31** were unstable and undergo either Neber or Lossen rearrangement yielding 2-oxa-6-azabicyclo[3.1.0]hexan-3-one⁴⁴ **32** and 5-aminofuran-2(3*H*)-ones⁴⁵ respectively **33**. Nitrile oxides with electron-withdrawing substituents lead *via* azirine intermediates (formally a cyclic analogue of Neber

reaction) to bicyclic products, whereas electron-donating substituents at nitrile oxides favoured Lossen rearrangement and lead *via* ketenimine intermediates to aminofuranes (Scheme 14).



7. Nitrones.

Isoxazolidines **34a-c** formation *via* 1,3 cycloaddition of substituted cyclopropenes to nitrones was described by a few groups of authors. It was found by Akmanova et al. that *N*-(2-oxo-2-(phenylamino)ethylidene)aniline oxide interacts with cyclopropene leading to corresponding adduct **34a** with 2-oxa-3-azabicyclo[3.1.0]hexane skeleton (Scheme 15).⁴⁶

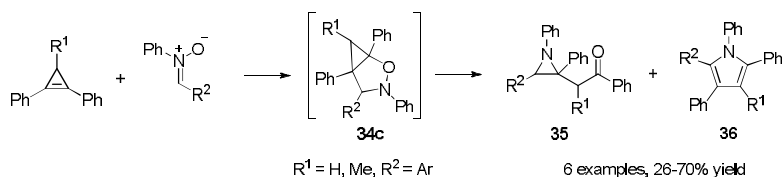


1,3-Dipolar cycloaddition of *C*-aryl, *N*-aryl (or *N*-methyl) nitrones with a number of substituted at the C3 position 1,2-diphenylcyclopropenes was studied by Diev et al.⁴⁷ They found that these reactions occur with the formation of expected “normal” (isoxazolidine ring containing) cycloadducts **34b** only when the *N*-methylnitrones are used, while other lead to products of their subsequent transformations (among them are corresponding *R*-acetophenyl aziridines and tetra- (or penta-) arylpyrroles). It was also shown that aziridines **35** and the normal cycloadducts **34c** can be thermally converted to the arylpyrroles **36** with moderate to good yields (Schemes 15 and 16). Substituted by an electron-withdrawing group at the C3 position cyclopropenes have decreased reactivity and reactions of nitrones with such cyclopropenes afforded complex mixtures containing isomeric ketones.

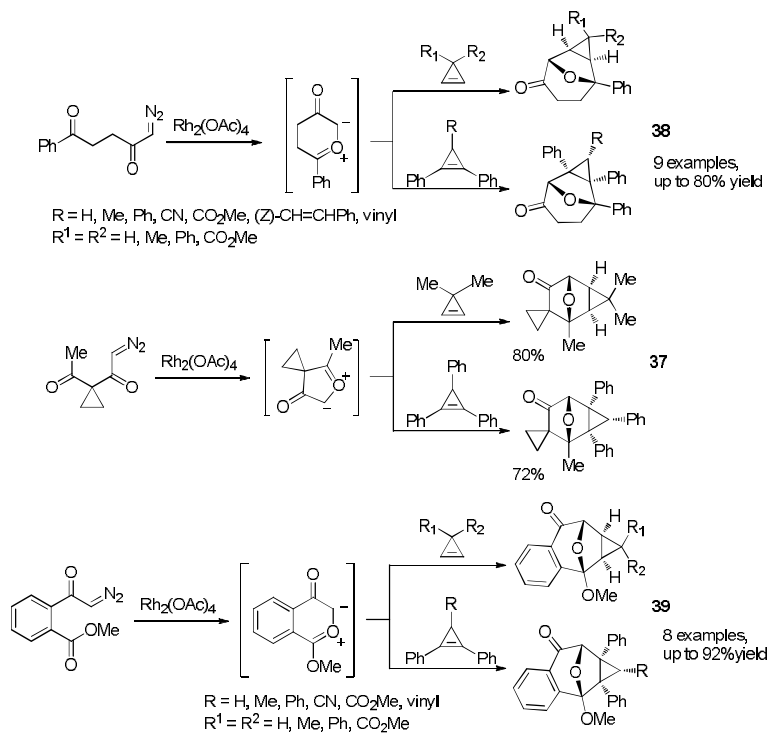
8. Carbonyl ylides

1,3-Dipolar cycloadditions of carbonyl ylides to cyclopropenes are promising synthetic route to oxygen-containing fused heterocyclic systems. Such carbonyl ylides generated by dirhodium catalyzed decomposition of diazocarbonyl precursors readily react with 3-substituted 1,2-diphenylcyclopropenes or

3,3-disubstituted cyclopropenes affording polycyclic compounds with 8-oxatricyclo[3.2.1.0^{2,4}]octane⁴⁸ **37** and 9-oxatricyclo[3.3.1.0^{2,4}]nonane^{48,49} **38** and **39** frameworks (Scheme 17). Generally, reactions proceed stereoselectively to give *exo* adducts by carbonyl ylide approach from the less-hindered face of cyclopropenes. Possible approaches of intermediate carbonyl ylides to cyclopropenes that helps to explain stereochemistry of obtained products is shown in Figure 3. The electronic properties of the substituent at the C3 position of cyclopropenes play an important role in governing the reactivity of cyclopropenes: when the C3 position is substituted by electron-acceptors such as methoxycarbonyl or cyano groups, the yields of adducts are decreased significantly.



Scheme 16. Reactions of nitrones with 3-substituted 1,2-diphenylcyclopropenes.



Scheme 17. Carbonyl ylide cycloaddition to cyclopropenes.

Another example of dirhodium catalyzed annulation reaction between two structurally different diazocarbonyl compounds that provides the donor-acceptor cyclopropane-fused benzoxa[3.2.1]octane scaffold **39** was described by Cheng et al.⁵⁰ This one-pot composite transformation occurs as 1,3-dipolar cycloaddition between carbonyl ylides formed from intramolecular carbene-carbonyl cyclization and donor-acceptor cyclopropenes generated from enoldiazoacetamides with excellent chemo-, regio-, and diastereoselectivity under exceptionally mild conditions (Scheme 18). The primary formed annulation products can be further transformed into benzoxa[3.3.1]nonane **40** and hexahydronaphthofuran **41**

derivatives with exact stereocontrol (Scheme 19). These methods allow the efficient construction of three fused and bridged ring systems, all of which are important skeletons of numerous biologically active natural products.

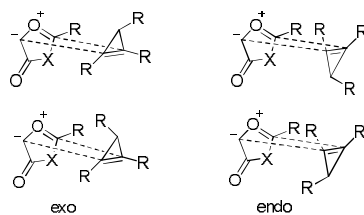
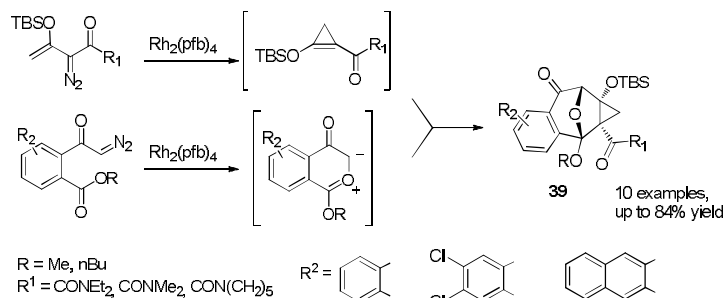
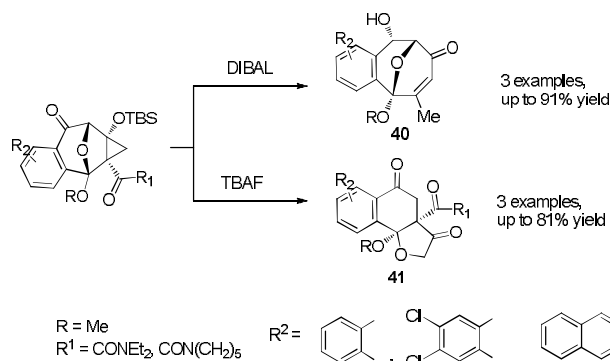


Figure 3. Possible approaches of intermediate carbonyl ylide to cyclopropane.

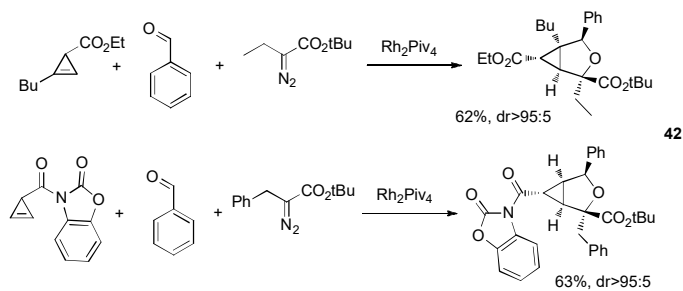


Scheme 18. Ring systems construction from by dirhodium catalyzed annulation of diazo compounds.



Scheme 19. Stereospecific transformation of annulation products into benzoxa[3.3.1]nonane and hexahydronaphthofuran derivatives.

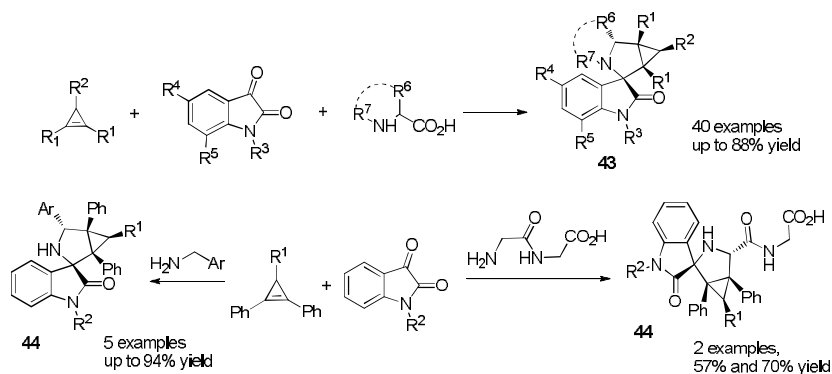
Interesting tandem three-component coupling reactions of cyclopropenes with carbonyl ylides was described by De Angelis et al. (Scheme 20).⁵¹ Compounds with fused 3-oxabicyclo[3.1.0]hexane scaffold **42** were obtained in good to excellent yields and excellent diastereoselectivity. Authors provided only a few examples utilized cyclopropane derivatives while a broad scope of dipolarophiles was studied to produce highly functionalized dihydro- and tetrahydrofuran products with excellent regio- and diastereoselectivity by carrying out the reaction at low temperature in the presence of Rh(II) catalyst. Therefore this method could be easily extended to other cyclopropenes.



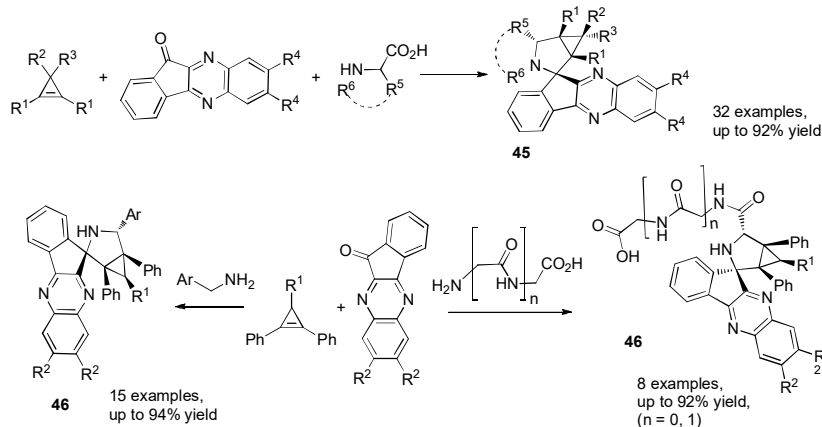
Scheme 20. Tandem three-component coupling reactions of cyclopropenes with carbonyl ylides.

9. Azomethine ylides

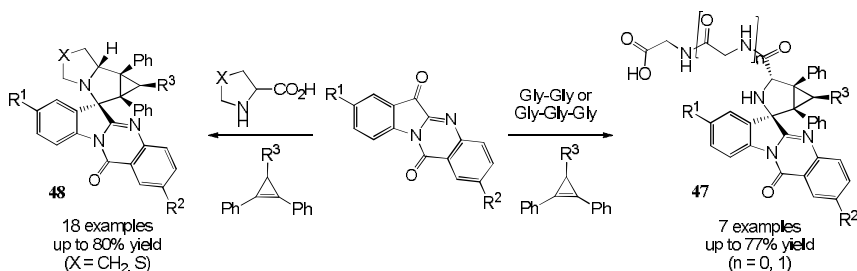
1,3-Dipolar cycloaddition reactions of generated *in situ* from carbonyl compounds and α -amino acids or benzylamines stabilized azomethine ylides are known to readily occur at activated double bond of alkenes as well as cyclopropenes and provide a convenient one-step method for preparation of pyrrolidines and pyrrolizidines. The high regio- and stereoselectivity achieved during cycloaddition processes using these ylides as starting materials provides a valuable route for the synthesis of complex heterocyclic systems containing up to four new chiral centers with the required configuration and spatial orientation of substituents, while starting compounds are relatively simple and commercially available. At the same time utilizing of cyclic carbonyl compounds allows to obtain spiro-fused heterocyclic systems. In such a way novel classes of complex heterocyclic systems containing azabicyclo[3.1.0]hexane or cyclopropa[a]pyrrolizine fragments spiro-fused to oxindoles⁵² **43-44**, indeno[1,2-b]quinoxalines⁵³ **45-46**, indolo[2,1-b]quinazolines (tryphantrines)⁵⁴ **47-48** or indenes⁵⁵ **49-51** were prepared in good to high yields and excellent diastereoselectivity (Schemes 21-24). Developed new simple and efficient methods allow to desired products to be obtained *via* stereoselective one-pot three-component 1,3-dipolar cycloaddition reactions of variously substituted cyclopropenes to azomethine ylides generated *in situ* from corresponding carbonyl compound and α -amino acids, benzylamines or simplest peptides. Performed quantum chemical investigations indicate that the reaction proceeds through the *S*-shaped azomethine ylide, the interaction of which with cyclopropenes proceeds *via* a less sterically hindered *endo*-transition state. Antitumor activity of some of the synthesized compounds against erythroleukemia (K562), cervical carcinoma (HeLa) and colon carcinoma (CT26) cell lines was evaluated additionally. The highest activity was found for adducts on the basis of ylides derived from *L*-asparagine and *L*-glutamine.



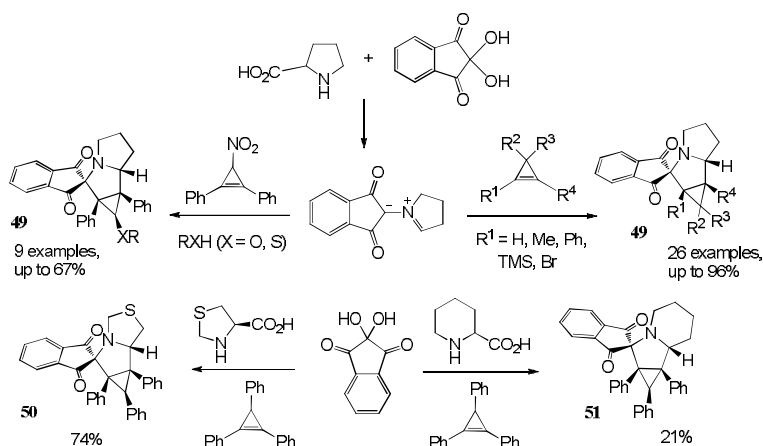
Scheme 21. 1,3-Dipolar cycloadditions of variously substituted cyclopropenes to azomethine ylides generated from isatines and α -amino acids, benzylamines or dipeptide.



Scheme 22. 1,3-Dipolar cycloadditions of variously substituted cyclopropenes to azomethine ylides generated from indeno[1,2-b]quinoxalines and α -amino acids, benzylamines or peptides.



Scheme 23. 1,3-Dipolar cycloadditions of variously substituted cyclopropenes to azomethine ylides generated from tryptanthrines and α -amino acids, di- or tripeptides.



Scheme 24. 1,3-Dipolar cycloadditions of variously substituted cyclopropenes to azomethine ylides generated from ninhydrine and proline.

Possible approaches of intermediate ylide to cyclopropene that helps to explain stereochemistry of obtained products is represented by the example of interaction of produced from ninhydrine and *L*-proline

stable azomethine ylide with 1,2-disubstituted cyclopropenes (Figure 4). It was shown by quantum chemical investigation that 1,5-regio- (in case of unsymmetrically substituted at double bond cyclopropene) and endo-stereoselective product formation in the observed reactions arises from charge and orbital control along with second orbital interactions

It is worth noting that *in situ* generation of azomethine ylides from 11*H*-indeno[1,2-*b*]quinoxalin-11-ones or indolo[2,1-*b*]quinazolines (trypanthrines) and primary α -amino acids, benzylamines as well as use of the peptides as an amine component has been described for the first time.

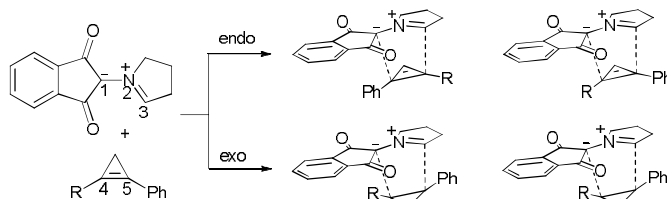
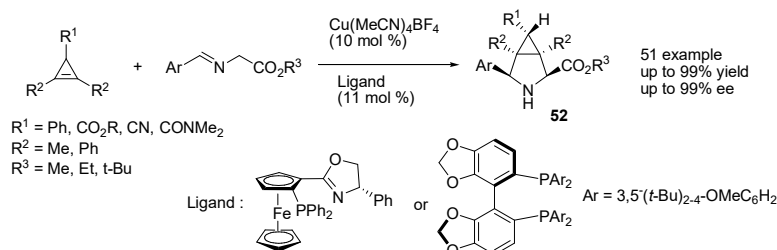


Figure 4. Possible approaches of intermediate azomethine ylide to cyclopropene.

More interestingly, carrying out cycloadditions of azomethine ylides and cyclopropenes under asymmetric conditions opens direct enantioselective access to new pyrrolidine moiety incorporated into azabicyclo[3.1.0]hexane framework **52** bearing five continuous carbon-stereogenic centers.^{56,57} This strategy was exemplified by copper-catalyzed 1,3-dipolar cycloaddition of *in situ* generated from benzylideneaminoacetate azomethine ylides to variously substituted cyclopropenes (Scheme 25). Desired products were obtained in high yield (up to 99%) as well as excellent diastereoselectivity (>99:1 d.r.) and enantioselectivity (up to 99%).



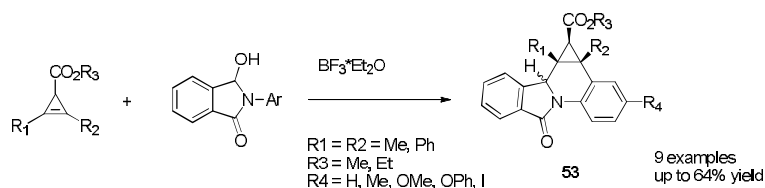
Scheme 25. Copper-catalyzed 1,3-dipolar cycloaddition/desymmetrization of substituted cyclopropenes with azomethine ylides.

Recently cyclopropa[*c*]isoindolo[2,1-*a*]quinolone framework **53** was synthesized *via* tandem reaction of cyclopropenes with *N*-acyliminium cations.⁵⁸ This method allows constructing tetra-fused heterocyclic system in one step, while none of these cycles were fused at starting material. Moreover this was the first example of the reactions of cyclopropenes with *N*-acyliminium cations. The complete reaction is described by sequentially processes of *in situ* generation of *N*-acyliminium cation from starting hydroxylactams *via* Lewis acid induced dehydroxylation followed by electrophilic attack on the cyclopropene double bond and intramolecular Friedel-Crafts reaction (electrophilic substitution at aromatic ring) to produce corresponding cyclopropa[*c*]isoindolo[2,1-*a*]quinolones in moderate yields (Scheme 26).

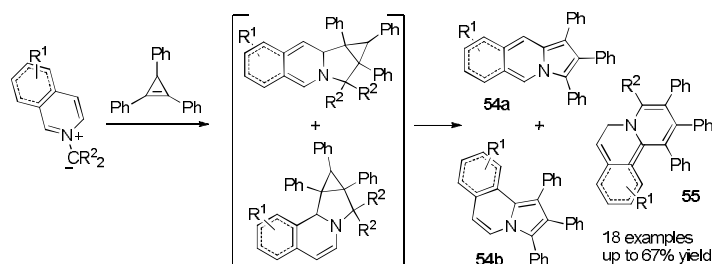
10. Immonium ylides

It was reported that cycloaddition reactions of various immonium ylides to cyclopropene derivatives allows to construct either fused heterocyclic systems containing cyclopropane moiety or indolizines and quinolizines when cyclopropane ring opening occurs after cycloaddition. Using pyridinium ylides (specifically methylides) most often result in indolizine **54a,b** formation accompanied by quinolizines **55**.⁵⁹

Herewith reactions of unsymmetrically substituted at pyridinium ring ylides proceed unselectively leading to mixture of regioisomeric products (Scheme 27).

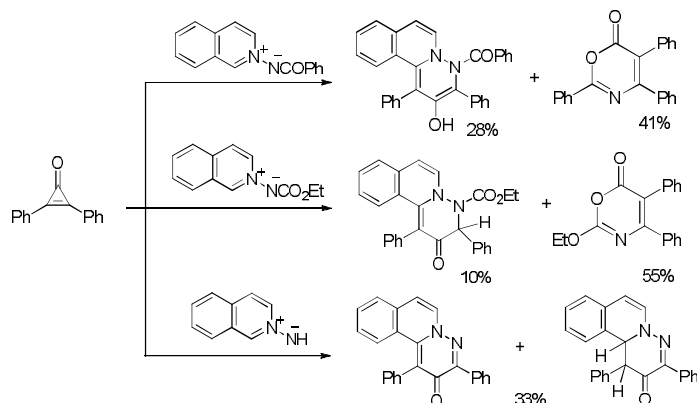


Scheme 26. Synthesis of cyclopropa[*c*]isoindolo[2,1-*a*]quinolones by reaction of cyclopropenes with *N*-acyliminium cations generated *in situ* from hydroxylactams.



Scheme 27. Cycloaddition of pyridinium and isoquinolinium ylides to 1,2,3-triphenylcyclopropene.

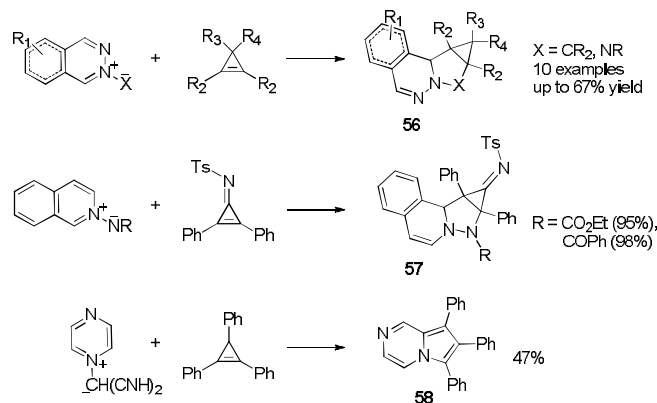
Reaction of diphenylcyclopropenone with isoquinolinium imines generally follows analogously and results in a mixture of products without retention of cyclopropane moiety (Scheme 28).⁶⁰ They therefore could be rarely used for the synthesis. In contrast, reactions of isoquinolinium imines or pyridazinium and phtalazinium ylides with triphenylcyclopropene lead to fused heterocyclic systems **56** and **57** that retain the cyclopropane ring,⁵⁹⁻⁶¹ while pyrazinium ylide (dicyanomethylide) produces 7-azaindoline derivative⁵⁹ **58** (Scheme 29).



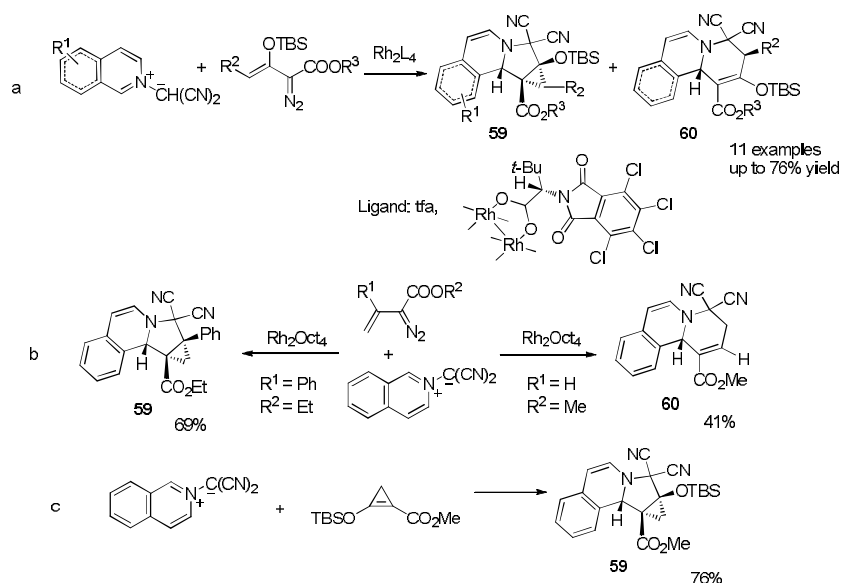
Scheme 28. Reaction of diphenylcyclopropenone with isoquinolinium imines.

Donor-acceptor cyclopropenes also readily react with isoquinolinium methylides to produce corresponding cyclopropapyrroloisoquinolines **59** via 1,3-dipolar cycloaddition (Scheme 30).⁶² However, these reactions, when *in situ* generation of cyclopropenes is used, are very sensitive to catalyst utilized, its amount and Lewis base used. In deed it was found that coordination of Lewis basic methylides to

dirhodium(II) induces the rearrangement of enol-carbene that is bound to dirhodium to provide donor-acceptor cyclopropene. Such formed donor-acceptor cyclopropene is in equilibrium with the dirhodium-bound enolcarbene and undergoes both diastereoselective [3+2]-cycloaddition by uncatalyzed reaction of the cyclopropene and enantioselective [3+3]-cycloaddition from the dirhodium-bound enolcarbene with isoquinolinium or pyridinium methylides (Scheme 30). This competing can be turned on or off with a higher mol % of catalyst loading or increasing amount of Lewis base. Substantial influence of vinyl substituent and complexity of this reaction could also be demonstrated by reactions of parent vinylazoacetate and its 4-phenyl substituted derivative. While former result in exclusive formation of [3+3]-cycloaddition product **60**, the latter afford only product of [3+2]-cycloaddition **59** (Scheme 30, b). Treating of independently obtained and therefore catalyst-free cyclopropene with isoquinolinium dicyanomethylide produce [3+2]-cycloaddition product **59** exclusively (Scheme 30, c).

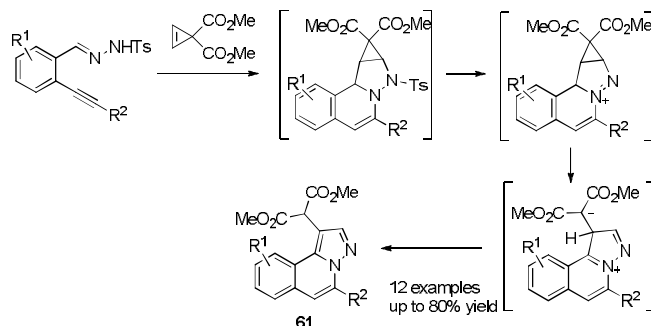


Scheme 29. Cycloaddition of cyclopropenes to isoquinolinium imines and pyrazinium, pyridazinium and phtalazinium ylides.



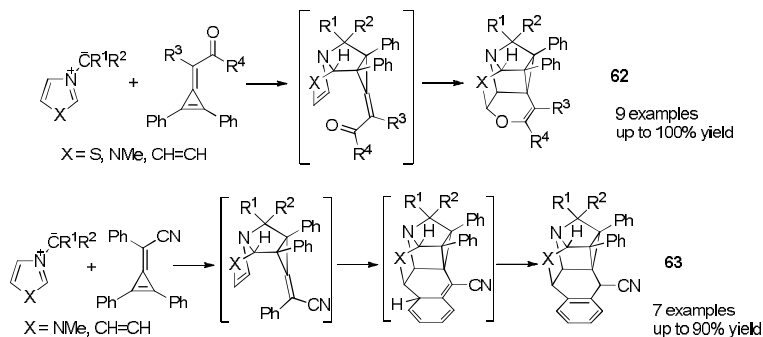
Scheme 30. Cycloaddition of isoquinolinium and pyridinium methylides to catalyst-free or *in situ* generated from enol diazoacetate donor-acceptor cyclopropenes.

Isoquinoline moiety of isoquinolinium ylides could also be formed *in situ* prior to cycloaddition processes that open new possibility for construction of heterocyclic systems. As an example could be mentioned generation of isoquinolinium imines *in situ* from 2-alkynylbenzylidene hydrazides under silver(I) catalysis. This methodology was used for pyrazolo[5,1-a]isoquinoline **61** synthesis *via* silver(I), rhodium(II) co-catalyzed tandem reaction between 2-alkynylbenzylidene hydrazide and cyclopropenes (Scheme 31).⁶³ The complete reaction is described by sequentially processes of 6-endo cyclization of 2-alkynylbenzylidene hydrazides leading to corresponding isoquinolinium ylides, [3+2]-cycloaddition of formed ylides and cyclopropenes, cyclopropane ring opening, and aromatization to produce pyrazolo[5,1-a]isoquinolines. Surprisingly, reaction failed when 2-substituted cycloprop-2-ene-1,1-dicarboxylates were employed in this transformation.



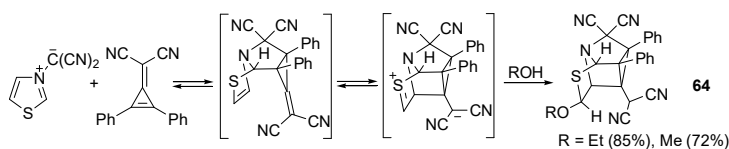
Scheme 31. Synthesis of pyrazolo[5,1-a]isoquinolines by tandem reaction of 2-alkynylbenzylidene hydrazides with cyclopropenes.

Interesting double cycloaddition reactions of pyridinium,⁶⁴ imidazolium⁶⁵ and thiazolium⁶⁶ *N*-methylides to methylenecyclopropenes with unsaturated substituents at the 4-position *via* consequent intermolecular 1,3-dipolar and intramolecular Diels-Alder cycloaddition reactions leading to cage compounds **62** and **63** was reported by Tsuge et al. Developed methodology allows double functionalization of nitrogen-containing aromatic heterocycles. At the first step, heterocycles are converted to corresponding aromatic azomethine ylide, while during the second step 1,3-dipolar cycloaddition of formed ylide to endocyclic double bond of methylenecyclopropene forms [3+2]-cycloadduct simultaneously leading to the collapse of aromatic character of starting heterocycle and further intramolecular Diels-Alder reaction occurs across the unsaturated system released on this heterocyclic ring producing cage compounds (Scheme 32).



Scheme 32. Double cycloaddition reactions of pyridinium, imidazolium and thiazolium ylides to methylenecyclopropenes leading to cage compounds.

It was also shown that while thiazolium methylide gave no adduct with 4-dicyano-substituted methylenecyclopropene during reaction in polar aprotic solvent (both reactants were quantitatively recovered), using protic solvents (alcohols) lead to formation of other type of cage compounds **64** (Scheme 33).⁶⁶

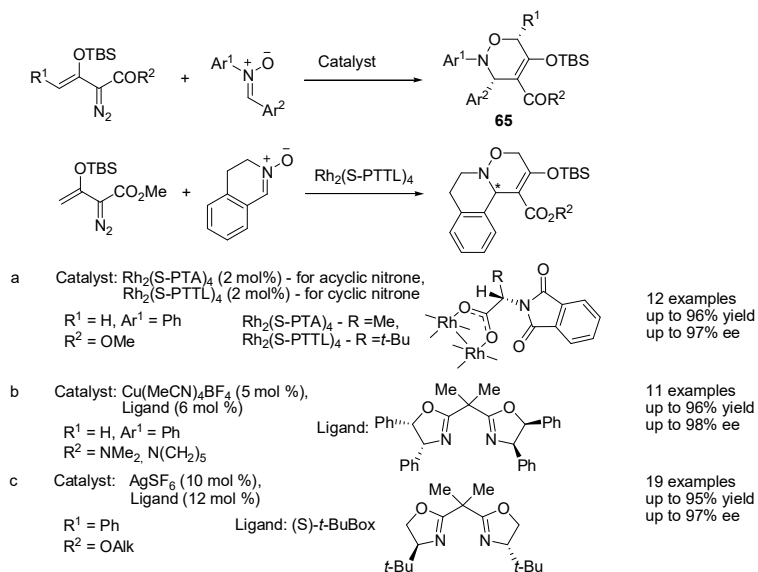


Scheme 33. Cage compounds formation *via* double cycloaddition reactions of thiazolium ylide to dicyano-substituted methylenecyclopropenes.

11. Asymmetric [3+3]-cycloaddition reactions

All previously described reactions include interaction of 1,3-dipole with cyclopropene double bond. However in some cases cyclopropenes themselves could be considered as dipole source. That is especially true for donor-acceptor cyclopropenes that are formed by transition-metal catalyzed decomposition of enoldiazo compounds. In a such cases interaction of 1,3-dipole with cyclopropenes could be seen as a kind of recombination of these two different dipolar species. Indeed formed in this way cyclopropenes are in equilibrium with metallo-enolcarbene intermediate, whose electrophilic center is delocalized to vinylogous carbon atom. These reactive metallo-1,3-dipoles suggest a huge potential for formal [3+3]-cycloaddition reactions *via* trapping with other dipoles. Utilizing these transformations became very popular last years since they open new possibilities for heterocyclic systems construction. Moreover, using chiral catalyst allows enantioselectively produce desired heterocycles.⁶⁷

The first such asymmetric cycloaddition of enoldiazo compounds was described by Dole et al. for 3,6-dihydro-1,2-oxazines **65** synthesis by dirhodium-catalyzed reactions of nitrones and *tert*-butyldimethylsilyl-protected vinyl diazoacetates as result of dinitrogen extrusion followed by intramolecular cyclization.⁶⁸ High enantiocontrol occurs with catalysis by *N*-phthaloyl-(*S*)-(amino acid)-ligated dirhodium carboxylates for reactions with both acyclic and cyclic nitrones (Scheme 34, a).



Scheme 34. 3,6-Dihydro-1,2-oxazines formation by asymmetric cycloaddition of nitrones to cyclopropenes.

The reaction was further extended for enoldiazoacetamides (Scheme 34, b)⁶⁹ and γ -phenyl-substituted enoldiazoacetates (Scheme 34, c)⁷⁰ as well as the possibility of utilizing base-metal-catalyzed vinylcarbene transformation (copper- and silver-catalyst). Proposed mechanism for most of these [3+3]-cycloadditions is illustrated in Figure 5.

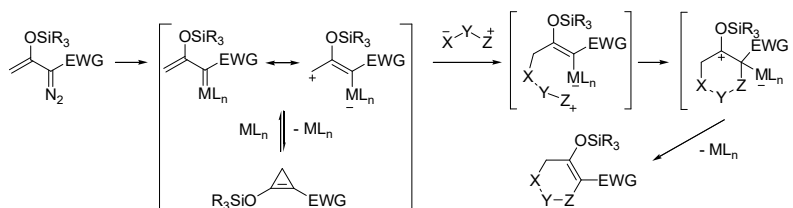
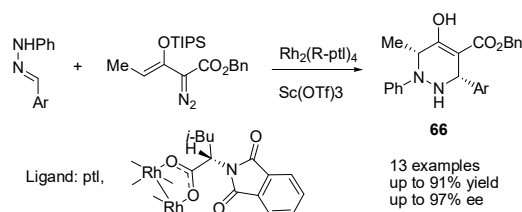


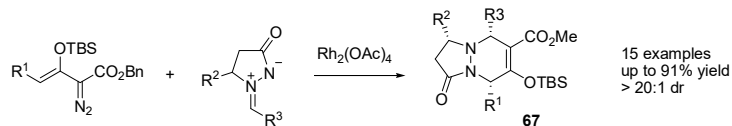
Figure 5. Proposed mechanism for formal [3+3]-cycloaddition reactions of metallo-enolcarbene intermediate with stable 1,3-dipoles.

Stepwise nature of these cycloaddition reactions could be clearly visualized by reaction of hydrazones with enoldiazoacetates. In this case corresponding 1,2,3,6-tetrahydropyridazines **66** were performed with excellent enantioselectivity and high diastereoselectivity *via* one-pot vinylogous controlled by chiral catalyst 1,4-N-H insertion followed by Lewis acid-catalyzed diastereoselective Mannich addition cascade process (Scheme 35).⁷¹



Scheme 35. Synthesis of 1,2,3,6-tetrahydropyridazines *via* enantioselective cascade reaction of hydrazones with enoldiazoacetates.

Followed this general methodology, other 1,3-dipoles were tested to examine their compatibility for such [3+3]-cycloaddition reactions. It was found that cyclic azomethine imines readily react with enoldiazoacetates producing bicyclic pyrazolidinones **67** in high regio- and diastereoselectivity (Scheme 36).⁷²

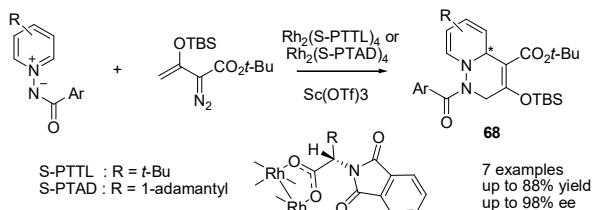


Scheme 36. Synthesis of bicyclic pyrazolidinones *via* catalyzed [3+3]-cycloaddition of azomethine imines to enoldiazoacetates.

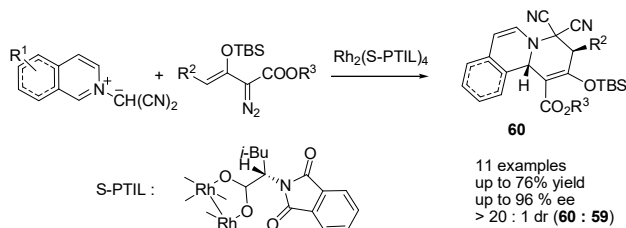
This strategy allows also asymmetric synthesis of heterocyclic structures with more than one nitrogen atom that was illustrated by *N*-acyliminopyridinium ylides cycloaddition (Scheme 37).⁷³ Indeed application on these ylides as stable dipoles in dirhodium-catalyzed reactions with enoldiazo compounds allowed to produce 1*H*-pyrido[1,2-*b*]pyridazines **68** in high yield and exceptional stereocontrol.

It was shown previously (Scheme 30), that immonium (pyridinium and isoquinolinium) ylides undergo 1,3-dipolar cycloaddition when treated with catalyst-free donor-acceptor cyclopropenes to give corresponding cyclopropapyrroloisoquinoline **59** derivatives.⁶² They, however, could find more interest

implementation in [3+3]-cycloaddition reactions, while both heterocyclic systems are very interesting. So, carrying out enantioselective reaction of isoquinolinium and pyridinium methylides with enol diazoacetates gave corresponding product of formal [3+3]-cycloaddition **60** (Scheme 38).⁶²



Scheme 37. Enantioselective dearomatizing formal [3+3]-cycloaddition of *N*-acyliminopyridinium ylides to electrophilic enol carbene intermediates.



Scheme 38. Enantioselective dearomatizing formal [3+3]-cycloaddition of isoquinolinium and pyridinium methylides to enol diazoacetates.

12. Conclusions

There are many selective and synthetically useful transformations that utilize cyclopropene derivatives in the construction of heterocyclic systems. Some of them provide a unique approach for the creation of such systems that are very hardly or even not available other ways. It is only recently that a range of powerful synthetic methodologies as well as asymmetric metal-catalyzed reactions have been reported for the first time allowing selective creation of complex fused heterocyclic systems. Therefore, many possibilities exist for the development of new strategies that use cyclopropene and its derivatives for the construction of heterocyclic systems.

Acknowledgements

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