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New types of 'combined' pericyclic reactions

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Abstract. The review is concerned with 'combined' pericyclic reactions, *i.e.*, multistep one-pot reactions involving a cascade of pericyclic steps, as well as concerted processes whose transition states represent superpositions of transition states of two pericyclic reactions. Some typical examples of cascade pericyclic reactions are presented, demonstrating their significance for synthetic practice. The review mainly concerns reactions with a 'combined' pericyclic transition state, *e.g.*, dyotropic shift, bispericyclic reactions and hiscotropic rearrangements. The attention is focussed on detailed analysis of various types of coarctate reactions due to their importance for synthetic chemistry and to thorough elaboration of their theoretical basis, which is in essence a continuation and further development of the Woodward – Hoffmann theory for spirocyclic conjugated systems. The bibliography includes 115 references.

I. Introduction

The history of studies on pericyclic reactions is long and full of contradictories and findings.[1] In 1965, R Woodward and R Hoffmann formulated the 'orbital symmetry conservation' rules for concerted reactions;[2–4] this became the triumph of the theory of molecular orbitals. The Woodward – Hoffmann rules became particularly vivid for pericyclic reactions, *i.e.*, concerted processes proceeding *via* cyclic transition states.

Since then the orbital approach has become a valuable tool for organic chemists because the frontier orbital approximation in most cases quite correctly describes the properties of complex organic and organometallic compounds for which a rigorous quantum chemical analysis and *ab initio* calculations are too cumbersome. A qualitative consideration of the structure and properties of compounds, or 'pictural orbital chemistry' according to R Hoffmann, is rather simple and readily available and allows one to understand many aspects and to predict various consequences interesting to synthetic chemists, *e.g.*,

— is the reaction between compounds A and B possible?
— will the reaction under study be regioselective?
— what is the stereochemical outcome of the reaction?

and many other features.

The composition of molecular orbitals, determination of their symmetry and possible interactions by the so-called paper-and-pencil method[5] is the language of modern organic chemists.

Pericyclic reactions include many well-known synthetically important reactions, *e.g.*, cycloaddition and cyclodecomposition, 1,3-dipolar cycloaddition, electrocyclic reactions, sigmatropic shifts, *etc.* Recently, particular attention has been paid to 'combined' pericyclic reactions, *i.e.*, multistep reactions involving a cascade of pericyclic steps as well as concerted reactions whose transition states can formally be treated as superpositions of transition states of two pericyclic reactions. Cascade pericyclic reactions are of undoubtful interest for stereoselective one-pot synthesis of various classes of organic compounds; however, their theoretical consideration is not very interesting because the mechanisms of particular steps of these reactions are well known. One-step concerted processes involving two coarctate pericyclic reactions are quite a different story.[6] Research on their mechanisms and especially transition states is of great theoretical interest, being carried out as a continuation of the development of the orbital approach proposed in the classical studies by R Woodward and R Hoffmann. Reactions with 'combined' pericyclic transition states are still poorly studied, although a large number of examples are available. The theory of coarctate reactions has been best elaborated. This is not the best known, but an abundant class of pericyclic reactions. A characteristic feature of coarctate reactions consists in simultaneous breaking and formation of at least two bonds at one or more atoms. The theory of coarctate transition state was developed about two decades ago by German chemist P Herges[7] in a continuation of the classical orbital

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approach to pericyclic reactions. More recently, this theory was updated, refined and improved.

This review concerns 'combined' pericyclic reactions. In Section I we discuss a number of typical examples of cascade pericyclic reactions in order to show their importance for synthetic practice. Other Sections deal with reactions with 'combined' transition state. The emphasis is placed on detailed analysis of various types of coarctate reactions. This is due to synthetic importance of many coarctate reactions and to detailed elaboration of their theoretical basis [7] laid down in the fundamental studies by Herges. More recently, the theory of coarctate reactions was refined and improved. One can trace how progress in computational and experimental methods makes it possible to revise many known reactions from the standpoint of their mechanisms. The development of theoretical grounds of coarctate reactons led to reneval of interest in the known pseudopericyclic reactions. Numerous studies on analysis of the possibility of competition between coarctate and pseudopericyclic transition states to occur were reported in the last five to seven years. Such a comparison seems to be quite logical because in both cases the transition state involves two orthogonal p-orbitals (see below). Such reactions are widely used to synthesize complex heterocyclic systems. Quite recently, the homology principle for coarctate reactions was proposed; it enables a targeted search for reactants for highly efficient and stereoselective reactions of this type.

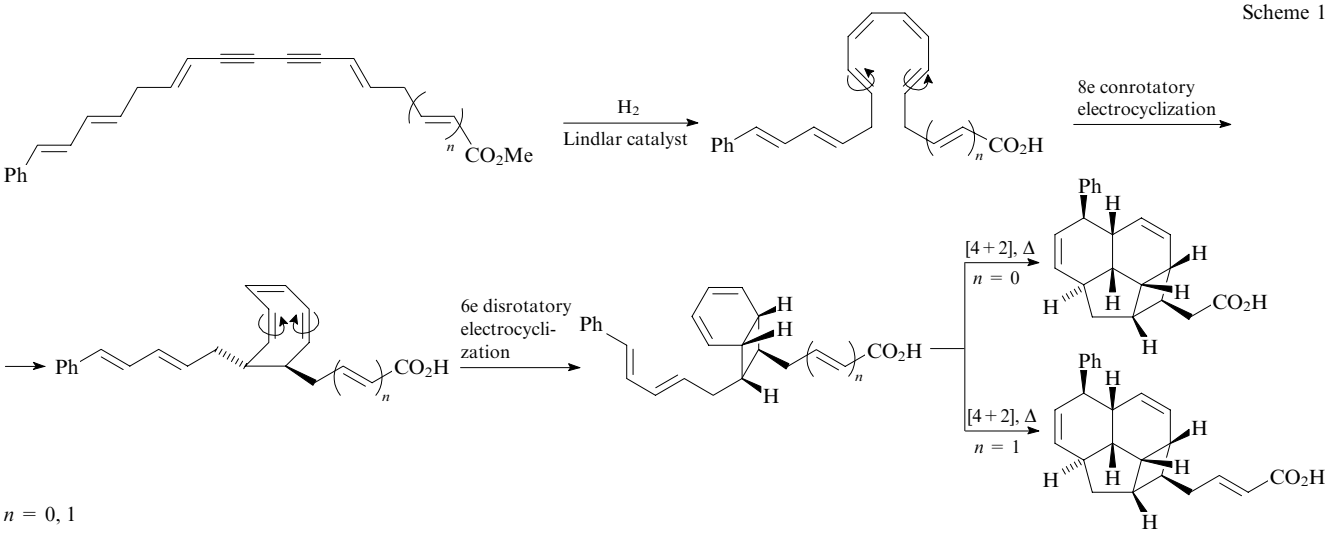
II. Cascade pericyclic reactions

Cascade pericyclic reactions represent two or more pericyclic reactions proceeding in consecutive fashion as a one-pot reaction. They are of particular interest for targeted synthesis because they provide not only a rather simple way of constructing complex carbon skeletons and thus obtaining compounds with many stereocentres but also allow one to predict the stereochemistry of products as a result of consecutive stereoselective reactions. For instance, various combinations of cycloaddition, electrocyclization, sigmatropic shift and other pericyclic reactions are often used to synthesize a variety of natural compounds, namely, steroids, alkaloids, terpenes, *etc*. (see Refs 8 – 13 and references cited therein). Some typical examples are given below.

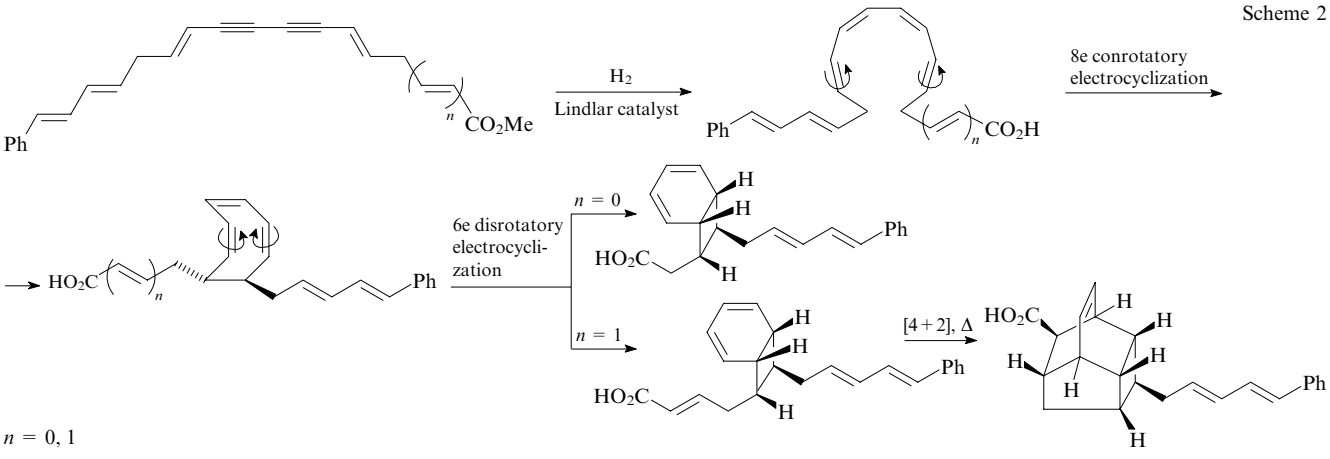
Endiandric acids of different structure from *Endiandra intorsa* plants growing in Australia were obtained [10] from rather simple linear achiral precursors by conducting consecutive thermally allowed, almost barrierless pericyclic reactions (8e and 6e electrocyclic reactions followed by [4 + 2]-cycloaddition). It should be emphasized that the stereochemical purity of products is very high (Schemes 1, 2).

Enantioselective synthesis of oxindole is also noteworthy. The process is characterized by high enantiomeric purity (98% *ee*) and involves consecutive [3 + 2]-cycloaddition of substituted nitrone to ketene and [3,3]-sigmatropic shift (Scheme 3).[14]

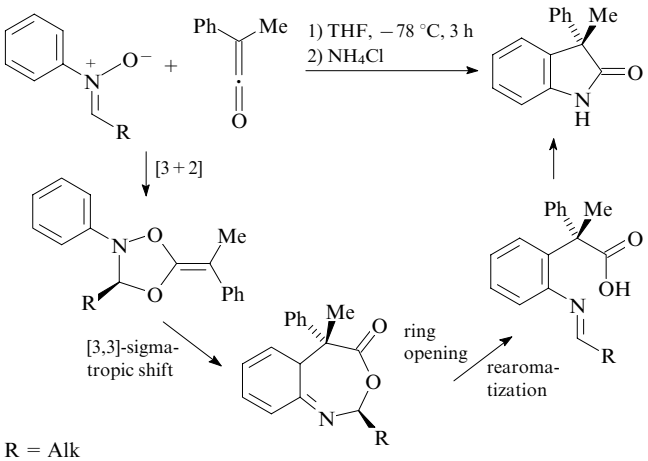
Scheme 1



Scheme 2



Scheme 3



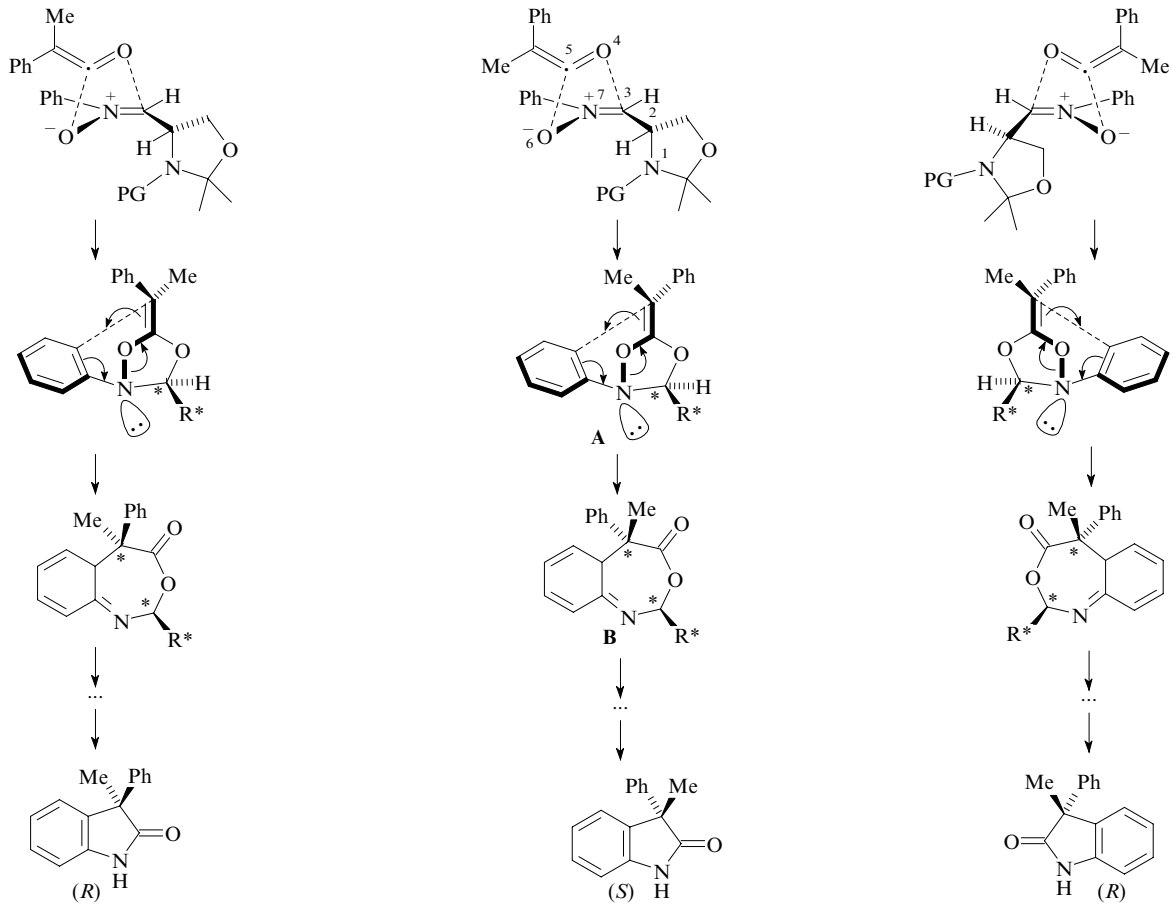
High enantioselectivity of the reaction is due to chirality transfer in the course of consecutive pericyclic reactions, as shown in Scheme 4.

Dipolar 1,3-addition leads to formation of a stereogenic centre at the C(3) atom and an unsymmetrically substituted C=C double bond in the intermediate **A**. Then, stereochemical information is transferred to the next intermediate **B** through stereospecific [3,3]-sigmatropic shift. This is followed by ring opening and rearomatization and results in elimination of the stereocentre at the C(3) atom; the quaternary chiral centre, C(sp^3), remains unchanged. Thus, the stereochemistry of this chiral centre in the imino acid and in oxindole is established in the [3+2]-cycloaddition step and depends on two factors, namely, the mutual position of alkene and 1,3-dipole in the course of the cycloaddition reaction and the orientation of ketene in which the phenyl group can occupy either a *cis*- or *trans*-position relative to the O(6)–C(5) bond. The energetically most favourable transition state corresponds to the 'head-to-head' interaction and *trans*-position of the phenyl group; as a result, a *trans*-alkene is formed. Subsequent sigmatropic shift leads to formation of an *S*-stereocentre. This is consistent with the results of quantum chemical calculations of the energetically most favourable reaction pathway leading to the (*S*)- rather than *R*-oxindole; the latter is obtained upon a change in the mutual orientation of the reactants or arrangement of substituents in the ketene.[14]

Yet another very interesting cascade reaction involving consecutive steps of coarctate cyclization leading to the formation of isoindazolylcarbenes, subsequent [1,3]-migration of the carbene centre along the polyyne chain and [1+2]-cycloaddition reaction will be considered in Section IV.2.e (see Scheme 64).[15]

Cascade pericyclic reactions are highly efficient in the synthesis of carbocyclic systems. The sequence of steps with low activation barriers allows one to carry out a one-pot reaction without isolation of intermediates, rapidly and stereoselectively. An example is provided by the reaction of substituted cyclopentadienone with but-1-en-3-yn-2-ol in the presence of catalytic amounts of 1,4-diazabicyclo[2.2.2]octane (DABCO).[16] The reaction follows different

Scheme 4



PG is a protective group, R* is an auxiliary chiral group

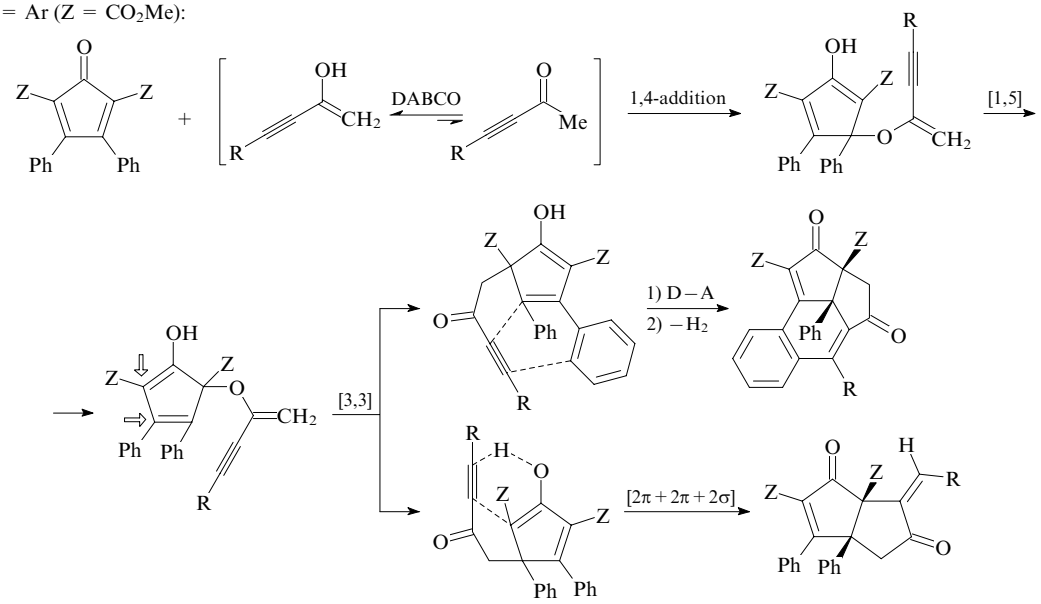
pathways depending on the nature of substituent in the but-1-en-3-yn-2-ol molecule. For R = Ar (Scheme 5), the 1,4-addition reaction followed by [1,5]- and [3,3]-sigmatropic shifts gives a tetracyclic or bicyclic product depending on what follows the [3,3]-sigmatropic shift, namely, the Diels – Alder (D – A) reaction or the $[2\pi + 2\pi + 2\sigma]$ intramolecular reaction. If the reaction involves a terminal alkyne (R = H), the final step of the cascade process is different, namely, a Michael addition occurs. This can be explained by the fact that terminal alkynyl ketones are active Michael acceptors and therefore the Michael reaction proceeds faster than the [4 + 2]-addition or $[2\pi + 2\pi + 2\sigma]$-process.

It should be noted that the cascade reactions shown in Scheme 5 proceed under mild conditions, at room temperature and involve consecutive formation of C – C bonds; this is of paramount importance for synthetic practice.

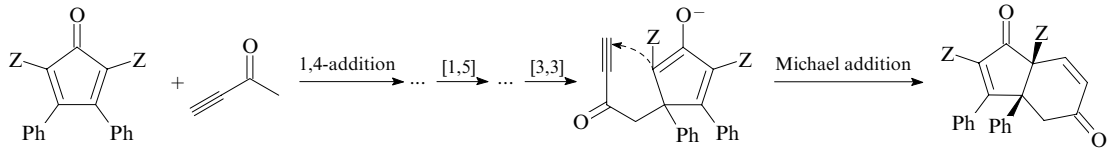
The sequence of pericyclic reactions affording steroids from acyclic precursors with an overall yield of 79% (see Scheme 6) resembles the so-called 'zipper-mode' process.[17] Two cycloaddition reactions proceed consecutively. Regioselective addition of proximal diene to dienophile resulting in bicyclic *endo*-adduct as the major product is followed by

Scheme 5

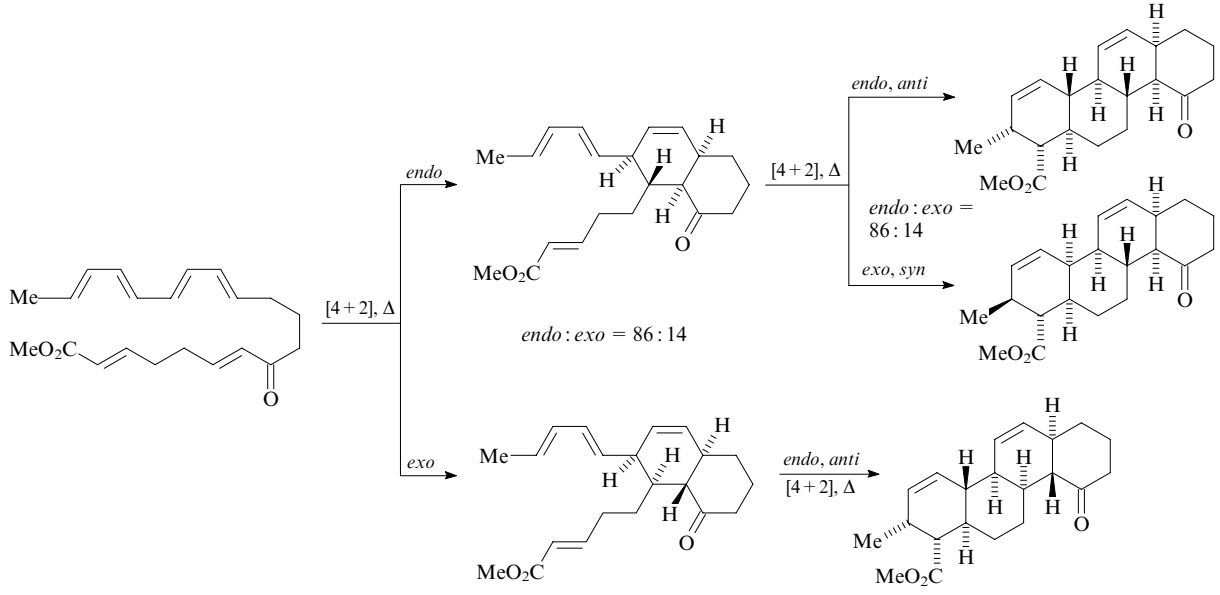
R = Ar (Z = CO_2Me):



R = H (Z = CO_2Me):



Scheme 6



the cycloaddition reaction giving a tetracyclic compound. The latter reaction, which also affords the *endo*-compound as the major product, is faster than the former because no products formed in the first step were isolated. Thus, here one deals with a 'domino'-process.

Examples of the synthesis of complex carbocyclic and heterocyclic systems similar to natural compounds follow modern trends in 'green chemistry' (development of atom and redox economy methods as well as step 'economy').[18] Pericyclic reactions (cycloaddition and electrocyclization reactions, sigmatropic shifts) provide striking instances of atom economy reactions because almost all atoms of the initial reactants are present in products; side products (if any) usually have low molecular masses (CO_2, N_2, *etc*). Also, most pericyclic reactions are not accompanied by changes in the oxidation states of elements and can thus be treated as redox-saving processes. Finally, cascade one-pot pericyclic reactions make it possible to create complex carbon skeletons using a minimum number of steps, which is also a key aspect in the concept of sustainable chemistry.

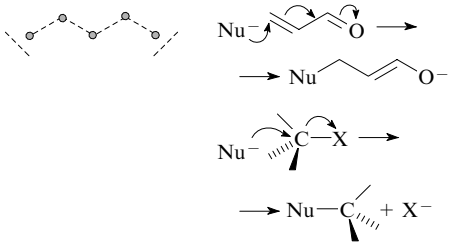
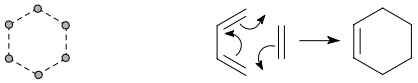
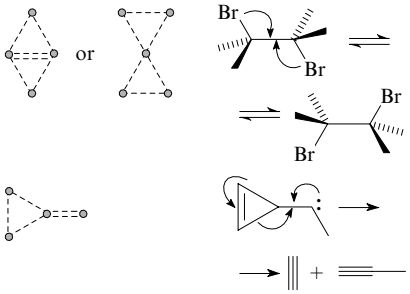
III. Pericyclic reactions with 'combined' transition states

Of particular interest are one-step processes combining two or more pericyclic reactions. In this case, the transition state of the concerted reaction is a 'superposition' of the transition states of individual steps. Such reactions are much less known than 'conventional' pericyclic reactions, but they do exist. The idea of organizing a concerted process by fusion of two transition states obeying the Woodward–Hoffmann rules seems to be quite promising because it offers prospects for the discovery of new types of reactions and for revision of the mechanisms of the known processes.

To understand the position occupied by such reactions in the general hierarchy of concerted reactions, we will consider the topology of the electron shift, *i.e*., the sequence of arrows denoting the electron shift direction and, hence, the alternating sequence of breaking and forming bonds (Table 1). Most organic reactions are characterized by linear topology of electron shift along the atomic chain, which leads to charge transfer from one to another fragment of the system. Examples are provided by such well-known reactions, as the Michael addition, S_N2 nucleophilic substitution, *etc*. Cyclic electron shifts in the course of a reaction represent the case for cyclic topology. If the electron shifts are concerted, one deals with pericyclic reactions. The third type of electron shift topology is the so-called 'combined' topology, namely, bicyclic, spirobicyclic or coarctate. It can be described as a combination of linear and cyclic shifts or two cyclic shifts. For instance, in coarctate reactions the arrows denoting the electron shifts make coarctations at some points, thus giving the name to this type of reactions, whereas in 'simple' pericyclic reactions with cyclic topology one deals with unidirectional arrows that indicate the electron shift.

To date, a number of concerted reactions whose transition states are 'superpositions' of transition states of 'simple' pericyclic reactions are known. Depending on the type of processes whose transition states are combined, the resultant transition state may contain a shared atom, a shared bond or a shared bridge. Consider different types of reactions from this class.

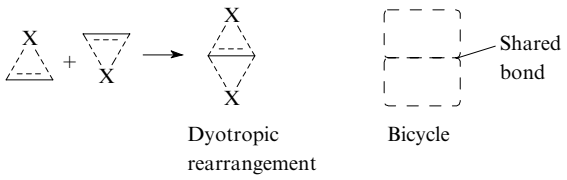
Table 1. Classification of organic reactions with respect to the topology of electron shift.

Topology of electron shift	Schematic	Examples
Linear		
Cyclic		
Combined (bicyclic, spirobicyclic, coarctate)		

1. Dyotropic shift

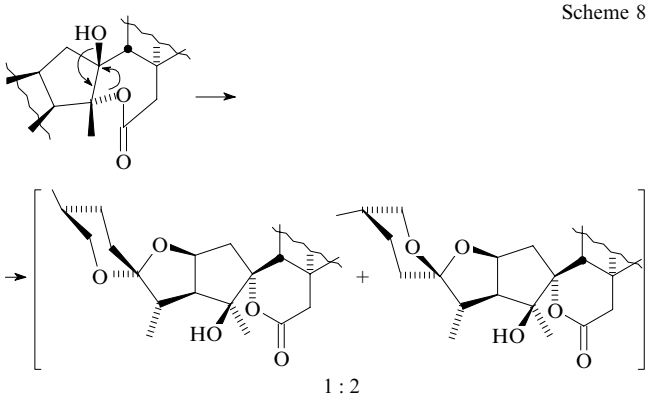
The term 'dyotropic shift' was introduced[19–21] to describe reactions with two concerted sigmatropic shifts. For this type of reactions, the transition state can be represented as combination of transition states of two different sigmatropic shifts, which form a structure with a shared bond or linked by intercrossing π-systems. As an illustration, Scheme 7 presents a combination of two [1,2]-shifts.[6]

Scheme 7



There are two types of dyotropic shifts. In one case, the two groups are shifted in opposite directions in such manner that a positional interchange occurs. In the second case, two different groups are shifted unidirectionally. A considerable literature on dyotropic rearrangements is available.[22–40] This reaction often appears to be useful for synthetic practice. For instance, recently it has been shown that dyotropic shift can be efficiently used in the synthesis of spirolactones, precursors of an analogue of 23′-deoxy cephalostatin used in pharmaceutical industry (Scheme 8).[32] The reaction under the action of $SOCl_2$ proceeds as one-pot reaction with a yield of 94% (*cf*. a three-step synthesis with an overall yield of 27%).

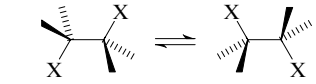
Scheme 8



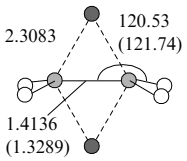
Rearrangement of vicinal dihaloalkanes[33] is also described by Scheme 7. This is a rare example of dyotropic rearrangement for which detailed activation energy calculations were carried out by the density functional theory (DFT) method.

Scheme 9 shows the transition state and calculated geometric parameters (distances are expressed in Å and angles are given in degrees) of a basic model process involving a dyotropic shift of a halogen atom in 1,2-dichloroethane (for comparison, geometric parameters of ethylene molecule are given in parrentheses). A comparative analysis of possible competing pathways of migration of the halogen atom (first of all, elimination with the formation of an alkene) was reported.[33] It was found that the activation energy of the elimination reaction is much higher and equals 57.6 kcal mol^{-1} (*cf.* 41.9 kcal mol^{-1} for the energy of dyotropic rearrangement in 1,2-dichloroethane).

Scheme 9



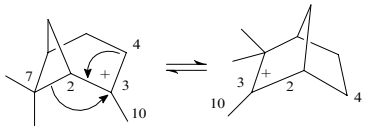
X = Cl, Br



Transition state (X = Cl)

Double alkyl shift in various carbocations[34,35] can also be treated as dyotropic shift. A quantum chemical study[35] of the mechanism of the reaction resulting in monoterpenes exhibiting a broad spectrum of biological activities showed that a key step consists in concerted but not completely synchronous [1,2]-migration of two alkyl groups (Scheme 10).

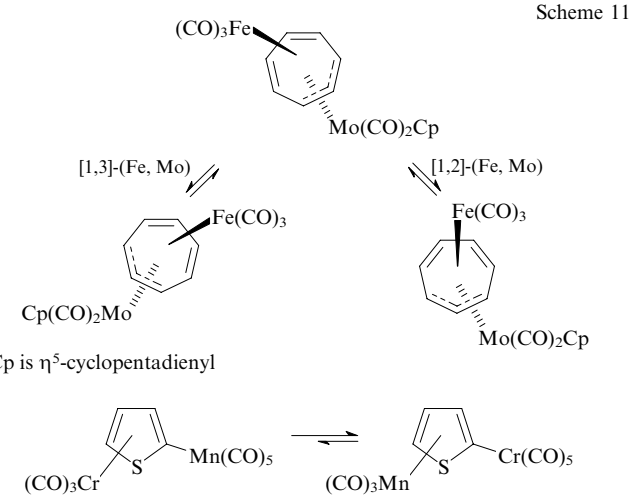
Scheme 10



The cation formed from pinene is transformed to another terpene cation, *viz.*, camphene cation. In this case, concerted dyotropic shift results in avoiding the formation of a less stable secondary cation, which was earlier proposed as the most probable intermediate of cation rearrangements typical of terpenes. According to DFT calculations,[35] the activation barrier to dyotropic shift in the pinene cation is ~8 kcal mol^{-1} and the energy benefit about 10 kcal mol^{-1}.

Concerted migration (dyotropic shift) of two alkyl groups or H atoms is also observed in neutral molecules.[36] For organometallic compounds, migrations of metal-containing fragments are allowed.[37,38] Scheme 11 presents examples of π,π- and σ,π-dyotropic shifts of two metal-containing groups.[37]

Scheme 11

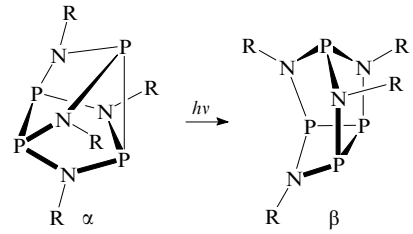


Cp is η^5-cyclopentadienyl

In the former case, a concerted [1,2]- or [1,3]-migration of organometallic fragments occurs.[39] In the latter case, dissolution of crystals in a polar solvent, *e.g.*, acetone is followed by spontaneous migration of metal carbonyl groups; the equilibrium is attained after 24 h at 30 °C.[40]

Photochemical dyotropic rearrangement of α- to β-phosphazane (Scheme 12) was studied.[41]

Scheme 12



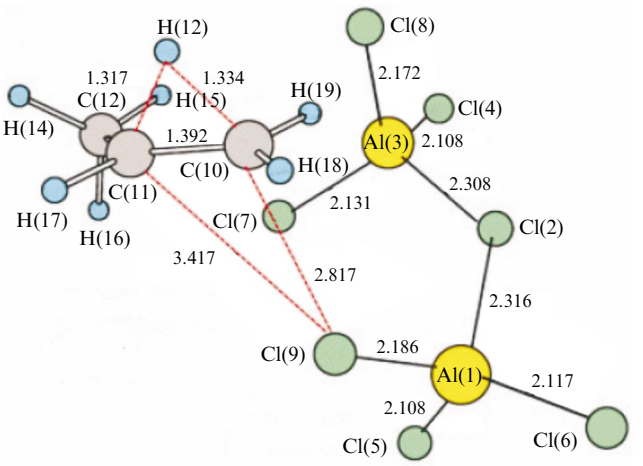


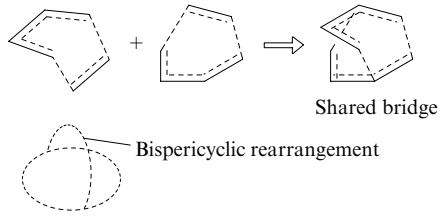
Figure 1. Transition state of isomerization of n-propyl fragment with concerted shift of H(12) and Cl(9) atoms.[42]
Distances are given in Ångströms.

The Friedel–Crafts reaction (alkylation of aromatic compounds) was discovered more than 100 years ago and its mechanism is part of all textbooks of organic chemistry; however, it is not known with certainty. Recently, a detailed comparative DFT study[42] of the mechanisms of the Friedel–Crafts alkylation and acylation of arenes revealed some interesting aspects. In particular, it was shown that carbocation rearrangement in the course of benzene alkylation with 1-chloropropane in the presence of aluminium chloride does occur as concerted dyotropic [1,2]-shift of the H(12) atom in propyl cation and the Cl(9) atom from the $Al_2Cl_7^-$ anion (Fig. 1).

2. Bispericyclic reactions

Processes involving fusion of transition states of two cycloaddition reactions (*e.g.*, [4+2] cycloaddition reactions) are called 'bispericyclic' ones (Scheme 13).[6]

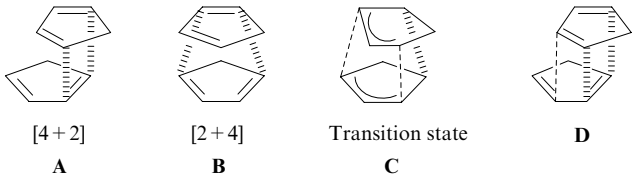
Scheme 13



Usually, they are characterzed by complex potential energy surfaces with a number of bifurcation points. Typical examples can be found in the literature.[43–47]

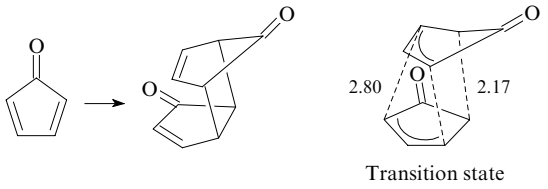
In this context, it is interesting to consider the dimerization of cyclopentadiene which affords the *endo*-adduct. Woodward and Hoffmann made an attempt to explain the observed stereochemistry using their concept of 'secondary orbital interactions'.[48] However, this concept still has no rigorous theoretical substantiation and is often questioned because in almost all cases alternative interpretations of the observed stereochemistry were also possible.[49,50] It was found[45] that dimerization of cyclopentadiene proceeds *via* a bispericyclic transition state (**C** in Scheme 14), which is a superposition of transition states of the [4+2]- and [2+4]-cycloaddition reactions (**A** and **B**, respectively) and differs from the Woodward and Hoffmann scheme of secondary orbital interactions (**D**) proposed[48] to explain the observed stereochemistry.

Scheme 14



Even more striking example of the fusion of two allowed cycloaddition reaction pathways is provided by the dimerization of cyclopentadienone which proceeds in the gas phase at 40 K and results in the *endo*-dimer as the sole product (Scheme 15, distances are given in Ångströms).

Scheme 15

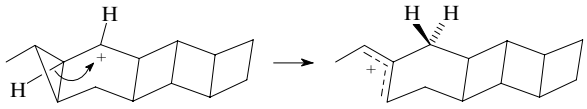


In this case, electrostatic interactions enhance the reactivity compared to cyclopentadiene and the higher stereoselectivity can be explained by more efficient relief of antiaromaticity in the bispericyclic transition state.[45]

3. Hiscotropic rearrangements

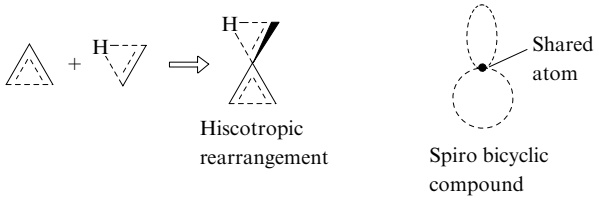
The transition states of complex one-step reactions considered above include a transition state in which the cyclic electron systems of each component form a shared bond or shared bridge. One can assume that systems connected through a shared atom can also exist. Indeed, reactions resulting in such systems were discovered. According to DFT calcualtions, a rearrangement affording 'ladderanes' involves a [1,2]-sigmatropic shift of H atom combined with a 2e electrocyclic reaction of three-membered ring opening (Scheme 16).

Scheme 16



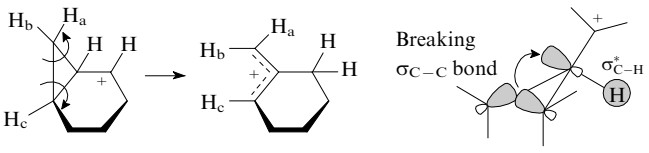
This is a concerted reaction, although not synchronous one. Attempts to locate a cyclopropyl cation failed; an open-chain cation is immediately formed instead. The transition state directly connects the structures shown above. It involves electron delocalization over the conjugated spirobicyclic system (Scheme 17). This process was called hiscotropic rearrangement.[6] As far as we know, this is the only example of such a process, but more exactly it should be classified as [1/2]/2e-hiscotropic rearrangement.

Scheme 17



A detailed theoretical analysis of the activation energy, stereochemistry and synchronicity of the hiscotropic rearrangement was made using a simpler model reaction (Scheme 18) as an example.[6]

Scheme 18



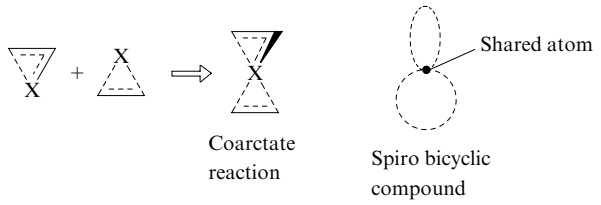
It was shown that the reaction is concerted, but the hydride shift and ring opening occur asynchronously. The two-electron electrocyclic reaction proceeds in disrotatory fashion, being favoured by interactions between the orbitals of the breaking σ-C–C bond and the σ*-orbital of the C–H bond. These interactions govern the ring opening direction (see Scheme 18).

The activation energy of the hiscotropic rearrangement under study appeared to be rather high, namely, 25–42 kcal mol^{-1} depending on the nature of substituents,[6] although the [1,2]-hydride shift and opening of the cyclopropyl cation usually occur almost barrierlessly. A possible reason is partial loss of conjugation in the early steps of the reaction pathway. This should be done before the hydride shift can occur (empty p-orbital should rotate to ensure the overlap with the C–H bond rather than the C–C bond in the three-membered ring). However, it should be noted that the activation energy of hiscotropic rearrangement is comparable with that of the DePuy reaction (25–35 kcal mol^{-1}).[51] At first glance, one can assume that a hydride ion is not a good leaving group compared to bromide or sulfonate ion, but in the hiscotropic reaction its elimination should be facilitated by the close-lying cationic centre.

4. Coarctate reactions

Spirobicyclic electron delocalization in the transition state is characteristic of yet another type of reactions called coarctate ones (see Section III). These reactions can also be treated as combinations of several pericyclic reactions whose transition states share one or more atoms and(or) have overlapping π-systems (Scheme 19).[6]

Scheme 19

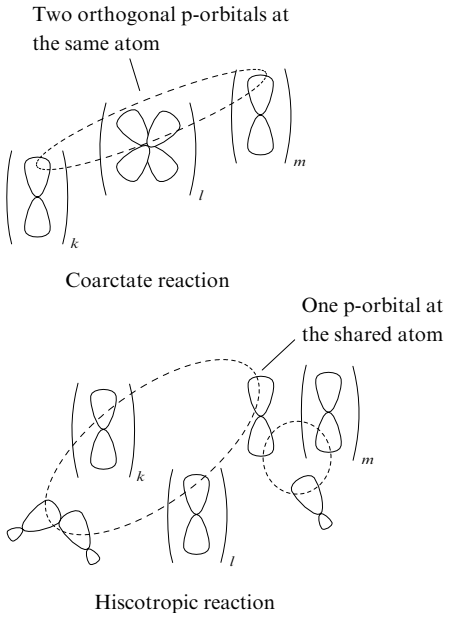


Unlike hiscotropic rearrangements, in coarctate reactions two delocalized cyclic systems are linked involving two orthogonal p-orbitals rather than one p-orbital. This is due to the fact that coarctate reactions invlove simultaneous breakdown and formation of at least two bonds at one or more atoms; therefore, the orbital basis set includes two orbitals of each atom (Scheme 20; for more details, see Section IV).

The theory of coarctate transition state was elaborated in the 1990s by German chemist Herges.[7] In essence, this is a continuation and further development of the Woodward–Hoffmann theory for spirocyclic conjugated systems. The appearance of this theory *per se* is remarkable. It points that the orbital approach to organic reactions laid down in the 20th century by eminent chemists such as Fukui, Woodward, Hoffmann, Dewar and Zimmerman still has a great potential and can be extended to other types of concerted reactions.

Among reactions with complex topology of the electron shift and bicyclic delocalized transition state, *i.e.*, dyotropic, bispericyclic, hiscotropic and coarctate reactions, the last-mentioned processes belong to the most intensively studied ones. Therefore, this review includes a large corresponding

Scheme 20



Section (see Section IV). Topological analysis of reaction mechanisms made it possible to re-examine experimental data obtained in the 1970–1980s and to take a new look at these reactions. Understanding of reaction mechanisms is also basic to the design of targeted synthesis. In particular, recently coarctate reactions have served as a basis for intensive development of novel approaches to the synthesis of complex heterocyclic systems. As most pericyclic reactions, these processes have low activation barriers, proceed under mild conditions and are characterized by high degree of stereochemical control; this makes them particularly promising for synthetic practice.

IV. Coarctate reactions

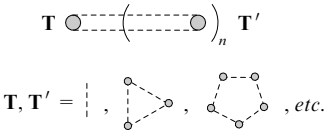
This Section deals with different categories of coarctate reactions following the classification proposed by Herges in 1994 [7] and present relevant examples. An analysis of more recent publications showed that the main conclusions and predictions made by Herges [7] appeared to be correct, but in some cases progress in computational methods and experimental techniques led to refinement of reaction mechanisms. Methods for comparison of coarctate and pseudopericyclic transition states from the standpoint of both understanding the reaction mechanism and the applicability to various types of substrates and their vinylogues were updated.

1. Topological analysis of reactions proceeding *via* a coarctate transition state

As mentioned above (see Introduction), coarctate reactions form a rather large class of reactions characterized by simultaneous breakdown and formation of at least two bonds at one or more atoms. It includes a variety of reactions involving carbenes and their hetero analogues, as well as some other reactions.

A formal general scheme of coarctate reactions can be represented [7] by a linear sequence of breaking and forming bonds, which includes *n* atoms and is limited by two 'terminators' **T** and **T′** (Scheme 21).

Scheme 21

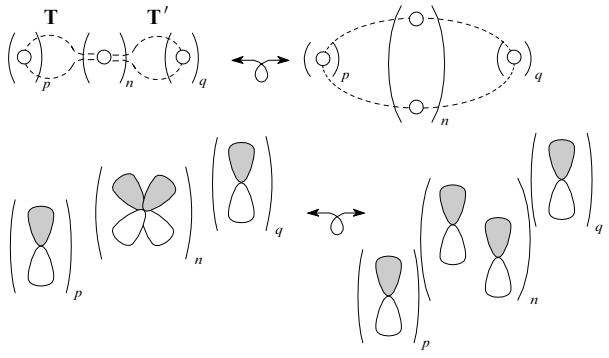


Terminators are molecular fragments in which only one bond breaks or forms at each atom in contrast to a linear coarctate subsystem where at least two bonds at each constituent atom simultaneously break and form. Terminators can be either lone electron pairs (denoted by vertical dashed line in Scheme 21), which are made or removed as a result of reaction as in, *e.g.*, the case of reactions involving carbenes, or pericyclic fragments with different number of atoms (cyclic electron shift).

In developing the theory of coarctate reactions Herges [7] used the topological method based on the transition state aromaticity and proposed earlier for pericyclic reactions.[52–56] Cyclic transition states of pericyclic reactions can have a Hückel or Möbius topology. Since transition states of coarctate reactions simultaneously include both cyclic and linear subsystems, Herges [7] proposed a method which allows one to construct orbitals of coarctate transition states by topological transformation of the molecular orbitals of aromatic systems.

For instance, the transition state of a reaction, which contains an *n*-atomic linear subsystems and two cyclic terminators including *p* and *q* atoms, can be obtained by topological transformation of a cyclic conjugated system composed of $(p+q+2n)$ basis orbitals (Scheme 22).[7] Each of the $p+q$ centres characterized by one breaking bond or one forming bond (an electron pair is made or removed) has one basis orbital. Each of *n* centres characterized by simultaneous cleavage and formation of two bonds has two orthogonal basis p-orbitals rotated by 45° relative to the remaining basis set. Opening of a linear subsystem ('compressed loop') is accompanied by the formation of a topologically equivalent cyclic system which can be analyzed using the concepts of Hückel or Möbius aromaticity.

Scheme 22



If a spirocyclic conjugated system has $(4n+2)$ electrons, where $n = 0, 1, 2$, *etc.*, and the number of inversions of the orbital phase *i* is even, one deals with the Hückel topology of the transition state. The case for $4n$ electrons and odd number of inversions *i* corresponds to Möbius topology. Similarly to pericyclic reactions, coarctate thermal reactions mainly proceed *via* an aromatic transition state, whereas photochemical reactions proceed *via* an antiaromatic transition state. Also, two kinds of aromaticity and antiaromaticity, the Hückel and Möbius, are considered for coarctate systems.

If several stereochemically different reaction pathways are allowed, the most favourable one ensures a maximum overlap of the orbital basis set.

2. Various categories of coarctate reactions in the synthesis

Review [7] presents a detailed topological analysis of coarctate reactions with various terminators. The spectrum of known coarctate reactions is rather broad; however, the most abundant are reactions in which at least one terminator is an electron pair or the empty orbital of carbene. This is due to 'flexible' geometry, which makes it possible to 'tune' the number of electrons necessary to obtain an aromatic transition state.

Special rules for carbene reactions are as follows:[7]

— if the orientation of the carbene centre is not stereochemically fixed, it is determined by the number of electrons in the remaining orbital basis set; if it includes $4n$ electrons, the carbene is rotated to donate its electron pair to obtain a $(4n+2)$-electron Hückel topology;

— if the remaining orbital basis set includes $(4n+2)$ electrons, the empty p-orbital of carbene is involved in the transition state; explicit consequences may arise only if the free orientation of the carbene centre is hindered (*i.e.*, it is stereochemically fixed).

In this review we will present only a few typical examples first considered by Herges in order to illustrate his principles of analysis. The emphasis will be placed on the studies reported after the Herges review;[7] this concerns new approaches to the synthesis of heterocycles and to comparison of pseudopericyclic and coarctate reactions.

a. Lone electron pairs as terminators

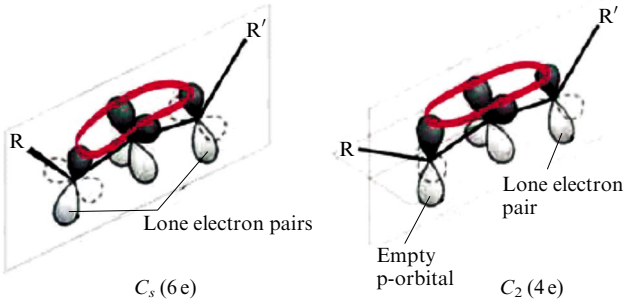
This reaction class includes migration of the triple bond in singlet carbenes (Scheme 23).

Scheme 23



Depending on the conformation, either the empty orbital of carbene (4e, therefore, one can expect a photochemical reaction) or its lone electron pair (6e, thermal reaction is allowed) (Scheme 24) can participate in the reaction.[7,57]

Scheme 24



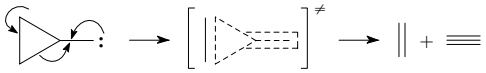
C_s (6e) C_2 (4e)

This type of reactions is exemplified in Refs 58–60.

b. Carbene electron pair and three- and five-membered rings as terminators

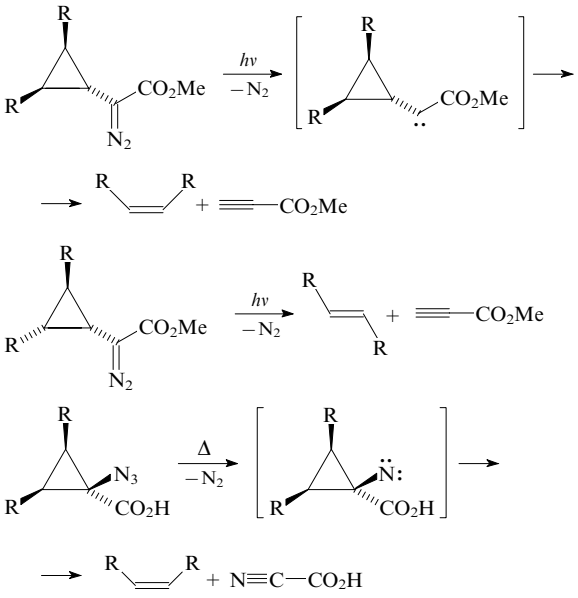
Many coarctate reactions have long been known and used in synthetic practice; however, their mechanism was understood only after the development of topological analysis by Herges.[7] An example is provided by the fragmentation of cyclopropylcarbenes (Scheme 25) discovered by Friedman and Shechter in 1960.[61]

Scheme 25



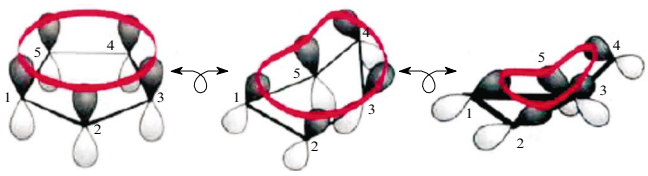
This is a common reaction allowed not only for carbenes, but also nitrenes (Scheme 26).[62–64]

Scheme 26



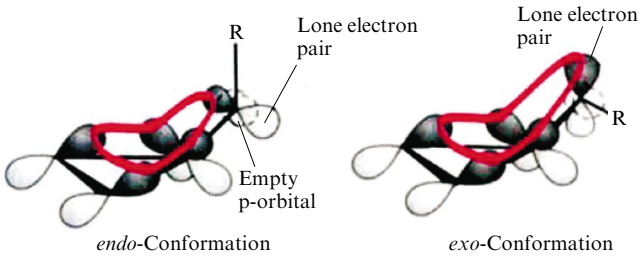
A distinctive feature of the reactions shown in Scheme 26 is high stereoselectivity, namely, the configuration of the cyclopropane ring in the alkene product is retained. The transition states of these reactions (Scheme 27) are iso-conjugated to that of the five-centre six-electron pericyclic reaction (*e.g.*, 1,3-dipolar cycloaddition). Although the mechanisms of these two reactions are fundamentally different, their transition states are stabilized through the same interactions.

Scheme 27



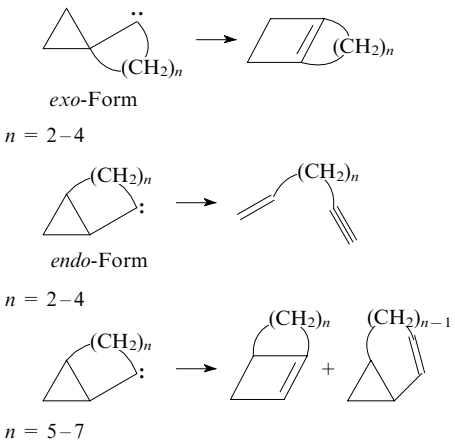
A topological analysis of a reaction showed[7] that, since the stereochemistry of the carbene centre in this case is not stereochemcally fixed, it can exist as *exo*- and *endo*-conformers (Scheme 28) and different transition states with participation of the empty orbital of carbene or its electron pair are theoretically allowed.

Scheme 28



The transition state involving the lone electron pair of carbene (6 π-electrons, Hückel aromaticity) is thermally allowed. Therefore, one can expect that the reaction is facilitated in the case of *endo*-isomer. This is clearly illustrated by the experimental data for bicyclic carbenes with fixed geometry of the carbene centre. Scheme 29 shows that a coarctate fragmentation reaction readily proceeds in the case of the *endo*-isomer,[65] whereas a carbene insertion leading to extension of the ring occurs for the *exo*-isomer.[66–68]

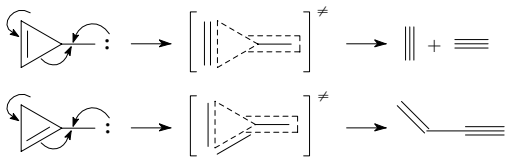
Scheme 29



The reaction of conformationally flexible bicyclic carbenes ($n = 5–7$) used instead of the *endo*-systems with stereochemically fixed geometry results in a mixture of products.[69, 70]

A topological analysis[7] of the fragmentation of cyclopropenylcarbenes gives similar results because the double bond is not involved in the reaction and the reaction proceeds *via* the same transition state with 6 π-electrons. High yields were obtained for both carbenes[71–73] and their nitrogen-containing analogues, nitrenes.[74–76] A general scheme of this reaction is presented in Scheme 30; the composition of products depends on position of the double bond in the ring.

Scheme 30

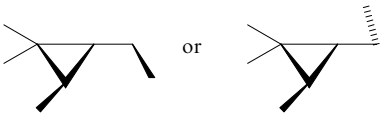


Ab initio calculations[7] revealed only two stationary points corresponding to the cycloprop-1-enylcarbene structures with different orientation of the substituent at the

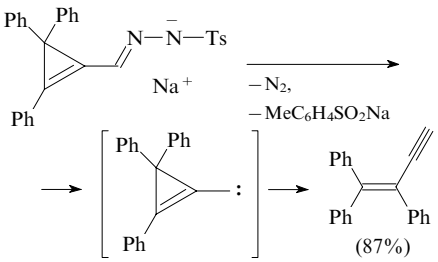
carbene centre; in both cases, it lies in the ring plane, but the respective torsion angles differ by 180° (Scheme 31). Deviation of the substituent from the ring plane by more than 20° causes a spontaneous rearrangement.

The results of calculations are in good agreement with the Hückel topology of the 6e coarctate transition state in the *endo*-conformation (see Scheme 28).[7]

Scheme 31

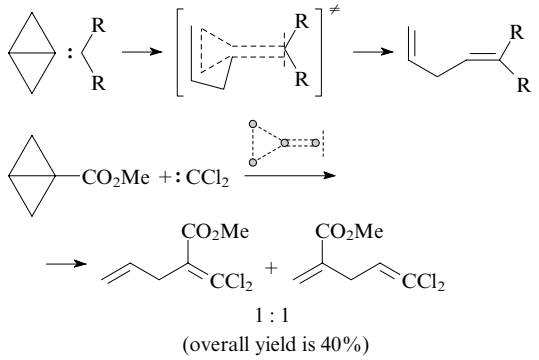


Structures corresponding to stationary points



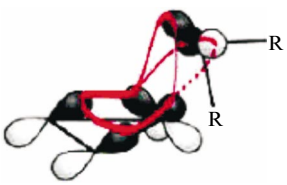
Yet another interesting reaction is carbene addition to bicyclobutanes affording 1,4-dienes. It was for the first time reported by von E Doering[77] in 1965, but its mechanism was proved only in 1985.[78] It was found that it is a concerted reaction involving singlet carbene (Scheme 32)[78] rather than a biradical process assumed earlier.[77, 79]

Scheme 32



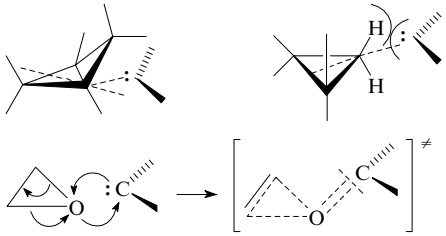
Scheme 32 shows that, formally, one cyclopropane fragment is involved in the reaction. However, the reaction of cyclopropane with carbene proceeds by the insertion mechanism and leads to ring expension. What is the reason for the occurrence of a coarctate process for bicyclobutanes? The answer is provided by the topological analysis[7] and MNDO calculations,[78] which indicate that most favourable is the transition state in which carbene is above the cyclopropane ring plane (angle between the cyclopropane ring plane and the bond with carbene is 30°) (see Scheme 33 where only one three-membered ring is shown).

Scheme 33



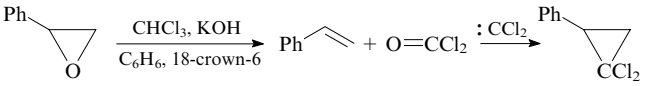
It becomes understandable why bicyclobutanes rather than cyclopropane enter the reaction. The reason is the effect of steric hindrances, *viz*., a hydrogen atom in cyclopropane precludes the attack of carbene, whereas the one and only substituent in the bicyclobutane molecule is oriented away from the attacking carbene (Scheme 34).[78] These steric hindrances can be eliminated by replacing a CH_2 group in cyclopropane molecule by an O atom (*i.e*., on going to oxirane molecule) Indeed, such a reaction was reported.[80]

Scheme 34

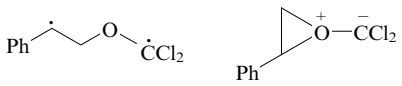


The synchronicity of cleavage of both C–O bonds in the deoxygenation of styrene oxide was evaluated using the kinetic isotope effect.[81] It was found that the reaction (Scheme 35) is not synchronous, namely, one C–O bond is cleaved somewhat faster than the other.

Scheme 35



An early transition state is realized; however, no intermediate (biradical or ylide)



is also observed because the reaction immediately results in stable products (Fig. 2).

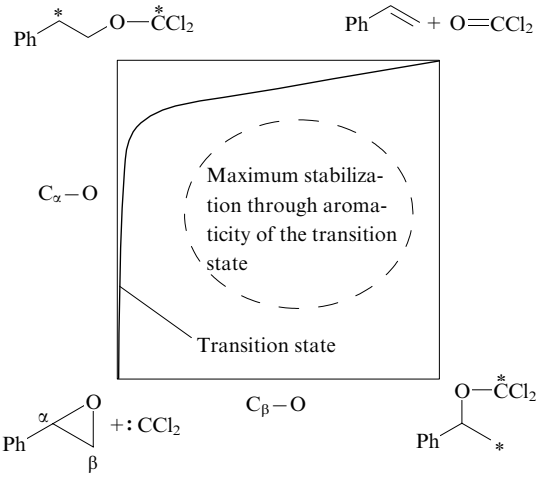
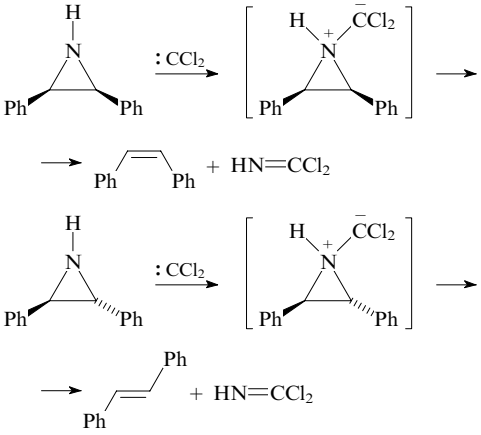


Figure 2. More O'Ferrall–Jencks diagram for styrene oxide deoxygenation by dichlorocarbene.
The asterisk denotes '•' or '+/–'.

In due course time, Dewar showed that exactly synchronous bond cleavage is rather rare to occur even in concerted reactions.[82] This asynchronicity may preclude only additional stabilization of transition state through its aromaticity (as in pericyclic and coarctate reactions). The issue as to how the aromaticity of a transition state facititates synchronicity should be solved individualy for each particular case.

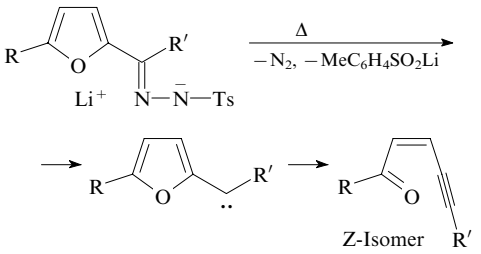
In a study of aziridines,[83] it was proved that the addition of carbenes proceeds by the stepwise dipolar mechanism with the formation of ylide as intermediate (Scheme 36).

Scheme 36



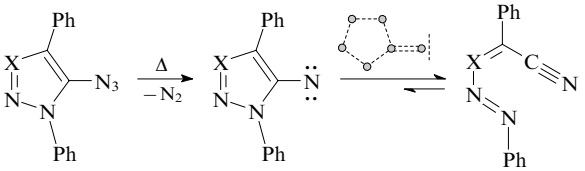
Reactions of carbenes containing five-membered rather than three-membered rings as substituents also have long been known. For instance, rearrangement of furylidenes was discovered by Hoffman and Shechter[84] in 1971. It was found that the the furan ring opening (Scheme 37) proceeds stereoselectively and yields only the *cis*-isomer.[85]

Scheme 37



Similar reactions were also reported for pyrazoles[86] and triazoles[87,88] (Scheme 38).

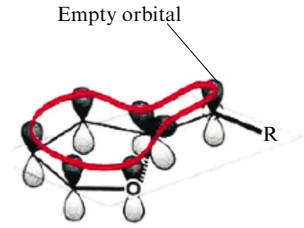
Scheme 38



X = CH, N

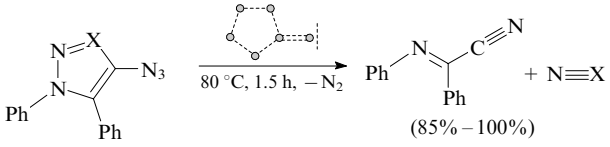
Herges[7] who studied the mechanism of the reactions shown in Schemes 37 and 38 assumed that the processes are coarctate. Stereochemical control of these reactions is basically different from the case for three-membered terminators (*e.g.*, oxirane). With the five-membered terminator, the orbital basis set contains two more electrons; therefore, the empty orbital of carbene should be involved to attain a transition state with 6e Hückel aromaticity. To this end, the substituent at the carbene centre should lie in the five-membered ring plane. The transition state shown in Scheme 39 is iso-conjugated to tropylium cation.[7]

Scheme 39



Reactions presented in Scheme 40 are also expected to proceed. Here, substrates differ in the relative position of the carbene centre and double bonds, but the orbital basis is the same. Indeed, such reactions are known for nitrenes containing nitrogen atoms in the five-membered ring.[88,89] The driving force of these reactions is the formation of thermodynamically stable compounds with a triple bond, N_2 and $N{\equiv}CR$.

Scheme 40



X = N, CH, CR

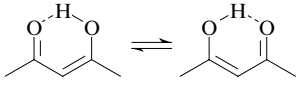
Fragmentations of carbenes containing no heteroatoms in the five-membered ring were not reported at that time; however, reactions predicted by Herges in 1994 were conducted experimentally. This made it possible to study how the nature of heteroatom influences the reaction mechanism. It was found that opening of the cyclopentadiene ring is a coarctate reaction, whereas in the case of furan and pyrrole derivatives the reaction proceeds as pseudopericyclic process.

c. Coarctate and pseudopericyclic reactions

The notion 'pseudopericyclic reactions' was formulated by Ross[90] in 1976. According to his definition, 'a pseudopericyclic reaction is a concerted transformation whose primary changes in bonding compass a cyclic array of atoms, at one (or more) of which nonbonding and bonding atomic orbitals interchange roles'. This means a 'disconnection' in the overlapping orbitals because the orbitals that switch their functions are orthogonal. An important consequence is that pseudopericyclic reactions cannot be orbital symmetry forbidden.

Pseudopericyclic reactions include[90] various well-known reactions, *e.g.*, prototropic tautomerism of β-dicarbonyl compounds (Scheme 41).

Scheme 41

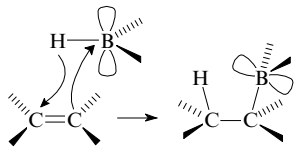


The lone electron pair and the bonding orbital of the O – H bond at two oxygen atoms switch functions; the

reaction proceeds *via* a planar cyclic six-membered transition state.

Hydroboration of alkenes (Scheme 42) can also be considered as pseudopericyclic reactions.

Scheme 42



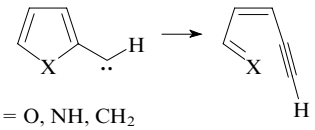
The empty orbital of the B atom becomes a bonding orbital and the σ-orbital of the B–H bond becomes the nonbonding orbital of the B atom; the reaction proceeds *via* a planar 4e transition state.

The pseudopericyclic mechanism was also proposed[90] for sigmatropic rearrangement in tetra(trifluoromethyl)thiophene-*S*-oxide (so-called 'Dewar thiophene'). However, more recently this assumption was rejected.[91] It was found that [1,3]-sigmatropic shifts in this compound and in the structurally similar bicyclo[2.1.0]pentene are typical pericyclic reactions.

Since the notion of coarctate reactions was introduced much more recently than that of pseudopericyclic reactions, a first comparative study was reported only in 2000.[92] The idea to compare was reasonable because in both cases one deals with concerted reactions involving two orthogonal basis orbitals.

Consider the opening mechanism of the five-membered ring in corresponding carbenes (Scheme 43).

Scheme 43

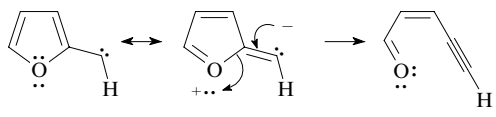


X = O, NH, CH_2

Experimental data and results of calculations point that in all cases the five-membered ring is opened readily, namely, the barrier is about 4.7 kcal mol^{-1} for the *anti*-conformation and 1.2 kcal mol^{-1} for the *syn*-conformation.[93] If a reaction proceeds by the coarctate mechanism, its transition state is a 'compressed loop' involving the empty orbital of carbene (6 electrons), as was assumed by Herges (see Scheme 39).[7] However, more recent calculations for furans (X = O) revealed a planar transition state geometry.[92] At the same time, the coarctate transition state should be nonplanar; otherwise, the breaking orbitals of the σ-bond lying in the ring plane cannot overlap with π-orbitals lying out of this plane.

On the other hand, the transition state of a pseudopericyclic reaction should be planar, and there is a disconnection between two orbital systems.[94–96] This is clearly seen in the resonance scheme (Scheme 44).[92]

Scheme 44



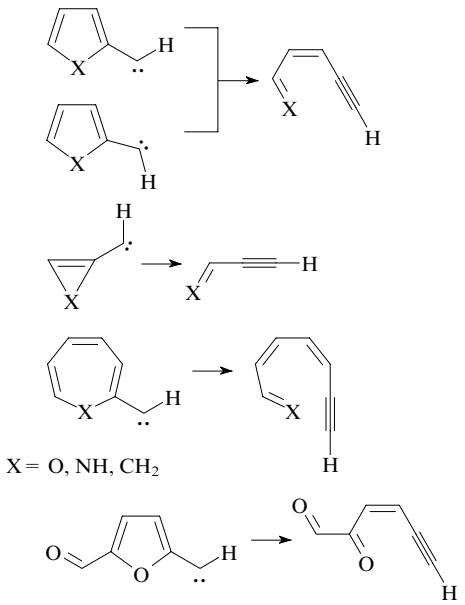
Disconnection in the overlapping orbitals leads to two consequences.[92]

1. The transition state cannot be aromatic or antiaromatic because there is no 'loop' of the overlapping orbitals. Therefore, reaction cannot be orbital symmetry forbidden.

2. Since there is no inter-electron repulsion unavoidable for cyclic orbital overlap, the reaction can proceed almost barrierlessly.

One can decide between two possible transition state topologies (pseudopericyclic or coarctate) based on the respective chemical consequences. For instance, a pseudopericyclic reaction with a planar transition state should also be allowed for vinylogues of the initial furylcarbene (Scheme 45).

Scheme 45



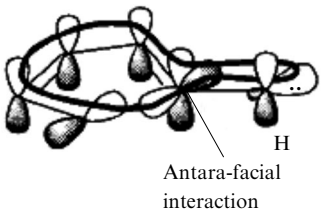
If the reaction proceeds *via* a nonplanar coarctate transition state, for vinylogues the number of electrons in the transition state will be different. This will lead to realization of various ring opening pathways, namely, disrotatory or conrotatory, which is equivalent to the Hückel or Möbius topology, respectively. This unavoidably should lead to different stereochemistry of reaction products. The conclusions drawn are in excellent agreement with the results of calculations.[92]

In the case of cyclopentadienylcarbene (X = CH_2), the initial molecule is also planar. However, the transition state should not be planar because cleavage of the σ-bond and formation of the π-bond requires rotation of both H atoms of the CH_2 group (two electrons of the σ-bond go to the π-system). According to calculations, the highest occupied molecular orbital (HOMO) is a linear combination of orbitals of the breaking σ-bond and the lone electron pair orbital of carbene; the lowest unoccupied molecular orbital (LUMO) is a π*-orbital. Considering the interaction between the frontier orbitals of the breaking σ-bond and the π-system, one can see that maximum overlap between the LUMO and HOMO requires a conrotatory motion of the electron pairs of carbene and CH_2 group.

The same result can be obtained by considering the transition state of a coarctate reaction. It has 8 electrons (4π-electrons + 2σ-electrons + 2 electrons from carbene). It is important that in the transition state participate both the electron pair and the empty orbital of carbene (contrary to the assumption by Herges,[7] see Scheme 39). Thus, the

transition state (Scheme 46) has a Möbius topology with one inversion.[92]

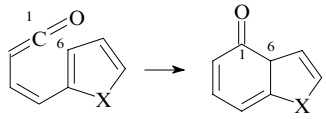
Scheme 46



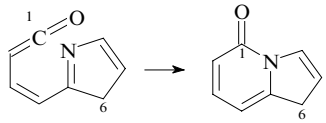
If the opening of cyclopentadienylcarbene proceeds in a conrotatory fashion (8e), a disrotatory process can be expected for its vinylogues (6e and 10e). This was confirmed by calculations and experimentally.[92]

Pericyclic and pseudopericyclic reactions were also compared in another study[97] whose authors considered the influence of the nature and position of heteroatom on the mechanism of cyclization of dienyl ketenes resulting in cyclohexadienones (Scheme 47).

Scheme 47



X = O, NH, CH_2, S



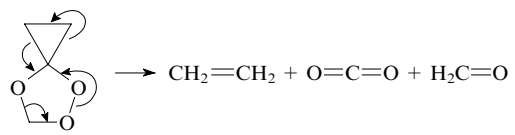
It was found that the upper reaction in Scheme 47 can be treated as pericyclic one with well-defined aromatic transition state, whereas the lower reaction is pseudopericyclic.

d. Reactions of systems with three- and five-membered cyclic terminators

Coarctate reactions with three- and five-membered terminators are more rarely to occur than reactions with the lone electron pair as terminator (carbene). This is due to the fact that in the case of carbenes and carbene analogues the Hückel number of electrons can be obtained using the empty orbital or the lone electron pair of carbene in the transition state. In most cases, this is readily attained by changing the conformation of the carbene centre, which is usually impossible for cyclic terminators.

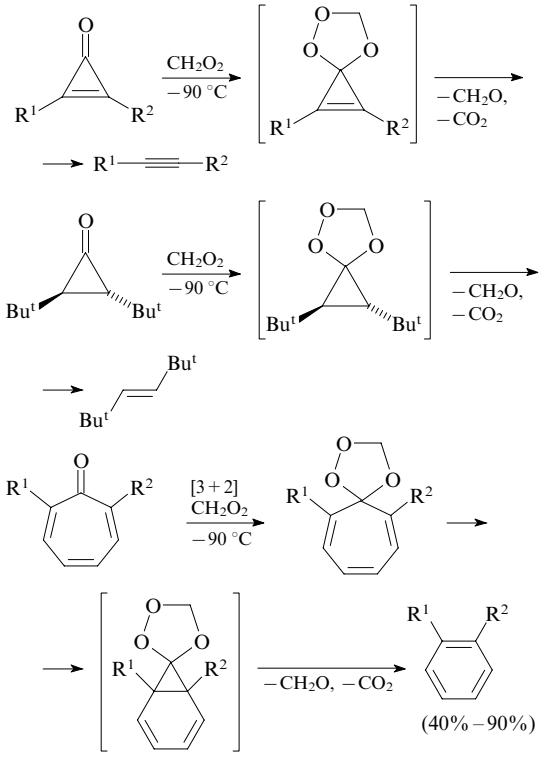
Spontaneous fragmentation of spirocyclic secondary ozonides is a typical example of a coarctate reaction with two breaking C–C bonds and two forming C–O bonds (Scheme 48).[98]

Scheme 48



Spirocyclic ozonides are synthesized *in situ* by the [3 + 2]-cycloaddition of formaldehyde *O*-oxide [$CH_2^+-O-O^-$] to various ketones.[99] At −90 °C, the ozonide decomposes to alkenes, alkynes or 1,2-disubstituted arenes, the reaction being stereoselective (Scheme 49).

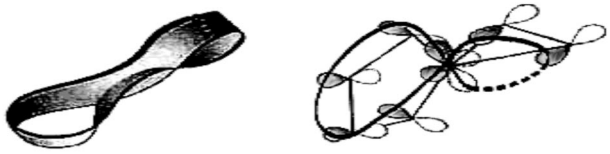
Scheme 49



R = H, Alk, Ph, Hal

The unexpectedly low activation barrier to this reaction can be explained by the fact that the process proceeds *via* a 8e (for cyclopropyl or cyclopropenyl ketones) or 12e (for cycloheptatrienyl ketones) coarctate transition state with one inversion, which is aromatic according to Möbius (Scheme 50).[98]

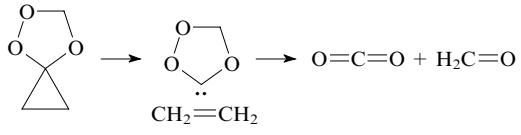
Scheme 50



One can expect that fragmentation of the spirocyclic ozonide obtained from cyclopent-3-enone (orbital basis set includes 10 electrons) will be symmetry forbidden because, according to stereochemical selection rules for coarctate reactions, it should proceed *via* a planar Hückel transition state impossible for the spiro compound. This was confirmed experimentally.[98]

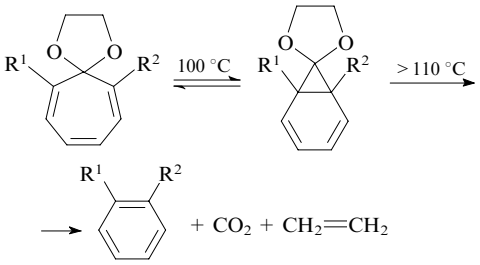
Calculations of alternative two-step reaction pathway with the formation of carbene intermediate (Scheme 51) revealed[95] no stationary point corresponding to carbene on the reaction coordinate. Carbene immediately undergoes a spontaneous fragmentation to CO_2 and CH_2O. Therefore, in this case the two-step reaction mechanism is hardly probable.

Scheme 51



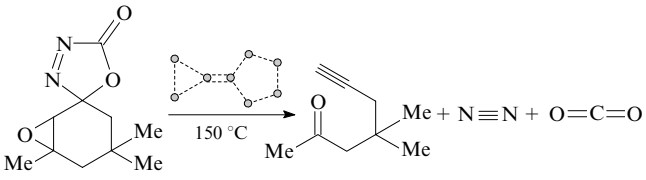
An analogous fragmentation can also be done for acetals (Scheme 52); however, this requires heating to nearly 100 °C.[98] The reason is that the energy of the C–O bond (85 kcal mol^{-1}, see Ref. 100) is much higher than that of the O–O bond (40 kcal mol^{-1}, see Ref. 98).

Scheme 52

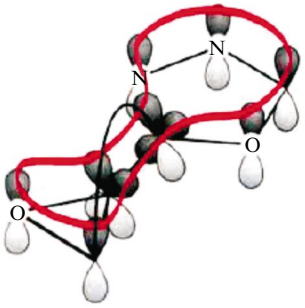


Some examples of coarctate reactions with three- and five-membered terminators were also considered by Herges.[7] One of them is shown in Scheme 53. The Hückel type transition state of this reaction includes 10 electrons (Scheme 54).[7]

Scheme 53



Scheme 54

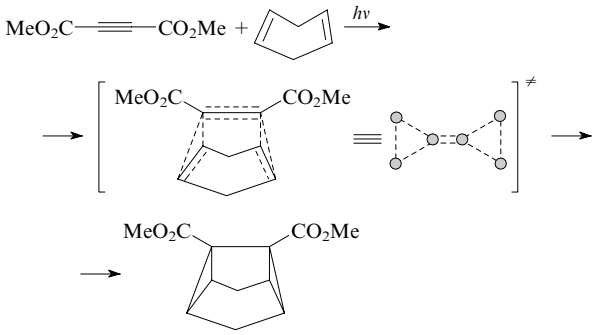


The addition of acetylenes to cyclohexa-1,4-diene is one of a few examples of coarctate reactions whose analysis does not require a topological transformation of the orbital basis set (acetylene has two pairs of orthogonal orbitals). Here, there is a 8e transition state (number of inversions $i = 0$) with Hückel antiaromaticity (Schemes 55 and 56). Therefore, a photochemical reaction should be allowed, which was proved experimentally.[101–103]

Scheme 55



Scheme 56

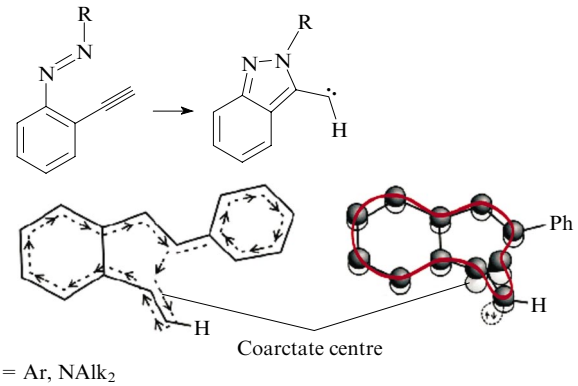


e. Synthesis of heterocyclic systems

The development of novel methods for the synthesis of heterocyclic compounds and extension of the knowledge of the mechanisms of known reactions is of particular interest because N-, S- and O-containing heterocycles are constituents of many biologically active compounds and pharmaceuticals. The use of concerted reactions characterized by clear stereochemical control and tolerance to introduction of various functional groups seems to be very attractive for synthetic practice. Recently, there has been intensive research in this field. In the text below we will present some examples of such reactions whose mechanisms were studied by computational or other methods. Knowledge of the reaction mechanism is of particular importance because this often allows one to choose an optimum strategy of synthesis.

Coarctate cyclization of (2-ethynylphenyl)phenyldiazenes and (2-ethynylphenyl)triazenes affords substituted isoindazoles (Scheme 57).[104–106] These reactions have low activation barriers and proceed under mild conditions. Scheme 57 shows the 10e transition state of coarctate cyclization of phenyldiazene (empty orbital of carbene is involved) and the orbital overlap topology.[104]

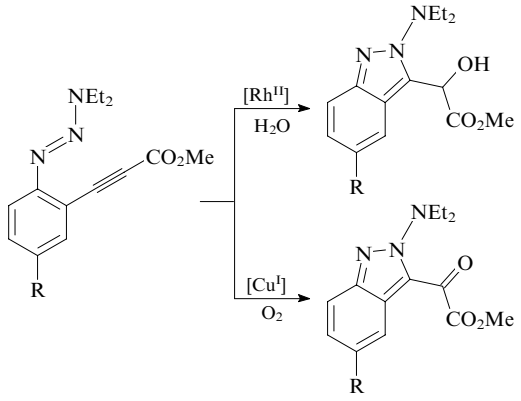
Scheme 57



R = Ar, NAlk$_2$

More recent studies of the same authors revealed that coarctate cyclization of azo-ene-yne systems is a common reaction tolerant to the presence of various functional groups. The introduction of an ester group into the acetylene fragment reduces even more the transition state energy and stabilizes the carbene.[107] The reaction can be initiated with CuCl or $[Rh(OAc)_2]_2$ and the isoindazole-containing carbene can be trapped with molecular oxygen or water; this makes it possible to obtain α-ketoesters or α-hydroxyesters in high yield (Scheme 58).

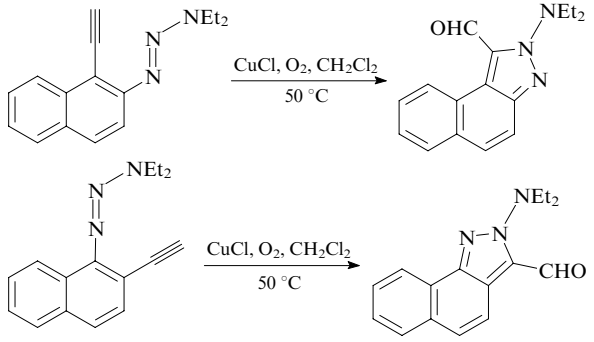
Scheme 58



R = H, Me, Bu^t, OMe, CF_3, NO_2, Cl, CN

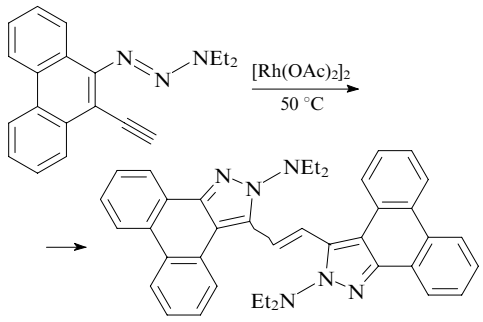
This approach was developed in a study of benzannelated derivatives of azo-ene-yne systems to synthesize heterocycles with extended π-system.[108] It was found that the introduction of naphthalene moiety has little effect on the transition-state energy. Cyclization of 1,2-substituted naphthalenes also furnishes benzisoindazoles (Scheme 59).

Scheme 59



Further extension of the π-system of dieneyne (going from naphthyl to phenanthrenyl derivatives) on the one hand showed that the reaction (see Scheme 57) is common in character and can be used to synthesize heteroaromatic compounds with extended π-system (they are of interest for fabrication of devices for optics and electronics). On the other hand, it disclosed some differences. For instance, it was established that phenanthrenyl derivatives are much more prone to dimerization (Scheme 60) than phenyl- and naphthyltriazenes.[109]

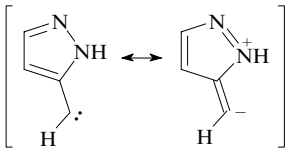
Scheme 60



According to DFT calculations,[109] pyrazoles (especially benzannelated ones) can effectively stabilize the singlet carbene formed in the course of the coarctate cyclization. The more stable the carbene the higher its stationary concentration and, therefore, the contribution of competing dimerization reaction.

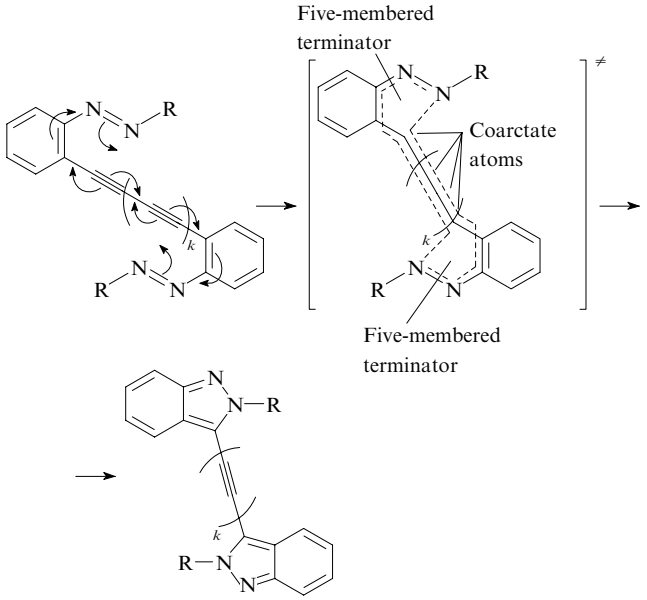
Singlet carbenes are stabilized through the interaction between the empty p-orbital of carbene (LUMO) and the HOMO of the close-lying heteroaromatic π-system. The extent of the interaction is determined by the width of the LUMO–HOMO energy gap and causes the $C_{carbene}-C$ bond in the coarctate carbene to shorten. Clearly, this type of stabilization is impossible for phenylcarbene (Scheme 61).

Scheme 61



A series of acetylene-bridged bis-2*H*-indazoles was synthesized by double coarctate cyclization of bis(phenyltriazenes) or bis(phenyldiazenes) with acetylene or butadiyne bridges.[110] Although this is a rather complex reaction involving a large number of bonds, it proceeds in a neutral medium under mild conditions (on minor heating) and affords the target heterocycles with yields exceeding 90%. According to DFT calculations,[15] this is a concerted reaction (although not rigorously synchronous) proceeding with the formation of short-lived carbene-type intermediate and involving a simultaneous cleavage and formation of sixteen bonds (Scheme 62).

Scheme 62

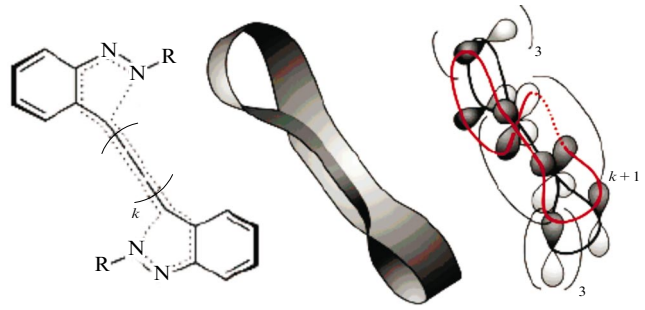


R = NEt_2, Ph; k = 0, 1

The transition state has a Möbius topology (16, *i.e.*, $4n$, π-electrons) with two five-membered isoindazole rings lying in perpendicular planes (Scheme 63).[110]

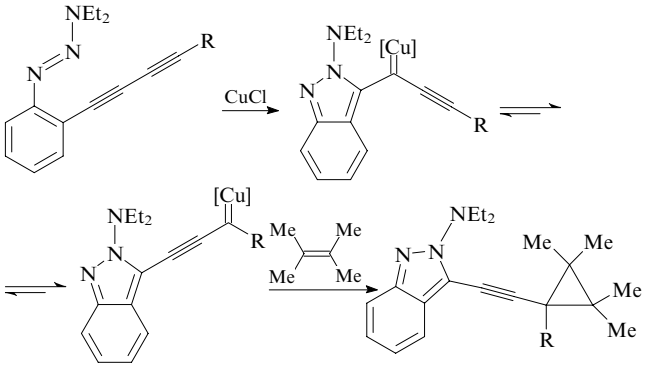
The fact that butadiyne systems participate in the reaction confirms the homology principle for coarctate reactions (see Section IV.3).

Scheme 63



Interest in tandem or domino-type cyclization reactions is due to the desire to find a simple and efficient route to heteropolycyclic systems. Coarctate cyclization of azo-ene-yne systems yielding isoindazolylcarbenes (see above) can be combined with 1,3-migration of the carbene centre along the polyyne chain followed by [1 + 2]-cycloaddition of the forming carbene resulting in the cyclopropane derivative (Scheme 64).[15]

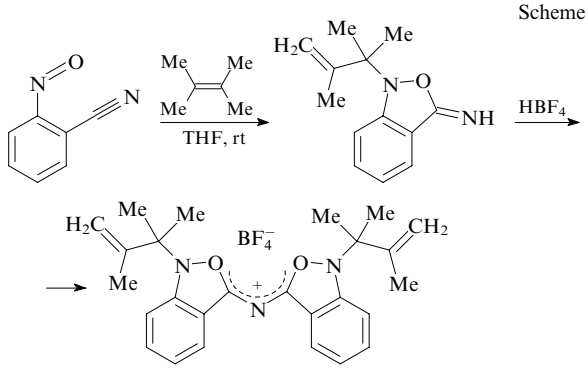
Scheme 64



R = Ph, biphenyl-2-yl

One would also expect an analogous coarctate cyclization for 2-nitrosobenzonitrile in which the aza group is replaced by a nitroso group. However, a tandem intramolecular cyclization (Scheme 65) resulting in substituted benzo[*c*]isoxazole-3(1*H*)-imines proceeds instead.[111]

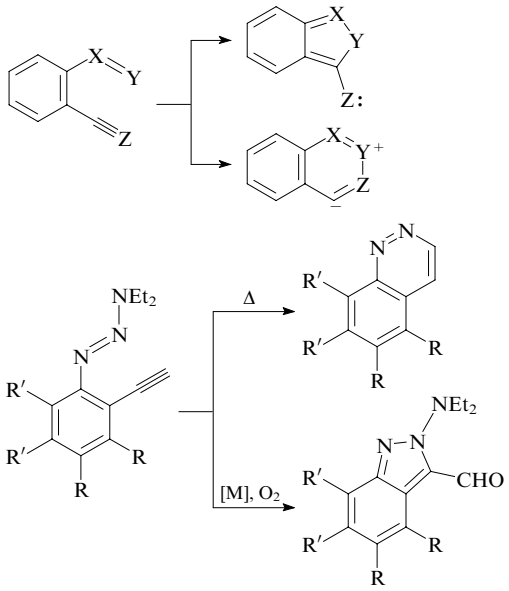
Scheme 65



rt is room temperature

An interesting feature of azo-ene-yne systems is their dual reactivity. In the presence of carbene-stabilizing metal salts, one deals with coarctate cyclization affording five-membered heterocycles, *e.g.*, isoindazoles (see above), whereas heating causes another pericyclic reaction, namely, the formation of six-membered heterocycles to occur.[104, 108, 109] Scheme 66 presents an example and a general formal scheme of two possible reaction pathways.

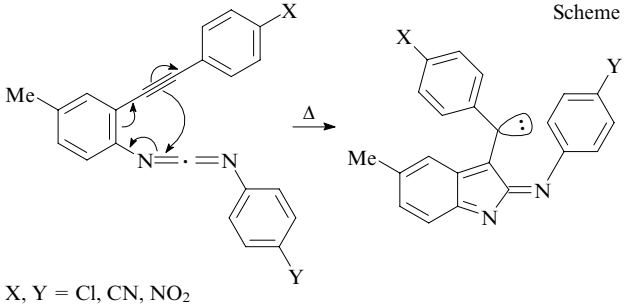
Scheme 66



R = R′ = H; R = H, R′–R′ is benzo; R–R = R′–R′ is benzo

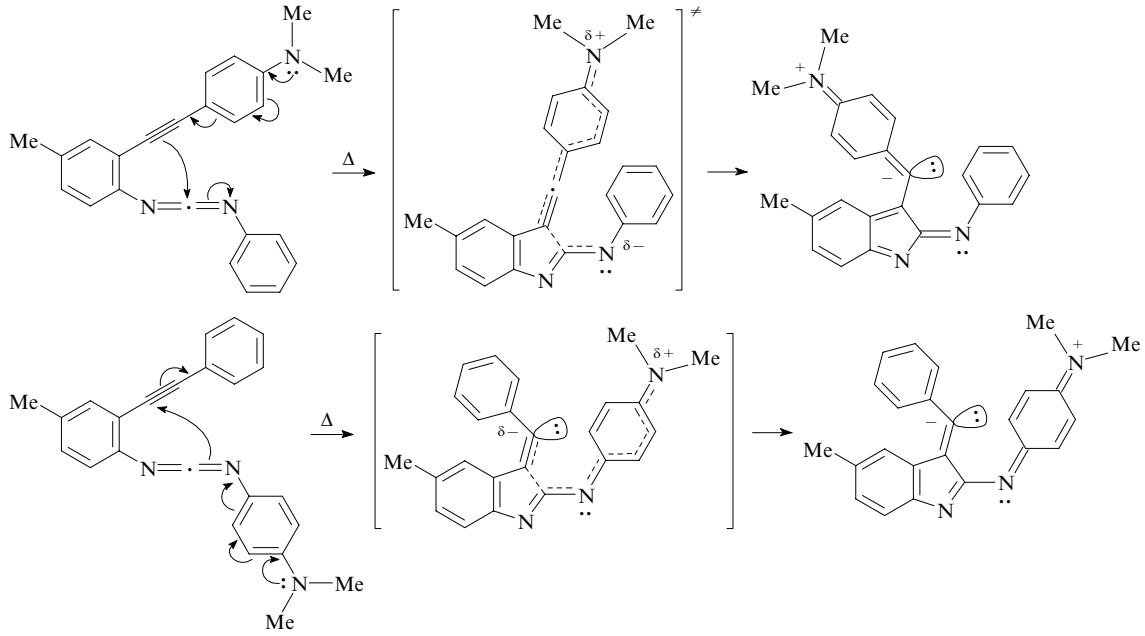
A computational analysis of the reactivity of diene-yne systems containing various heteroatoms to find optimum substrates for further experimental research on these two types of reactions was reported.[112] It seems very attractive to synthesize different heterocyclic systems from the same precursor by varying experimental conditions. It was pointed [112] that both reactions proceed in concerted fashion. The five-membered ring can be obtained by coarctate cyclization resulting in carbene while a six-membered zwitter-ion is formed in the pericyclic reaction. Both reactions are endothermic and characterized by late transition states, thus being reversible. The transition state energy decreases if the reaction product is aromatic. This occurs if the triple bond attacks the heteroatom capable of donating its electron pair to form an aromatic system. The more nucleophilic the heteroatom the lower the activation barrier to the reaction. Coarctate cyclization with the formation of a five-membered ring will be favourable if the forming carbene is stabilized or involved in a subsequent fast reaction with, *e.g.*, Cu^{I} or Rh^{II} salts. According to calculations,[112] compounds with Y = NNH_2 or Y = NPh (see Scheme 66) are expected to be good candidates for coarctate cyclization; this is confirmed by the data presented above. A compound with Y = PH and Z = CH not studied so far may appear to be yet another promising substrate. Six-membered hetero-

Scheme 67



X, Y = Cl, CN, NO_2

Scheme 68



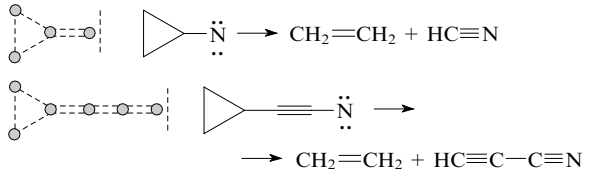
cycles are formed under severe conditions, namely, on heating phenyltriazenes at 200 °C for a few hours.[104]

The mechanism of thermal C(2)–C(6)-cyclization of enyne-carbodiimides was studied.[113] Interest in this reaction is due to the fact that analogous processes occur when DNA is damaged by natural ene-diynes, *e.g.*, neocarcinostatin, calicheamicin, *etc*. It was found that the starting compounds with electron-withdrawing substituents readily undergo coarctate cyclization affording carbene (Scheme 67), whereas cyclization of enyne-carbodiimides with electron-donating substituents X and Y is strongly zwitter-ionic (Scheme 68). The change of the reaction mechanism is indicated by a nonlinear dependence of the rate constant for the reaction on the Hammett constant σ_p of the substituent.

3. The homology principle for coarctate reactions

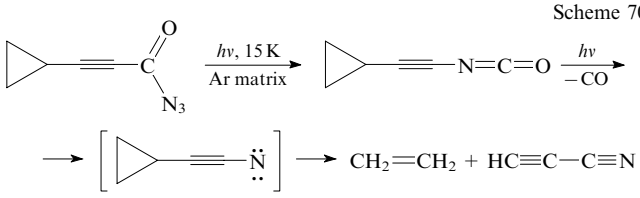
In 2000, in elaboration of his theory Herges[114] proposed a homology principle for coarctate reactions. For polar reactions, the principle of vinylogy is known, *i.e.*, compounds with similar properties differ structurally by one ethylene unit, thus being vinylogues. The introduction of ethylene unit into a pericyclic system leads to alternation of properties. It seems logical to assume that in the case of coarctate reactions, homologues should differ by one triple bond and both π-bonds should be involved in the reaction. This theoretical assumption was confirmed experimentally taking the fragmentation of cyclopropylnitrene (Scheme 69) as an example.

Scheme 69



Extension of the linear subsystem by two atoms does not change the nature of the reaction, which was proved taking photolysis of azides as an example (Scheme 70).[114]

Scheme 70



The synthesis of bis(isoindazoles)[110] considered in detail in Section IV.2.e is yet another illustration of the homology principle for coarctate reactions. The reaction equally readily proceeds for systems with acetylene and butadiyne bridges and seems to be extended to substrates with longer polyyne linkers (see Scheme 62, $k > 1$).

* * *

More than 70-years history of the theory of pericyclic reactions and the evolution of concepts of corresponding reaction mechanisms are full of contradictions and passions which do not subside up to date. Even seemingly such well-known reactions, as 1,3-dipolar cycloaddition or the Diels–Alder reaction still resonate among theoreticians. For instance, the idea that pericyclic reactions proceed concertedly but asynchronously[115] has supporters and detractors which continuously find new arguments supporting their points of view. Maybe this is as it should be because new theoretical and experimental methods incessantly give new points to ponder. A violent dispute concerning mechanisms of reactions that were named reactions without a mechanism in the mid-20th century should be recalled More recent studies revealed that pericyclic reactions can have complicated mechanisms and, which is of particular importance, offer great prospects for modification and combination of transition states (based on the Woodward–Hoffmann rules) and, therefore, the discovery of previously unknown reactions.

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