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CHAPTER **7**

Electrophilic additions to dienes and polyenes

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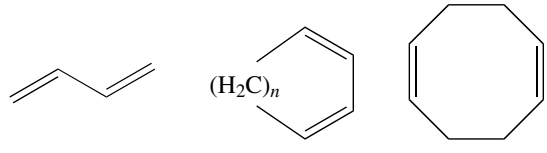
I. INTRODUCTION

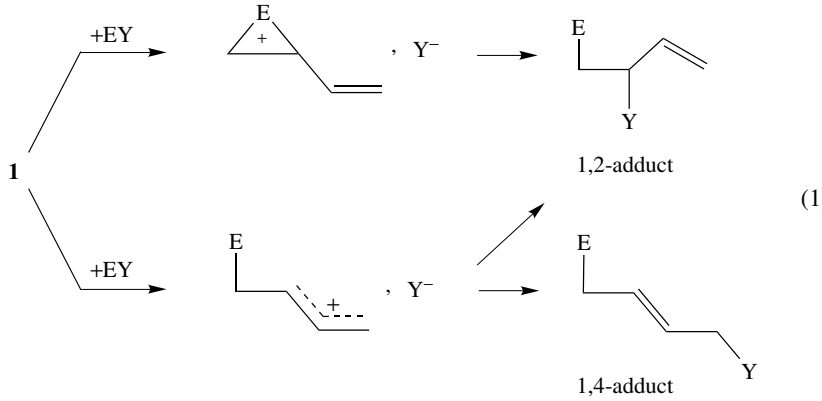
Electrophilic additions to carbon–carbon double bonds, a very large chapter in any organic textbook[1], have been for a long time[2] and recently[3] the object of intensive research because of their interest in fundamental mechanistic approaches, synthetic methodology and industrial procedures. In this context, the electrophilic reactions of dienes and polyenes have been reviewed frequently in specific paragraphs of extensive reports[2] on the reactivity of carbon–carbon bonds and, sometimes, more specifically[4] as a particular class of unsaturated compounds exhibiting properties markedly different from that of monoethylenic compounds. When there is no interaction between the several double bonds included in a polyenic molecule, the reactivity of each of these bonds toward usual electrophiles is not altered by the presence of other double bonds. No particular attention will be paid in this review to this category of polyenes since many previous reports on electrophilic reactivity covered the field[2]. In contrast, when two or more ethylenic bonds interact, a particular reactivity of the system is expected. The present review on studies carried out over the last 25 years is focused on this second category which involves mainly acyclic and cyclic conjugated 1,3-dienes, derived from **1** and **2**, respectively, and non-conjugated cyclic dienes, *cis*,*cis*-1,5-cyclooctadiene **(3)** being the most popular representative in this series.



(1) **(2)** **(3)**

The few kinetic results and the extensive product data on the electrophilic reactions of these dienes have been mainly interpreted in terms of the simplistic mechanism described in equation 1 and postulated by analogy to that established a long time ago[5] for the reactions of monoethylenic compounds. According to this naive picture, an ionic intermediate with two possible limiting structures would be formed by electrophilic addition

of the molecule EY to one of the two double bonds, viewing the dienic system as a monoethylenic compound substituted by a conjugated vinyl group. This approach was actually justified very early by the pioneering work of Tidwell and coworkers[6] in their extensive kinetic investigation of the acid-catalyzed hydration of ethylenic compounds, including a number of substituted 1,3-dienes. The rates of addition to the conjugated dienes fitted fairly well the general structure–reactivity relationship for monoenes when the appropriate substituent constant for the vinyl group was used. Unfortunately, no further studies have been undertaken to support the reliability of this conclusion for other electrophiles. It is also surprising that the numerous recent details and improvements of the general mechanism for electrophilic additions to monoenes[2d,3,7] (including the role of charge transfer complexes, the reversibility of the intermediate-forming step, the solvent-independent bridging and nucleophilic solvent assistance, etc.) have not been extended to reactions of dienes.



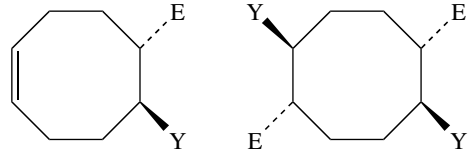
(1)

Actually, the main specific feature of the reaction of conjugated dienes has been the competition between 1,2- and 1,4-additions, which has to be associated with the Markovnikov/anti-Markovnikov regiochemistry and the *anti* vs *syn* stereochemistry usually exhibited in the monoene reactions[2,3,8]. The product mixtures obtained from conjugated polyenes are highly complex. Therefore, most of the interest in these reactions was focused on the reaction products and interpretation of their formation in terms of allylic and/or bridged structures of the ionic intermediates. A basic experiment on the deuterium incorporation in 1,3-pentadiene in its reaction with DCl raised this problem very early[9]. Not only 1,2- but also 1,4-adducts were observed as a result of the fast interconversion of the two isomeric ion pairs (*vide infra*). From this result and many others emerged the idea of two limiting structures for these intermediates, an allylic carbenium ion with extensive charge delocalization into the second double bond and a bridged cation whose charge is stabilized by the entering electrophile. Therefore, 1,2-adducts would result from nucleophilic trapping of strongly bridged intermediates whereas 1,4-additions would arise from an unbridged allylic carbocation. In agreement with this assumption, significant amounts of 1,4-adducts were obtained with electrophilic fluorine[10], a poorly bridging atom, while electrophilic sulfur additions which involve an efficient bridging afforded mainly 1,2-products[11]. Moreover, the bridged vinyl-substituted intermediate is expected to lead to a mixture of Markovnikov and anti-Markovnikov addition products. *Syn* adducts with a predominant Markovnikov regioselectivity should also be obtained from an allylic intermediate. Indeed, the addition of sulfenyl halides to butadienes[12] afforded *anti* 1,2-adducts with either a Markovnikov or anti-Markovnikov regiochemistry,

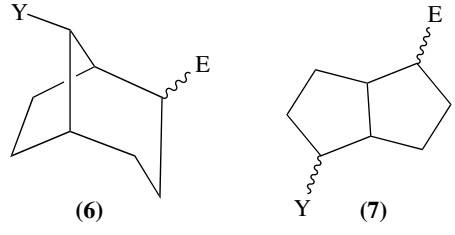
consistent with a vinyl-substituted thiiranium ion intermediate. Analogously, 1,2-bromine adducts were found to be mainly *anti*[13] whereas the 1,4-products were formed non-stereoselectively.

Nevertheless, the product data have been exceptionally interpreted only in these terms. (i) An allylic carbocation can afford significant amounts of 1,2-products. For instance, in the above-mentioned DCl addition, 1,2-adducts were the major products whatever the solvent. (ii) In addition to the electrophile and substituent dependence of the charge distribution in the intermediate, solvent and steric effects probably play an important role in the product-forming step of these reactions, as they do in the reactions of monoenes[7d,8]. (iii) 1,2-Adducts isomerize frequently to the more stable 1,4-adducts. Therefore, the kinetic or thermodynamic control of the product distribution[12,14] should be questioned. As a consequence, a number of early results were later revised when this problem was recognized. (iv) Finally, it has also been suggested[15] that 1,4-addition products do not necessarily arise from allylic intermediates but could also result from bridged intermediates via an S_N2' process implying a *syn* stereochemistry.

The electrophilic additions of reagents EY to non-conjugated cyclic dienes with two interactive double bonds such as in **3** have been also widely investigated because of their potential interest in organic synthesis[16–18] and also since they are useful models for hydrocarbon skeleton rearrangements of cyclic carbocations[19]. Mono- and bis-1,2-addition products, **4** and **5**, have been sometimes observed when the electrophilic atom was strongly bridging and under poorly ionizing and dissociating conditions, as for example in the reaction[20] of methanesulfenyl chloride with **3**. However, in most cases and in particular when strong interactions between the positive charge of the intermediate and the second double bond promoted transannular reactions, i.e. parallel and/or cross π-cyclizations, rearranged products such as **6** or **7** were usually obtained[21–23].



(4) **(5)**



(6) **(7)**

The industrial use of 1,3-dienes and of their electrophilic reactions has strongly stimulated the field in recent years. Because of the low cost of butadiene, abundantly available from the naphtha cracking process, very large scale applications in the synthesis of polymers, solvents and fine chemicals have been developed, leading to many basic raw materials of the modern chemical industry. For example, the primary steps in the syntheses of acrylonitrile and adiponitrile have been the electrophilic addition of hydrocyanic acid to butadiene[24]. Chlorination of butadiene was the basis of chloroprene synthesis[25].

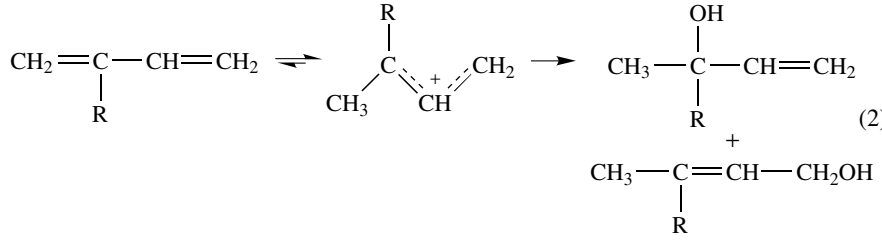
Its hydration opened the route[26] to a large scale production of solvents such as *n*-butanol and 2-ethylhexanol (>2 million tons in 1990). Most of these processes have involved the use of metal catalysts for activation of the π-system. The first catalysts used were mainly expensive noble or environmentally non-friendly metals, such as Rh, Pd or Ni. In this context, a number of works from academic laboratories reported in this review have been devoted to the catalytic activity of various other metals[27]. Their results on the selectivities of these catalyzed reactions were sometimes surprising and have not yet received consistent mechanistic interpretations.

In more general terms, the present review reports much experimental data, essentially on the distribution of addition products of a large variety of dienes. It is not the intention to provide a comprehensive approach to these highly versatile reactions. Many of the mechanistic interpretations suggested by the authors are still controversial or need to be confirmed. This is not surprising since the regio- and stereochemical outcome of the monoethylenic compounds reactions which a priori are simpler than those of dienes, is not yet fully understood despite recent significant progress[3,7,8]. Nevertheless, most of the presently available results on electrophilic additions to dienes are of great interest in many fields of organic chemistry.

II. ELECTROPHILIC HYDROGEN

A. Addition of Water and Carboxylic Acids

At the time when the $A_{SE}2$ mechanism of the acid-catalyzed hydration of alkenes was firmly established[2a,c], the reaction of conjugated dienes was also investigated. It was shown that the same mechanism also applied to dienes (equation 2). The first step is generally reversible but, under well-chosen reaction conditions, the formation of an allylic carbocation by proton addition to one of the two double bonds is rate-limiting. The fast trapping of the carbocation by water in the second step affords the two allylic alcohols corresponding either to a 1,2-addition or to a 1,4-addition. Several pieces of evidence supported this mechanism.



(2)

(i) The rates of acid-catalyzed hydration of 2-substituted-1,3-butadienes[6], $CH_2{=}C(R)CH{=}CH_2$, R = EtO, *c*-Pr, Me, H and Cl, fit the general structure–reactivity relationship[28] (equation 3) established for the hydration of 1,1-disubstituted alkenes, $R^1R^2C{=}CH_2$, under similar reaction conditions, with $\sigma_p^+ = -0.16$ for the vinyl substituent.

$$\log k = -12.3\sigma_p^+ - 10.1 \tag{3}$$

(ii) A linear dependence of $\log k$ for the hydration of a variety of dienes on H_0, the appropriate acidity function of aqueous solutions of sulfuric and perchloric acids (equation 4), was observed[6,29,30], as found also for alkenes. The slopes γ of these relationships were all close to unity, e.g. $\gamma = -1.00$, -1.16, -1.22, -1.2 and -1.3 for

chloroprene[6], isoprene[6], 1,3-butadiene[6], 1-Ph-1,3-butadiene[29] and 1,3-cyclohexadiene[30], respectively.

$$\log k_{obs} = \gamma H_0 + \varepsilon \quad (4)$$

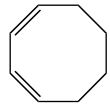
The acidity dependence of the activation enthalpies and entropies, $\Delta H^{\neq}$ and $\Delta S^{\neq}$, of the hydration of 1,3-cyclohexa- and 1,3-cyclooctadienes was ascribed[30] to a dielectric solvation effect in dilute acids, which is overcome by increasing solvent structure as the availability of water decreased in concentrated acids. This suggestion was one of the early premises of a more recent interpretation[31] of acidity effects in terms of water activity and solvation of cationic species.

(iii) The kinetic isotope effects, $k_{H_3O^+}/k_{D_3O^+}$, for the hydration of 1,3-cyclohexadiene[29] and 2-substituted 1,3-butadienes[6] were in the range of 1.1 to 1.8, very similar to those observed for the reaction of alkenes.

(iv) The effects of ring size on hydration rates and equilibria for 1,3-cycloalkadienes (C_5, C_6, C_7 and C_8 dienes) in aqueous sulfuric acid have been interpreted in terms of changes in free energy of conjugative stabilization of the allylic carbocation[32]. An approximately linear inverse relationship between strain energy and $\log k_{hydr}$ was obtained (Table 1). The comparison of these data with those obtained for the hydration of cyclic monoalkenes suggested earlier transition states for the diene hydration than those for the alkene reaction.

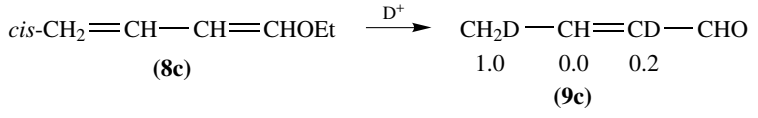
The regiochemistry of the acid-catalyzed water addition to *cis*- **(8c)** and *trans*- **(8t)** 1-ethoxy-1,3-butadienes leading to **9c** and **9t**, respectively[33], has been investigated in deuterium incorporation experiments (equations 5 and 6). The *cis*-isomer incorporated deuterium at the 2-position as well as the 4-position whereas deuterium was added to the *trans*-isomer exclusively at the 4-position. This result has been interpreted in terms of equations 7 and 8: γ-protonation in the *trans*-isomer was assumed to be controlled mainly by thermodynamic factors whereas α-protonation was assumed to arise from charge control

TABLE 1. Effect of ring size on hydration of 1,3-cycloalkadienes[a]

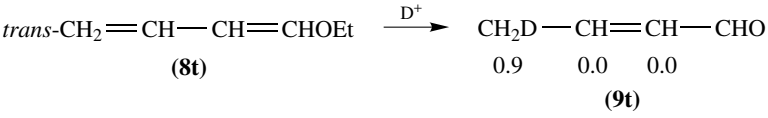
1,3-Cycloalkadiene	k_{rel}[b]	Strain energy[c]
	200	0.8
	2000	−1.2
	4	1.4
	1	3.8

[a]Data of Reference 32.
[b]Relative rates of hydration in 1.05 M H_2SO_4 at 80 °C.
[c]In kcal mol^{-1}.

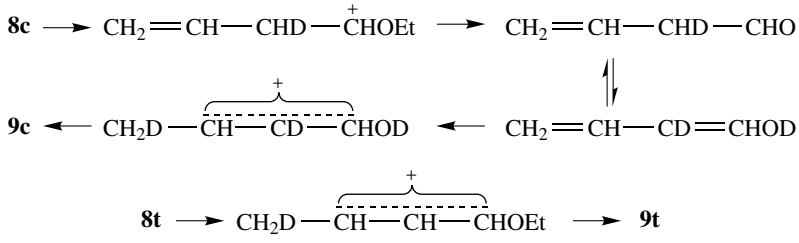
because the transition state for the *trans*-isomer is earlier than that for the *cis*-isomer. This interpretation was supported by the fact that **8t** reacted 14 times faster than **8c**.



(8c) **(9c)** (5)



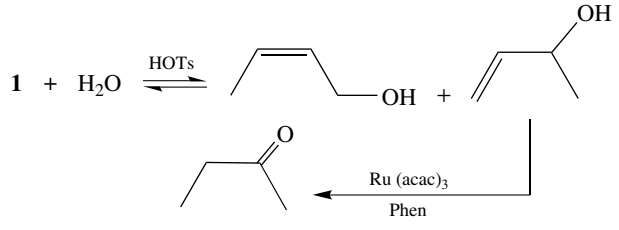
(8t) **(9t)** (6)



(7)

(8)

1,3-butadiene was converted[34] into methyl ethyl ketone with a yield of 90% in a one-pot synthesis at 155 °C with a conversion rate of 100 mol mol^{-1} h^{-1} (100 mol of butadiene per 1 mol of catalyst per hour) in water or in water–diglyme mixtures in the presence of a catalytic system involving a 1 : 2 : 14 (molar) ratio of ruthenium(acac)$_3$, 1,10-phenanthroline (Phen) and *p*-toluenesulfonic acid. Other transition metals (Pd, Rh or Ir) associated to various ligands (e.g. pyridines) with other Brönsted acids (H_2SO_4, H_3PO_4, CF_3CO_2H, HCl, CF_3SO_3H) also promoted the reaction, but with lower yields and selectivities. The reaction was suggested to occur in two consecutive steps: (i) 1,2- and 1,4-addition of water to 1,3-butadiene and (ii) rearrangement of the formed allylic alcohol, 3-buten-2-ol, into methyl ethyl ketone (equation 9). Formally, the primary allylic alcohol, 2-buten-1-ol, could rearrange into *n*-butanol. However, this has not been observed and instead, this alcohol which is involved in hydration–dehydration equilibrium with butadiene was also converted indirectly into methyl ethyl ketone.



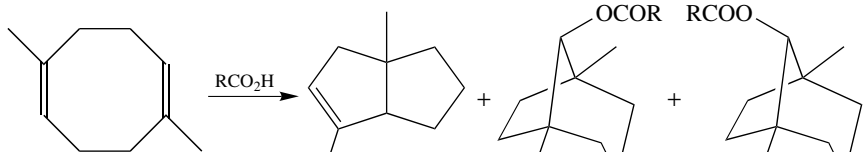
(9)

The first hydration step was promoted by Brönsted acids containing weakly or non-coordinating anions. In the second step, an intramolecular hydrogen transfer in the secondary alcohol was catalyzed by ruthenium(III) salts with chelating bipyridyl-type ligands. The possible complexation of the latter with the diene did not inhibit its catalytic activity in the allylic rearrangements, under acid-catalyzed hydration conditions.

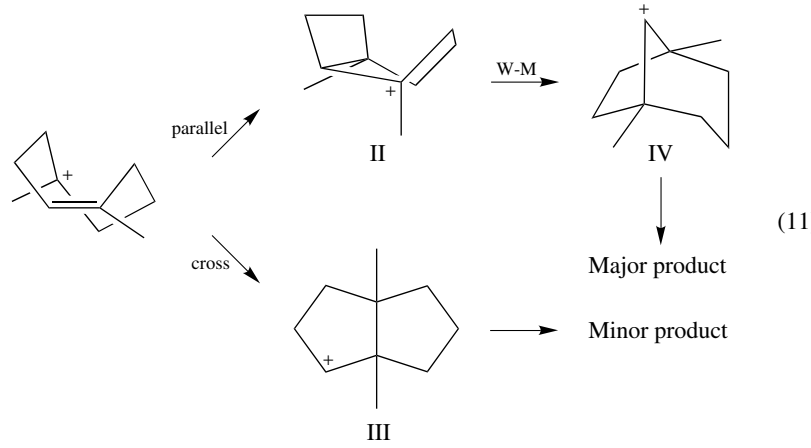
The procedure worked also with 1,3-octadiene and with isoprene which produced methyl isopropyl ketone in 80–85% yield.

These transformations have been potentially useful at an industrial level[35], considering the large-scale availability and application of butadiene and methyl ethyl ketone.

The electrophilic additions of formic and acetic acids to 1,5-dimethyl-1,5-cyclooctadiene yielded mainly[23] *syn*-8-substituted-1,5-dimethylbicyclo[3.2.1]octanes (equation 10) via parallel π-cyclization and subsequent Wagner–Meerwein (W-M) type rearrangement. Cross π-cyclization leading to bicyclo[3.3.0]octane derivatives, which were the major adducts in other electrophilic additions to unsubstituted 1,5-cyclooctadiene[21,22] comprised only a minor route. This different behavior has been interpreted (equation 11) in terms of a significantly larger stability of the tertiary carbocation II than that of the secondary ion III, both ions being the two potential intermediates derived from I by a parallel and a cross π-cyclization, respectively.



(10)

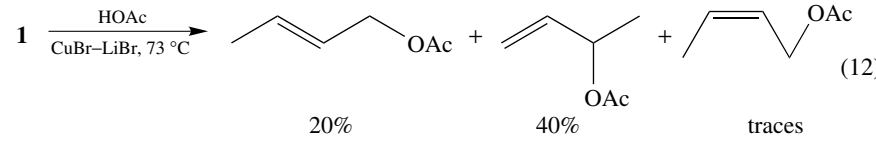


(11)

The predominantly *syn* stereochemistry of the products arising from the bicyclo[3.2.1] octyl cation IV would results from the large ring strain in II, the chair conformation of which, (but not boat) facilitate the Wagner–Meerwein type rearrangement.

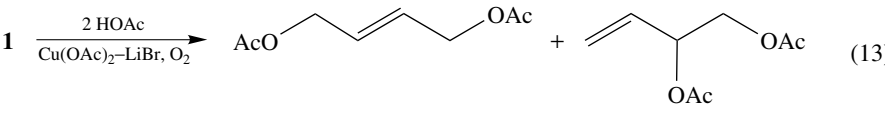
In a context of industrial interest, the copper-catalyzed addition of acetic acid[36] to **1** (hydroacetoxylation) in the absence of oxygen was shown to be non-regioselective, a 1 : 0.5 mixture of 1,2- and 1,4-addition products being obtained in a yield of 60% based on butadiene. The effect of various additives on the regiochemistry and the yield has been carefully studied. The butadiene conversion was mainly efficient with the CuBr–LiBr catalytic system (equation 12). The role of the catalyst in the reaction mechanism has been discussed but not fully understood. It has been shown that the dominant formation

of the 1,2-isomer during the acetic acid addition was kinetically controlled, the equilibrium mixture of the 1,2- and 1,4-isomers in the presence of the catalyst being 1 : 1. The results were compared with those obtained by the same authors for the hydrocyanation (*vide infra*) which was markedly more regioselective than hydroacetoxylation.



(12)

When this reaction was carried out under oxygen pressure (generally 10 bars) using $Cu(OAc)_2$ in association with LiBr as a catalyst in an acetic acid–acetic anhydride (2 : 1) solvent mixture, diacetoxylation[37] leading to 1,2- and 1,4-diacetoxyethylenic adducts took place (equation 13). The regioselectivity, which did not depend significantly on the reaction conditions, was poor in all cases, the 1,4- to 1,2-isomer ratio being close to unity. The formation of the 1,2-isomer seemed to be kinetically controlled, as was found for the hydroacetoxylation. A variety of reaction intermediates, such as an epoxybutene, and in particular hydroxyacetates, has been suggested but the mechanism is far from being elucidated. The absence of regioselectivity is in contrast to that found for the same reaction promoted by much more expensive palladium catalysts[38].



(13)

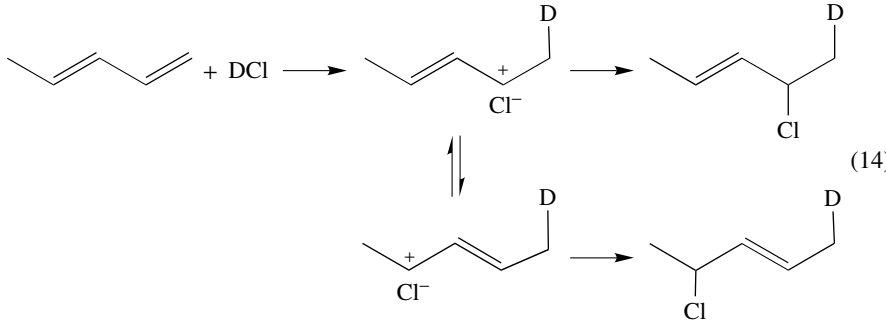
B. Addition of Hydrochloric Acid, Hydrocyanic Acid and Hydrogen Sulfide

The regiochemistry of the addition of DCl to *trans*-1,3-pentadiene was investigated very early in various solvents in order to understand the competition between 1,2- and 1,4 additions to conjugated dienes[9]. The results (Table 2) indicated a marked predominance of 1,2-addition. This has been interpreted in terms of ion pairing as described in equation 14, assuming that the addition of undissociated DCl gave the carbenium–chloride ion pair with the anion associated at C(2). Interconversion with the isomeric ion pair having the chloride associated with C(4) at a rate not much faster than that of the ion pair collapse would produce the 1,2-adduct in excess of the 1,4-adduct. These results were in contrast with those observed for other electrophilic additions in more dissociating solvents (*vide infra*).

TABLE 2. Regiochemistry of DCl addition to *trans*-1,3-pentadiene[a]

Solvent	T (°C)	% 1,2-Addition	% 1,4-Addition
None	−78	75.5	24.5
	25	61.5	38.5
Pentene	−78	77.7	22.3
	25	63.8	36.2
CH_3CO_2D	25	65.0	35.0
CH_3NO_2	25	67.7	32.3

[a]The two adducts result from at least 96% *anti* addition.



(14)

The orientation of the addition of HCl to a variety of halogen-substituted 1,3-butadienes has been extensively studied under preparative conditions[39–43]. The results are given in Table 3. No significant polymerization was observed and the products were in all cases those resulting from a 1 : 1 addition process. The regiochemistry control by the position of the chlorine atom was quite versatile. A Cl at C(1) favored formation of the 4,3-adduct whereas with Cl on C(2) the 1,4-adduct predominated. The competition between substitution by chlorine and methyl attenuated but did not markedly modify this orientation. However, all these reactions were quite slow and took from 5 to 10 h, even in the presence of a catalyst (mostly cuprous chloride). Therefore, product

TABLE 3. Product distribution in hydrogen chloride addition to halogeno-substituted 1,3-butadienes, $R^1CH{=}CR^2{-}CR^3{=}CH_2$

R^1	R^2	R^3	% 1,2-Addition[a]	% 1,4-Addition[b]	% 4,3-Addition[c]	% 4,1-Addition[d]	% Yield[e]	Conditions[f]	References
Cl	H	H	0	5	78	7	86	A	40
Cl	H	H	0	1	94	5	75	B	40
H	Cl	H	3	97	0	0	—	C	42
H	Br	H	2	85	0	0	—	D	42
H	Br	H	1	73	0	0	—	E	42
H	Cl	Cl	0	90[h,i]	0	0	63	F[j]	41
Cl	H	CH_3	3	9	75	13	90	E	43
H	CH_3	Cl	15	49	3	33	71	D	40
H	CH_3	Cl	3	57	1	39	—	E	40
H	CH_3	Cl	40	21	8	31	25	G	40

[a] $R^1CH_2{-}C(R^2)Cl{-}CR^3{=}CH_2$.
[b] $R^1CH_2{-}CR^2{=}CR^3{-}CH_2Cl$.
[c] $R^1CH{=}CR^2{-}C(R^3)Cl{-}CH_3$.
[d] $R^1CHCl{-}CR^2{=}CR^3{-}CH_3$.
[e] Overall yield.
[f] Reaction conditions (in every case, excess of HCl, vigorous stirring): A, 20% HCl + 25% CuCl + 7% NH_4Cl, 40–45 °C. B, A without catalyst. C, concentrated hydrochoric acid at constant [HCl], maintained by addition of gaseous HCl, in the presence of catalytic CuCl, at 40 °C. D, C without catalyst, at room temperature. E, C at room temperature. F, in CCl_4 in the presence of $FeCl_3$, at −10 °C. G, in ether at −15 °C.
[g] Substantial amounts (24% and 12%, with and without catalyst, respectively) of 1,3-dichloro-2-butene arising from bromine–chlorine exchange were formed.
[h] *cis* + *trans*.
[i] 5–15% of 1,2,3,6,7-pentachloro-2,6-octadiene were formed.
[j] In water, no addition products were formed.

isomerization either during the addition or the work-up (GC or fractional distillation) cannot be ruled out.

The addition of HCl to 1,3-butadiene in the gas phase at total pressures lower than 1 atmosphere and at temperatures in the range of 294–334 K yielded mixtures of 3-chloro-1-butene and (*E*)- and (*Z*)-1-chloro-2-butenes, in a ratio close to unity[44,45]. Surface catalysis has been shown to be involved in the product formation (Figure 1). The reaction has been found to occur at the walls of the reaction vessel with a high order in HCl and an order less than unity in diene. The wall-catalyzed process has been described by a multilayer adsorption of HCl, followed by addition of butadiene in this HCl layer. This highly structured process is likely to involve near simultaneous proton and chloride transfers.

Strong evidence for a π-allylnickel complex as an intermediate in the nickel catalyzed addition of hydrogen cyanide to conjugated dienes[46] has been obtained in a brief but clear-cut investigation of deuterium cyanide addition to 1,3-cyclohexadiene. This result has been of wide interest in relation to the mechanism of the industrial process for formation of adiponitrile in which two molecules of hydrogen cyanide added to butadiene via a three-step reaction catalyzed by nickel or palladium complexes (equation 15). The HCN addition to 1,3-cyclohexadiene in acetonitrile at 60 °C in the presence of $Ni[P(OPh)_3]_4$ with $P(OPh)_3$ produced 2-cyclohexenecarbonitrile with high selectivity. The same reaction using DCN afforded the two monodeuteriated nitriles **10** and **11** resulting from 1,2- and 1,4-additions, in approximately equal amounts. The postulated mechanism (Figure 2), which is analogous to that previously established for the hydrocyanation of monoenes, involves the following steps. The active catalytic species, $DNiL_3CN$

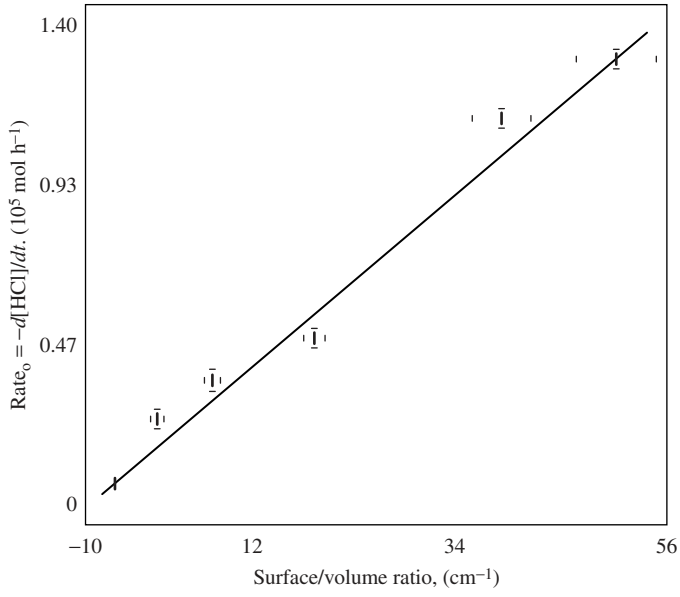


FIGURE 1. The variation in the initial rate of disappearance of hydrogen chloride (g) in the reaction of HCl with 1,3-butadiene as a function of the surface-to-volume ratio at 295 K. The initial concentrations of hydrogen chloride and 1,3-butadiene are 3.4×10^{-4} M and 1.6×10^{-4} M, respectively. (Reprinted from Reference 44, copyright 1991, with permission Elsevier Science)

[L = $P(OPh)_3$] formed by oxidative addition of DCN to NiL_4, coordinates one of the two double bonds of the diene. The coordination is followed by a *cis*-migration of the coordinated deuterium, producing a π-allyl nickel complex in which a further *cis*-migration of the cyanide gave the two products **10** and **11**.

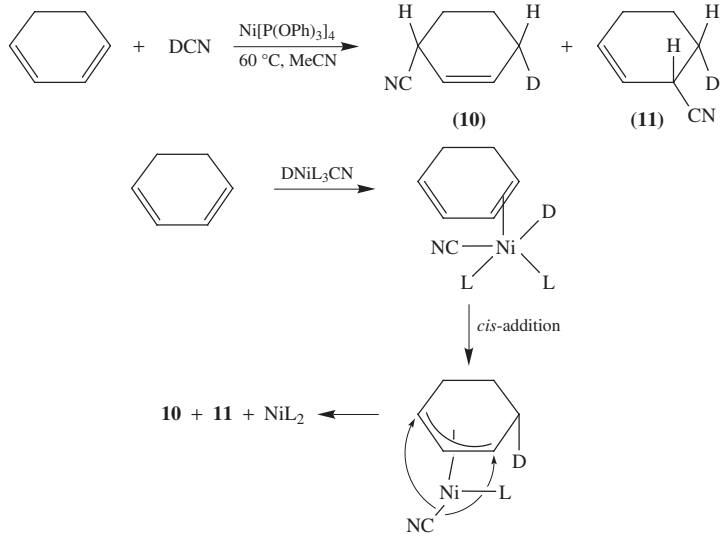
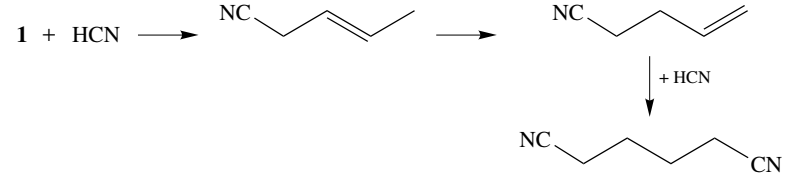


FIGURE 2. The mechanism of the nickel-catalyzed addition of hydrogen cyanide to 1,3-cyclohexadiene. Reproduced by permission of the Royal Society of Chemistry from Reference 46

In an extension of an early work on the nickel-catalyzed addition of hydrogen cyanide to unsaturated compounds, a basic reaction in various large-scale processes in the polymer industry, the hydrocyanation of butadiene (equation 15) and the efficiency of catalysis of this reaction by low-cost copper salts has been studied extensively by Belgium researchers[47,48].



(15)

Copper-catalyzed monoaddition of hydrogen cyanide to conjugated alkenes proceeded very conveniently with 1,3-butadiene, but not with its methyl-substituted derivatives. The most efficient catalytic system consisted of cupric bromide associated to trichloroacetic acid, in acetonitrile at 79 °C. Under these conditions, 1,3-butadiene was converted mainly to (*E*)-1-cyano-2-butene, in 68% yield. A few percents of (*Z*)-1-cyano-2-butene and 3-cyano-1-butene (3% and 4%, respectively) were also observed. Polymerization of the olefinic products was almost absent. The very high regioselectivity in favor of 1,4-addition of hydrogen cyanide contrasted markedly with the very low regioselectivity of acetic acid addition (*vide supra*). Methyl substituents on 1,3-butadiene decreased significantly the efficiency of the reaction. With isoprene and piperylene, the mononitrile yields were reduced

to 39% and 12%, respectively, and the percent of polymerization increased. With two methyl substituents, polymerization was the exclusive reaction. Kinetic studies have established a key activating role of a variety of organic and inorganic bromides, crotyl bromide being the most efficient. Several mechanisms involving π- or σ-allylcopper complexes, analogous to the well-established π-allylnickel intermediates, have been proposed.

Oxycyanation[27] affording 1,4-dicyano-2-butene occurred exclusively when the HCN addition was carried out under oxygen atmosphere ($P_{O_2} = 40-50$ psig). In addition to the catalytic CuBr–LiBr system which works conveniently in the monohydrocyanation, the presence of cupric iodide has been found necessary in order to avoid the oxidation of HCN into cyanogen. With 1,3-butadiene, the yield reached 60%. Much lower yields have been found with 1,3-pentadiene (17%) and isoprene (3%) in acetonitrile solvent. In pyridine or DMSO, 2-cyanopyridine probably resulting from the addition of cyanide radicals has been formed from 1,3-butadiene in poor yield (15%). This observation has suggested a solvent-dependent competition between the ionic pathway leading to the dinitriles and a radical pathway responsible for the cyclization to the pyridine ring.

The similarities and differences between copper-catalyzed oxycyanation and diacetoxylation (*vide supra*), which are summarized in Figure 3, have been discussed. The main difference in the regiochemistry of the two reactions, i.e. an almost exclusive 1,4-addition in the cyanation and a non-regioselective acetoxylation, has been emphasized but was not interpreted in mechanistic terms.

The electrophilic addition of hydrogen sulfide and 1-butanethiol to 1,3-conjugated dienes[49] in chloroform at $-10\,^{\circ}C$ has been reported in a quite old paper of a Russian team. The yields were generally low, in the range of 20%, even when the reaction was catalyzed by a mixture of two Lewis acids, $EtAlBr_2/EtAlCl_2$; however, polymerization of the diene was not significant.

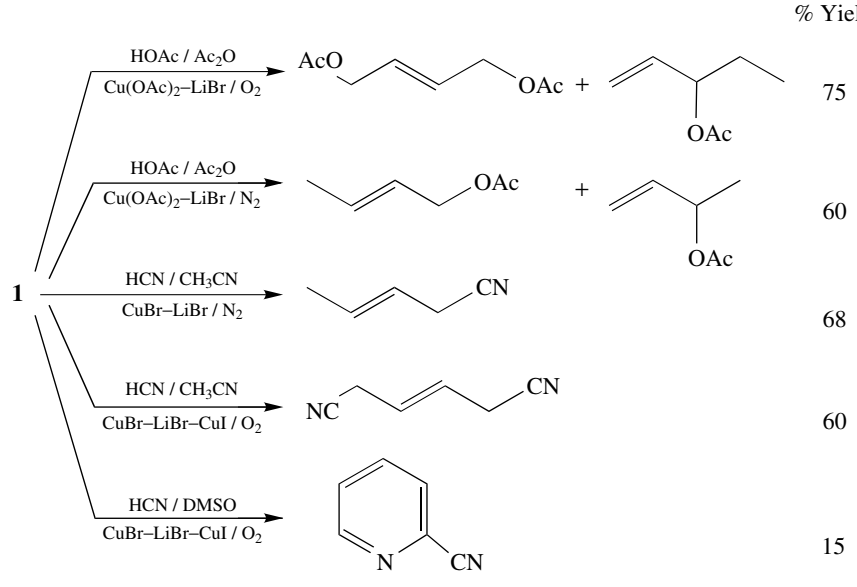
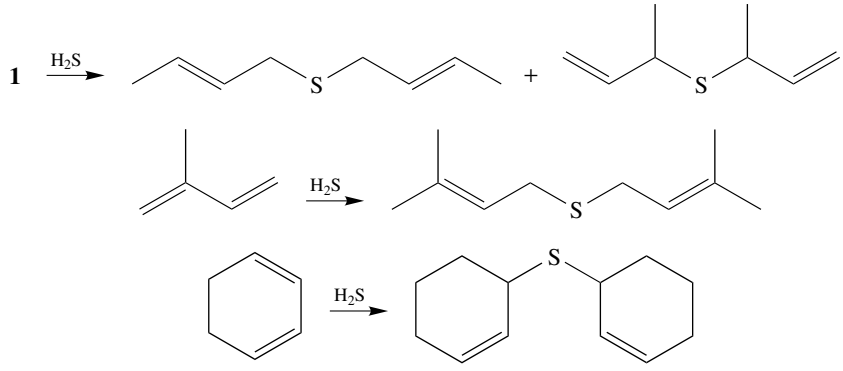


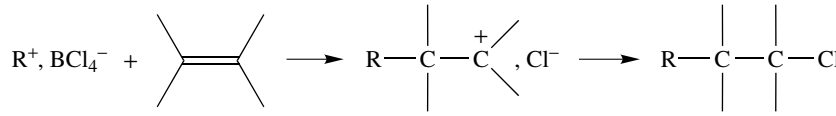
FIGURE 3. Copper-catalyzed additions of acetic and hydrocyanic acids to butadiene. Reproduced by permission of Academic Press from Reference 27

Depending on the linear, branched or cyclic structure of the unsaturated compound, a variety of dialkyl sulfides has been obtained in the reaction with H_2S (equations 16–18). The regiochemistry depended markedly on the structure of the diene. For a mechanistic purpose, some experiments have been carried out using deuterium sulfide, D_2S. The results have been interpreted in terms similar to those of Nordlander and coworkers[9] (*vide infra*). The thiylation of 1,3-dienes was assumed to start with a regiospecific addition of a proton or a deuteron to one of the two double bonds to form two isomeric ion pairs as in equation 14 which, in the poorly dissociating solvent, collapse into products with equal probability.



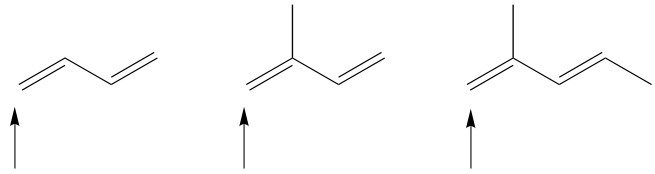
III. ELECTROPHILIC CARBENIUM IONS

In a review on the addition of carbenium ions to alkenes (equation 19) as a general procedure for carbon–carbon bond formation[50], Mayr reported on investigations which also include the reactions of a variety of 1,3-dienes toward electrophilic carbon species generated by Lewis acid-promoted heterolysis of alkyl chlorides.



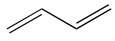
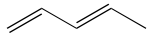
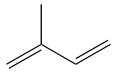
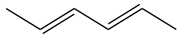
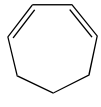
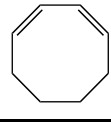
As a general rule, alkyl-substituted 1,3-dienes reacted so that the corresponding allyl cation with the highest possible number of alkyl substituents at the cationic center was formed, leading to the regioselectivity[51] indicated below. The subsequent nucleophilic addition to these cations afforded mainly mixtures of diastereoisomeric 1,4-addition products (>90%). An example is the reaction of *p*-methoxydiphenylcarbenium tetrachloroborate with 2-methyl- and 2,3-dimethyl-1,3-butadiene and 1,3-cycloalkadienes[52,53]. Nevertheless, some 1,2-addition products were also observed for 1,3-butadiene and 1-methyl-1,3-butadiene. This regiochemistry is in agreement with recent semiempirical AM1 calculations on the corresponding allyl cations[54].

The kinetic behavior of 1,3-dienes has also been investigated in as much detail as that of alkenes[52]. Some data are collected in Table 4. The effect of a vinyl group on the reactivity of carbon–carbon double bonds toward *p*-methoxydiphenylcarbenium ion has been compared with that of methyl and phenyl substituents (Table 5). Whereas butadiene reacted 21 times faster than propene, the reactivity of isoprene was significantly lower



Sites of attack by carbenium ions

TABLE 4. Rate constants and activation parameters[a] for the reaction[b] of *p*-methoxydiphenylcarbenium tetrachloroborate with various dienes

Compound	k ($M^{-1}\,s^{-1}$)	$\Delta H^{\neq}$ (kcal mol^{-1})	$\Delta S^{\neq}$ (cal $mol^{-1}\,K^{-1}$)	$k_{H_3O^+}$[a] ($M^{-1}\,s^{-1}$)
	9.39×10^{-4}	7.8	−33.3	2.38×10^{-9}
	2.33×10^{1}	5.0	−26.8	3.71×10^{-4}
	1.09×10^{1}	4.6	−30.4	2.40×10^{-7}
	1.93×10^{-2}			3.96×10^{-3}
	4.62×10^{1}	5.4	−23.7	
	1.56×10^{1}	5.5	−25.4	3.19×10^{-5}
	1.82×10^{2}	3.6	−29.7	
	1.74×10^{3}			7×10^{-7}
	2.75×10^{1}	4.4	−29.4	7×10^{-6}
	3.04	5.3	−29.4	1.4×10^{-8}
	3.26×10^{-1}			3.5×10^{-9}

[a] Data from Reference 52
[b] At −70 °C in dichloromethane.
[c] At 25 °C; data from Reference 55

TABLE 5. Comparison of substituent effects on the relative rates of carbenium ion addition to carbon–carbon double bonds

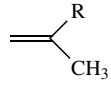
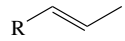
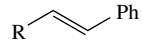
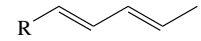
Alkene/R	Me	$CH{=}CH_2$	Ph
	1.00	21	1.2×10^4
	1.00	0.67	62

TABLE 6. Effect of the methyl group at the electrophilically attacked vinylic carbon by *p*-methoxydiphenylmethyl carbenium ion

			
k_{CH_3}/k_H	1.3	0.36	3.9
$\delta\Delta H^{\neq}$ (kcal mol^{-1})	−0.6	−0.9	−7.3
$\delta\Delta S^{\neq}$ (cal mol^{-1}K^{-1})	−2.6	−6.0	−27

than that of isobutene. It is also noticeable that the effect of a phenyl group is much larger than that of the vinyl group. The effect of a methyl group at the initially attacked vinylic carbon atom depended also on the nature of the unsaturated system as shown in Table 6.

The similar order of magnitude of the reactivities of methyl-substituted 1,3-dienes (Table 4) which depended on the number but not on the position of the substituent was strong evidence that allyl cations[55] serve as reaction intermediates in these reactions. The rate decrease with increase in the ring size of the cycloalkadienes was attributed to the increased deviation of the π-system from planarity. The reactivities of 1,3-dienes deviated markedly from the roughly linear relationship between the rates of proton and carbenium ion additions to alkenes. These deviations were ascribed to abnormally low reactivity[32] of the conjugated π-systems, although this interpretation was inconsistent with the similar behavior of alkenes and dienes in the structure–reactivity relationship for hydration[6].

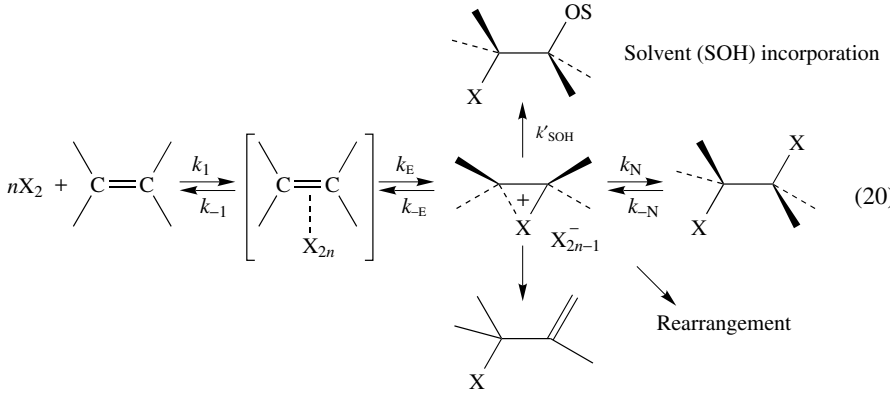
IV. ELECTROPHILIC HALOGENS AND POSITIVE HALOGEN DONORS

A. General Aspects

The electrophilic addition of halogens, interhalogens and pseudohalogens to carbon–carbon double bonds, although extensively studied and repeatedly reviewed[2], is still the object of kinetic and product investigations. The more recent studies, often concerning bromine additions[3,7c], have revealed the complexities that underlie the simple representation generally given in organic chemistry textbooks[1]. The structure of the intermediate, the kinetics of the reaction, and both its stereochemistry and regiochemistry are all complex functions of the nature and concentration of the halogenating agent, of the solvent, of the added nucleophiles and of the structure of the alkene.

The first step is usually the formation of a halogen–olefin charge transfer complex[3c,7c], which rapidly evolves to an ionic intermediate. Protic solvents can electrophilically assist

the ionization process through hydrogen bonding. This is not possible in non-polar solvents, but further halogen molecules may assist in removing X^- as polyhalides. The cationic moiety of the intermediate may be a bridged or weakly bridged halonium ion, or a β-halocarbenium ion, depending on the nature of the electrophile and on the olefin. Nucleophilic trapping of the intermediate by the counteranion, solvent or added nucleophiles yields the reaction products (equation 20).



(20)

The regio-, stereo- and chemoselectivities have been mainly interpreted in terms of bridging of the ionic intermediate and/or ion pair dissociation. Solvent-separated ion pairs and free ions have often been considered to explain the product selectivities of these reactions. Nevertheless, the stereochemical outcomes can also be determined by the relative rates of the ion pair dissociation and of the nucleophilic trapping of the intermediate, i.e. by the lifetime of the intermediate[7d].

The rate laws for the addition of halogens are generally complex. Second, third and fourth overall order terms have been identified (equation 21), depending on reagent and reaction conditions, solvent and added salts.

$$-d[X_2]/dt = [\text{Alkene}](k_2[X_2] + k_3[X_2]^2 + k_4[X_2]^3 + k_{X^-}[X_3^-]) \tag{21}$$

Furthermore, on the basis of the multistep mechanism reported in equation 20 and considering that the electrophilic and/or nucleophilic step may be rate determining depending on halogen and/or olefin, k_{obsd} is always a composite constant (equation 22), even under the simplified conditions where only one path contributes to the product formation and the reverse reaction (k_{-N}) does not occur.

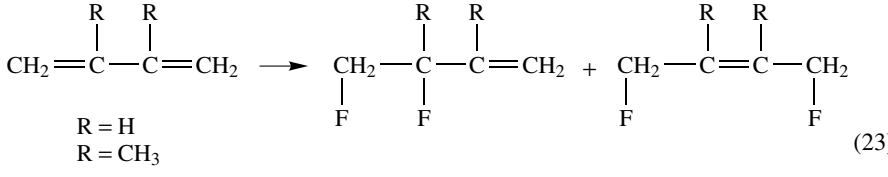
$$k_{obsd} = k_1 k_E k_N/(k_{-1}k_{-E} + k_{-1}k_N + k_E k_N) \tag{22}$$

Since the structural factors and the solvent can affect the individual rate constants in ways which may differ in magnitude and sign, comparison of the experimental rate constants for various systems cannot always be straightforward.

B. Fluorine

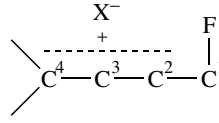
Fluorine is the most electrophilic halogen and only few examples of controlled addition of fluorine to carbon–carbon double bonds have been reported[56] Milder reagents, such as XeF_2, are generally used to form fluorine addition products.

The first data about fluorination of 1,3-dienes were reported[10] by Shellhamer and coworkers, who described the additions of xenon difluoride and (difluoroiodo)benzene to butadiene, 2,3-dimethyl-1,3-butadiene and *cis*- and *trans*-1,3-pentadienes, in chlorinated solvents. Both reagents give 1,2- and 1,4-difluoro adducts (equation 23). XeF_2 yields primarily 1,2-products while $C_6H_5IF_2$ gives significantly more 1,4-products.



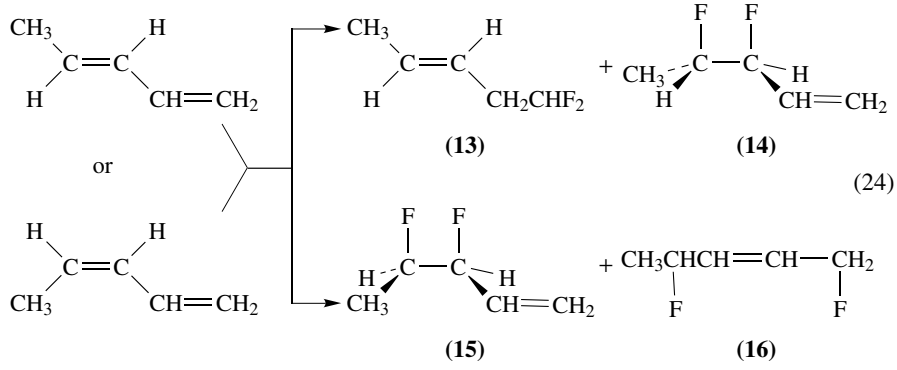
(23)

The difference in the product distributions has been attributed to the steric effect of the counterion, X^-. The steric interaction between the large anion $C_6H_5IF^-$ and the diene would favor the attack at the less-hindered C(4) atom of the intermediate **12**.



(12)

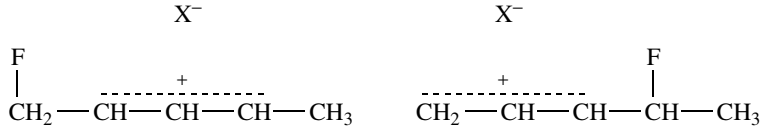
It is noteworthy that, at variance with bromination and chlorination which generally occur without isomerization of the disubstituted double bond, fluorine addition to the 1,2-bond of *cis*- and *trans*-1,3-pentadienes gives mainly the *trans*-adduct **13**, besides smaller amounts of compounds **14–16** (equation 24).



(24)

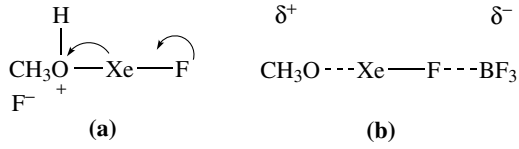
Thus, fluorination of 1,3-dienes proceeds through an allylic ion, while weakly bridged halonium ions are the intermediates in chlorination and bromination of dienes (*vide infra*). Furthermore, starting from the experimental evidence that **13** is produced under kinetic conditions and not from subsequent rearrangement of the 1,2- and 1,4-adducts, the authors suggested that **13** arose from rearrangement of the allyl cation intermediate, **17**. Consistent with an open ion pair intermediate is also the stereoselective formation of the *threo* isomer from both 1,3-pentadienes, as well as the preference for the addition to the 1,2-bond observed in the reaction of both isomeric pentadienes. This selectivity may indeed

be related to a significant charge delocalization into the adjacent double bond in the rate-determining transition state, which favors the formation of intermediate **17** over **18**.

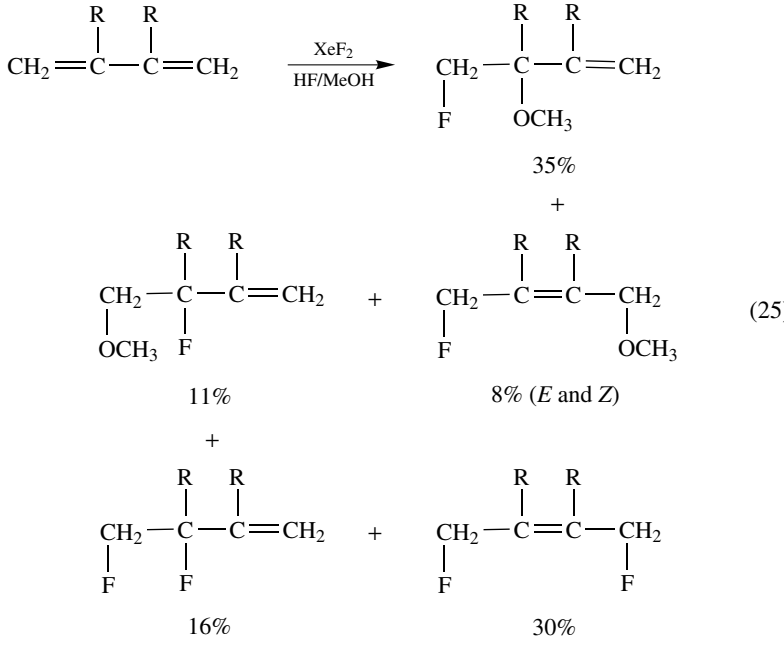


(17) **(18)**

A different stereochemical behavior has, however, been observed in methanol[57]. In this solvent XeF_2 reacts with the solvent to form an unstable reactive species (CH_3OXeF), which gives quantitatively formaldehyde by disproportionation in the absence of unsaturated hydrocarbons or with unreactive alkenes. Hydrogen fluoride generated *in situ* complexes the electrophilic CH_3OXeF species to form a protonated derivative **a** which reacts with activated dienes such as 2,3-dimethylbutadiene, as an apparent fluorine electrophile to give 1,4- and 1,2-fluoromethoxy products, together with 1,2- and 1,4-difluoro derivatives (equation 25).

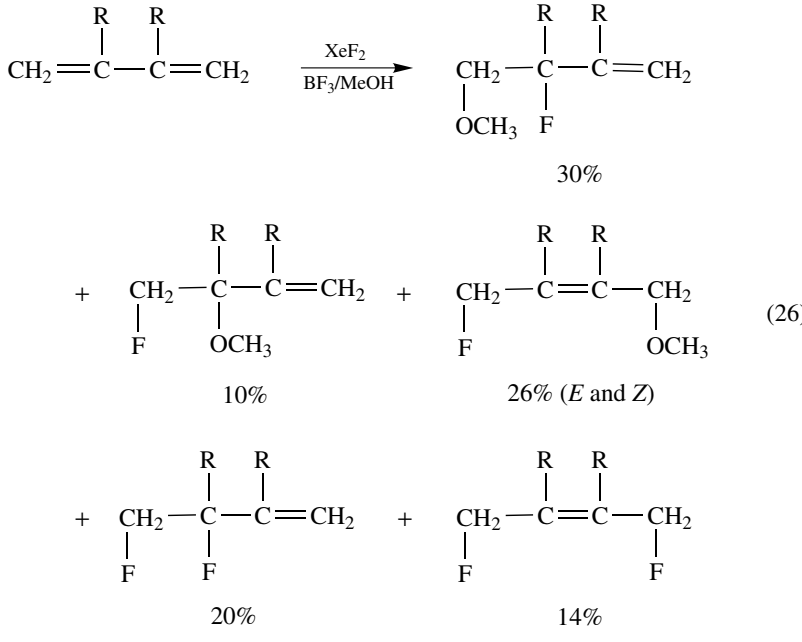


(a) **(b)**



(25)

Adducts of type **13**, arising from the rearrangement of the allylic intermediate, have never been observed. The product distribution in methanol depends, however, on the reaction conditions. When the addition of XeF_2 is carried out in the presence of boron trifluoride as a catalyst, the formation of the complex **b** has been suggested. This complex would react with 2,3-dimethylbutadiene as a positive oxygen electrophile to give, besides 1,2- and 1,4-difluoro derivatives, 1,4- and 1,2-fluoromethoxy products with a predominance of the anti-Markovnikov adduct (equation 26).



(26)

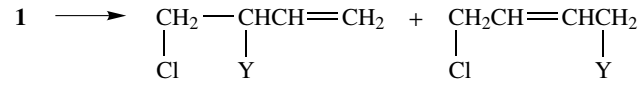
Furthermore, kinetic measurements have shown that the reaction is zero order in alkene when equimolar concentrations of XeF_2, alkene and BF_3 are used, whereas a dependence on olefin concentration is found when higher concentrations of alkene are utilized. On the basis of these kinetic data and taking into account that the regioselectivity of the reaction changes on increasing the olefin concentration, a mechanistic scheme has been proposed for this reaction in which two reaction pathways compete: in one the alkene is intercepted in a fast step, leading to both addition products and formaldehyde, and in a second one XeF_2 reacts directly with the olefinic bond.

C. Chlorine

1. Conjugated double bonds

The first studies of chlorine addition to the simplest diene, 1,3-butadiene, carried out in solvents of various polarity, showed[58] that the reaction always led to mixtures of 1,2- and 1,4-addition products, in ratios almost independent of the solvent polarity. Furthermore, the addition of Cl_2 in acetic acid gave, besides the 1,2- and 1,4-dichlorides, 3-acetoxy-4-chloro-1-butene and 1-acetoxy-4-chloro-2-butene arising from solvent incorporation (equation 27). By comparison of these data with those related to Br_2 addition

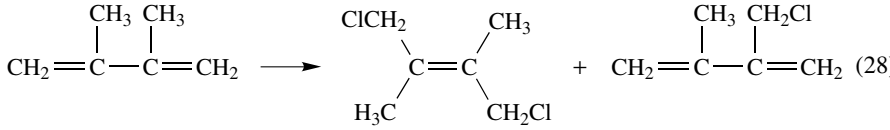
under identical conditions, it was suggested[58] that the intermediate involved in the ionic chlorine addition has a greater carbenium ion character with respect to that arising from bromine addition. However, the lack of any data on the product stereochemistry made it practically impossible to attribute a bridged or an open ion structure to the intermediate.



(27)

Y = Cl or OAc

The reaction of 2,3-dimethyl-1,3-butadiene with an equimolar amount of chlorine in carbon tetrachloride at $-20\,^{\circ}C$ has instead been reported[59a] to give mainly *trans*-1,4-dichloro-2,3-dimethyl-2-butene and 2-chloromethyl-3-methyl-1,3-butadiene, arising from the loss of one of the acidic hydrogen atoms in the ionic intermediate (equation 28).



(28)

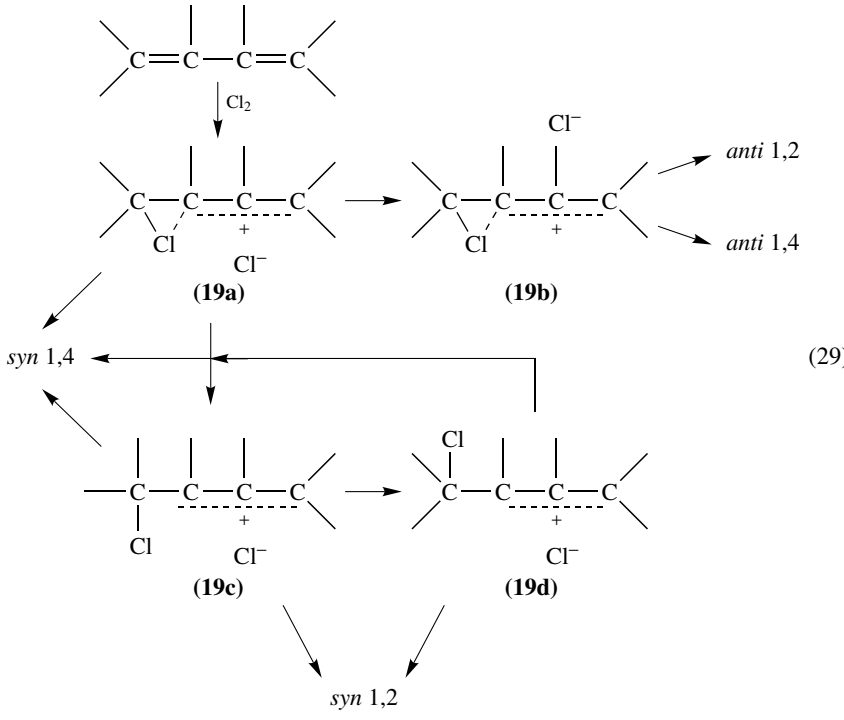
However, a later investigation of the chlorination of the same substrate has shown[59b] that the product distribution observed immediately after the end of the chlorine addition was markedly different. Small amounts (5%) of the kinetically favored 1,2-dichloride were detected. Furthermore, although the yields of 1,4-dichloro adducts from the two experiments were the same, the yield of the monochloride was much lower in the latter experiment in which detectable amounts of trichlorides were also found.

Later on, product distribution studies[15] of the ionic addition of chlorine to conjugated dienes, and in particular to cyclopentadiene, 1,3-cyclohexadiene, *cis*,*cis*-, *trans*,*trans*- and *cis*,*trans*-2,4-hexadienes, and *cis*- and *trans*-1,3-pentadienes have supplied the first stereochemical data, showing that the stereochemistry of 1,4-addition is predominantly *syn*, although to an extent smaller than that of bromine addition. Moreover, the 1,2-addition is generally non stereoselective, except for the addition to the 3,4-bond of *cis*- and *trans*-1,3-pentadienes where the attack is 89–95% *anti*. Finally, appreciable amounts of *cis*-1,2-dichlorides were obtained from the two cyclic dienes, whereas 2,4-hexadienes showed a preference for *anti* 1,2-addition, at least in the less polar solvents (carbon tetrachloride and pentane). On the basis of all these results the mechanism shown in equation 29 was proposed.

According to this mechanism, the first formed ion pair is **19a**. Owing to dispersal of charge in the allylic system, the bond between halogen and C(2) is weakened so that an open carbenium ion **(19c)** readily forms, allowing for the possibility of front-side attack by the anion with the resulting formation of *syn* 1,2-adducts. This intermediate explains the formation of the *cis*-1,2-adducts by chlorine addition to cyclic systems. However, *syn* 1,2-dichlorides can also result from linear dienes by rotation around the C(1)–C(2) bond in **19c** to produce **19d**, followed by back-side attack by the anion with respect to its position in **19d**. *Syn* 1,4-adducts should instead arise by attack of the anion on C(4) in either **19a**, **19c** or **19d**. Formation of *anti* dichlorides (1,2- or 1,4-) can only occur when there is appreciable translocation in the ion pair **19a** to give **19b**. Attack by the anion at C(2) in **19b** yields *anti* 1,2-dichloride and attack at C(4) yields *anti* 1,4-dichloride.

At variance with the earlier study[58] on butadiene, the data related to halogenation of these substituted dienes reveal also that solvents have striking effects on product ratios,

although the solvent-dependent product distribution cannot be interpreted in terms of the above mechanism, as evidenced by the authors.

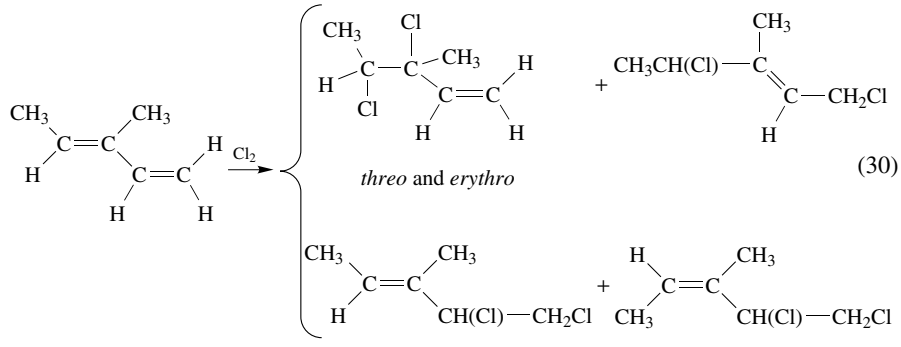


Independently of the latter observation, the stereochemical results of a subsequent study[60] on the chlorine addition to *cis*-3-methyl-1,3-pentadiene, which gives five products, different from those of 1,3-pentadiene, i.e. the 1,4-adduct, *threo*- and *erythro*-3,4-dichloro derivatives and *cis*- and *trans*-1,2-adducts (equation 30), have been interpreted once again on the basis of the mechanism reported above (equation 29). In this case, however, the presence of a methyl group at C(3) should reduce the bridging between the halogen and the carbon in the corresponding intermediate, decreasing the *anti* stereoselectivity of the reaction. Furthermore, the presence of the methyl group at C(3) has been assumed to promote the isomerization of the double bond observed in the formation of the 1,2-adducts starting from the *cis* but not from the *trans* isomer. The presence of two *cis* methyl groups in the ionic intermediate probably provides the driving force for the isomerization.

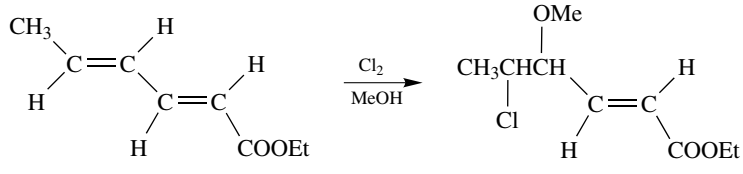
More recent data[61] on the chlorination of 1,3-pentadienes have confirmed that chlorine addition in 1,2-dichloroethane or carbon tetrachloride gives 4,5- and 1,4-dichloro-2-pentenes as main products, besides smaller amounts of 3,4-dichloropentenes, although chloropentenes have been detected as minor products. Furthermore, it has been shown that the yields of the latter products are reduced when the reaction is carried out in the presence of quaternary ammonium or phosphonium salts.

Finally, a high regioselectivity has been observed[62] in the chlorine addition to ethyl sorbate **(20)** in methanol (equation 31). Under ionic conditions the reaction gives mainly products arising from addition to the $\gamma-\delta$ bond and the solvent opens the corresponding ionic intermediate preferably at the allylic carbon to give product **21**. A bridged structure

has been proposed for the intermediate since nucleophilic attack at the δ carbon to yield *erythro*-**22** has been noted. Furthermore, taking into account the bridged nature of the intermediate, the minor formation of **23** has been rationalized as the result of an S_N2'-like reaction with the solvent when the halonium intermediate is formed at the $\gamma-\delta$ bond of **20**.

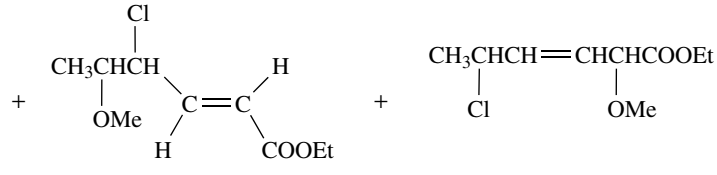


(30)



(20) **(21)** 83%

(31)

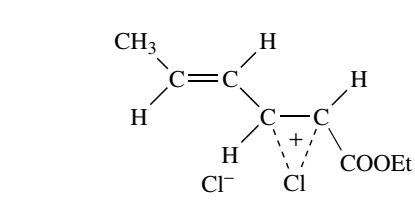


(22) 10% **(23)** 7%

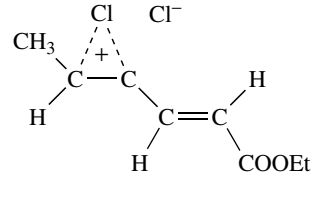
The different reactivity of the two double bonds of **20** has therefore been related to the relative energies of the transition states leading to the intermediates **24a** and **24b**. The preferential addition of an electrophile at the $\gamma-\delta$ bond has been attributed to its more nucleophilic character and to the fact that conjugation with the ester carbonyl is not disrupted. Furthermore, with the assumption that a later transition state should favor attack at the $\alpha-\beta$ bond, since a more stable (delocalized) intermediate can be formed, and taking into account that product distribution data show that the lower-energy transition state leading to addition to the $\gamma-\delta$ bond is favored with these electrophiles (chlorine and bromine), it has been concluded that the chlorine reaction has an earlier transition state than the bromine one in accordance with the relative product distribution data.

A complete regioselectivity has also been observed[63] in chlorine addition to *trans*,*trans*-1-phenyl-4-(2,6-dichlorophenyl)-1,3-butadiene **(25a)** leading to the addition product **(26)** on the more hindered double bond (equation 32). The *cis*,*trans*-isomer **25b** reacts similarly, although in this case the higher reactivity of the *cis* double bond might contribute

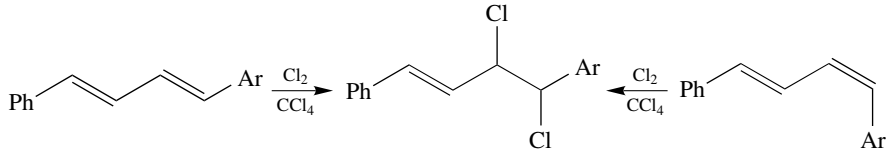
to the regioselectivity, which has been explained for **25b** in terms of a Cl–Cl interaction.



(24a)



(24b)



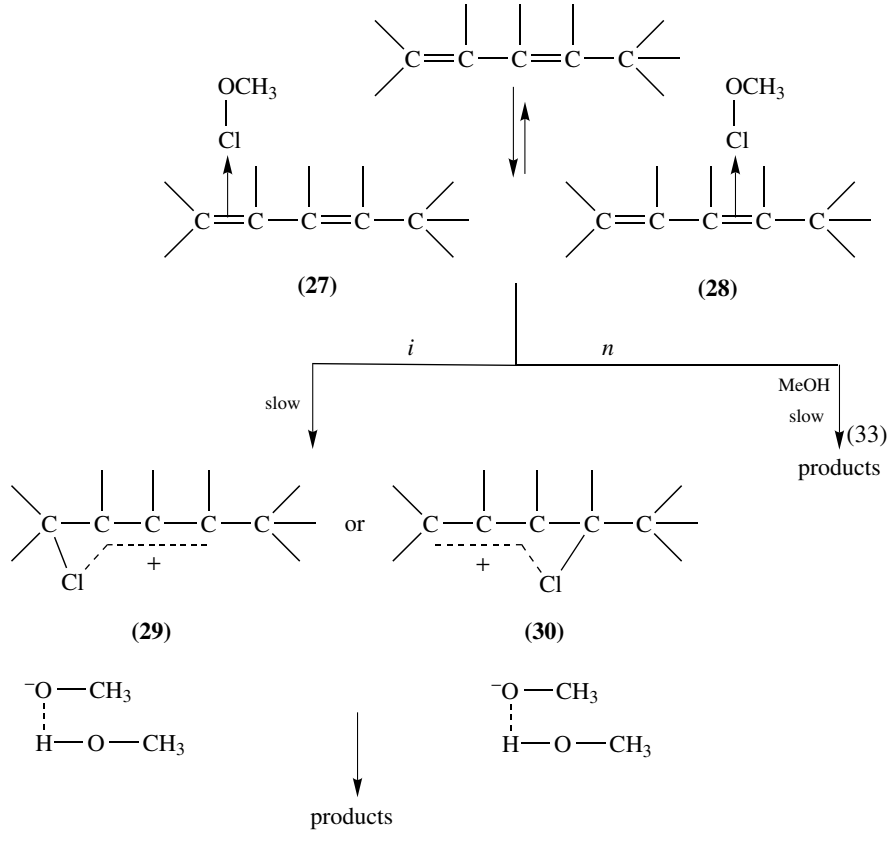
(25a) **(26)** **(25b)**

Ar = 2,6-dichlorophenyl (32)

Although bromination, iodochlorination and iodobromination of unsaturated compounds in aprotic solvents are generally described as following a third-order rate law, chlorination was always found to obey, in the presence of radical inhibitors, second-order kinetics[2b]. However, it has been recently shown[64], through kinetic studies on chlorine addition to 1,3-butadiene in carbon tetrachloride, that in the presence of *tert*-butylpyrocatechol as a radical chain inhibitor the reaction may follow a second-order (first order in halogen) or a third-order (second order in halogen) rate law, depending on the chlorine concentration. Furthermore, third-order kinetics were found in a selected concentration range for the formation of the 1,2-addition product only. The 1,4-adduct accumulated in agreement with a kinetic equation first order in chlorine. The third-order process was, moreover, characterized by a small and negative value of the effective activation energy (-3 kcal mol^{-1}) and a large and negative value of the activation entropy (-65 Kcal mol^{-1} deg^{-1}), which have been interpreted in terms of the molecular mechanism, previously proposed exclusively for bromination in non-protic solvents[2b]. Two chlorine molecules and one alkene molecule are assumed to form a 2 : 1 complex, which rearranges into a non-polar cyclic six-membered transition state without dissociation into ions or radicals. The exclusive formation of 3,4-dichloro-1-butene under third-order conditions has been considered as a further support of the molecular mechanism. Indeed, if a chloroalkenyl cation was formed in this reaction, delocalization of the electron density in the conjugated system would lead to the formation of 1,4-dichloro-2-butene in addition to 3,4-dichloro-1-butene.

Although alkyl hypochlorites have been extensively utilized in radical reactions, their electrophilic additions to dienes occurring through an ionic mechanism were observed only in polar solvents[65], or with boron trifluoride[66] as a promoter. The inertness of methyl hypochlorite toward alkenes in typical aprotic non-nucleophilic solvents, generally used for brominations and chlorinations, has been attributed to the inability of this reagent to form, with an alkene, the corresponding ion pair intermediate, because of the high basicity of the methoxy anion. Two possible mechanisms which could account for the role of methanol have therefore been suggested. As shown in equation 33, the diene

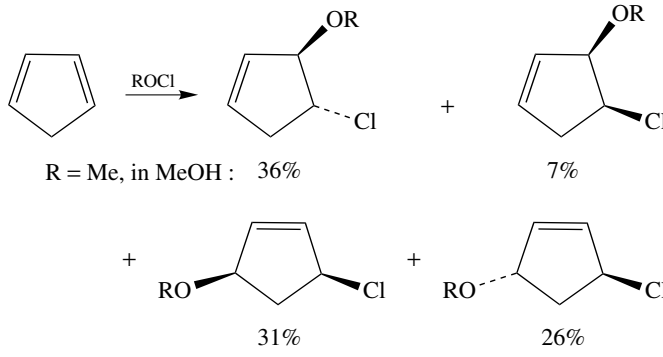
reacts with methyl hypochlorite in a fast reversible step to produce the complexes **27** and **28**. In mechanism *i* (ionization) the first formed π-complexes (or CTCs) undergo a rate-determining ionization, electrophilically assisted by the solvent acting as an acid, to give the ion pair intermediates **29** and **30**. Reaction of **29** or **30** with methanol or methoxide ion would take place in a fast step. In mechanism *n* (nucleophilic attack), the reaction occurs through a product- and rate-determining nucleophilic attack of the methanol on the first formed complexes.



Since chlorination of alkenes occurs rapidly in aprotic non-nucleophilic solvents by mechanism *i*, and since the products (chloroethers and dichlorides) obtained from the reaction of butadiene, isoprene and 1,3-pentadienes with chlorine and methyl hypochlorite in methanol are strikingly similar, it has been suggested that both reagents react essentially in the same way, via carbenium ion intermediates (path *i*). To support this hypothesis it has been remarked that, in agreement with an appreciable carbenium ion character of the rate-determining transition state, a higher reactivity of the 1,2-bond of 1,3-pentadienes has been observed with both reagents. The relative reactivities of the two double bonds should indeed be a reflection of the stabilities of the allylic ion pairs **29** and **30**. Furthermore, the fact that methyl hypochlorite gives an even larger percent of attack than that of chlorine at the 1,2-bond of 1,3-pentadienes, has been explained in terms of reactivity. The greater

reactivity of chlorine would imply an 'earlier' ionization transition state for the chlorine reaction than that for methyl hypochlorite.

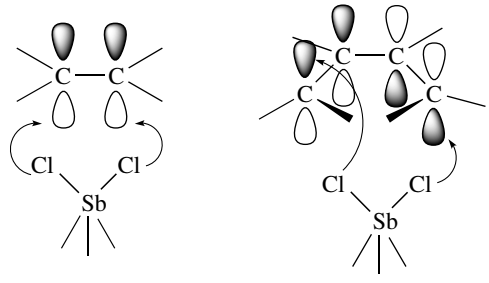
It is noteworthy that both methyl and *tert*-butyl hypochlorites react[67] in several solvents with cyclopentadiene to give 1,2- and 1,4-addition products arising from both *syn* and *anti* additions, although the amount of *syn* 1,2-products is the smallest in methanol (equation 34).



(34)

The formation of the *syn* adducts has been explained by considering that carboxylic acids or BF_3 catalyze the formation of the ionic intermediate by stabilizing the methoxy ion. This intermediate can then collapse directly to the *cis* product. Reactions in methanol give instead mainly the *trans*-1,2-adduct, the solvent collapse from the back-side being very rapid. Furthermore, the difference in *syn* selectivity, slightly larger for 1,4- than for 1,2-addition, has been attributed to a smaller steric hindrance for *syn* methoxy (methanol) attack at C(4) than at C(2).

Chlorination of olefins has also been achieved with $SbCl_5$ in chlorinated solvents, which gives with mono-olefins vicinal dichloroalkanes by a *syn* addition. A concerted mechanism was initially proposed[68] to rationalize this stereochemical behavior and the unexpectedly large amount of *cis*-1,4-dichloro-2-butene found in the reaction of butadiene. In this case, however, because of orbital symmetry control it has been suggested that the addition occurs in an antarafacial direction[69].

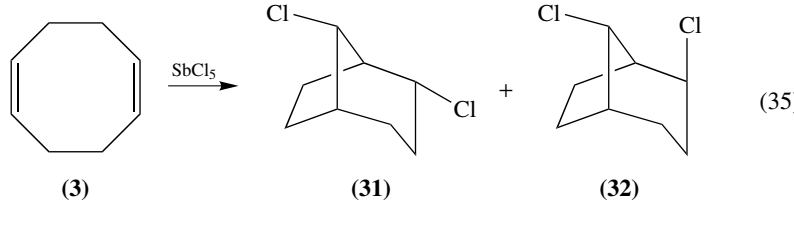


Subsequent studies on cyclopentadiene, in which the antarafacial concerted 1,4-addition is impossible because of interference between the antimony system and the methylene of cyclopentadiene, have however shown[70] that both butadiene and cyclopentadiene react with $SbCl_5$ through a stepwise mechanism involving a carbenium ion intermediate. In agreement with a non-concerted mechanism are also the data related to the 1,4-addition

to 2,4-hexadienes; nearly equimolar amounts of *syn* and *anti* 1,4-addition products were observed, although symmetry considerations indicated that a concerted mechanism should give only *anti* 1,4-addition. On the basis of experimental evidence arising from previous studies on $SbCl_5$ reactions with olefins and more recent data, essentially related to its reaction with dienes, it has been concluded that $SbCl_5$ can add to olefins and dienes either via a carbenium ion or by a concerted mechanism, depending on the stability of the ionic intermediate.

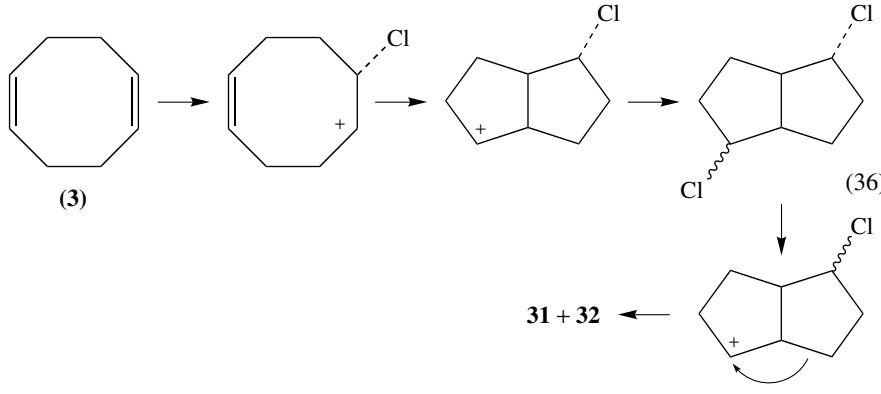
2. Non-conjugated double bonds

In agreement with a non-concerted mechanism, the chlorination of *cis*,*cis*-1,5-cyclooctadiene **3** with $SbCl_5$ in CCl_4 gives two products **31** and **32** both arising from a transannular interaction (equation 35)[71]. It is noteworthy that usually transannular cyclizations of **3** give bicyclo[3.3.0]octane derivatives. However, since $SbCl_5$ is a very efficient catalyst, at least for isomerizations of dichloronorbornanes, it has been suggested that, in agreement with a transannular cyclization, a mixture of *endo*,*endo*-2,6- and *endo*,*exo*-2,6-dichlorobicyclo[3.3.0]octanes is probably formed initially through the chlorocyclooctenyl cation and only a subsequent rapid isomerization yields the mixture of **31** and **32** (equation 36).



(35)

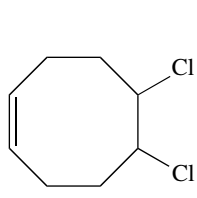
(3) **(31)** **(32)**



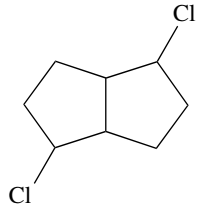
(36)

(3)

3 reacts also with chlorine at $-50\,^{\circ}C$ in CH_2Cl_2 to give a 93 : 7 mixture of 5,6-dichlorocyclooctene **(33)** and 2,6-dichlorobicyclo[3.3.0]octane **(34)** in 70% yield, whereas when the solvent is acetonitrile only the transannular 2,6-dichlorobicyclo[3.3.0]octane **(34)** was obtained as the sole product[22]. In agreement with a strongly solvent-dependent product distribution, the reaction in methanol gave, besides the 1,2-addition products **33** and **35**, also dichloro-9-oxabicyclo[3.3.1]nonane **(36)** arising from the electrophilic addition to the two double bonds.



(33)



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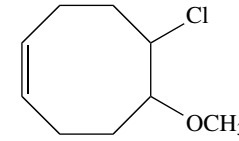

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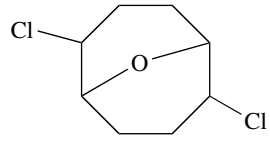
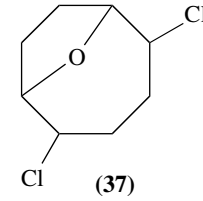


(36)



(37)

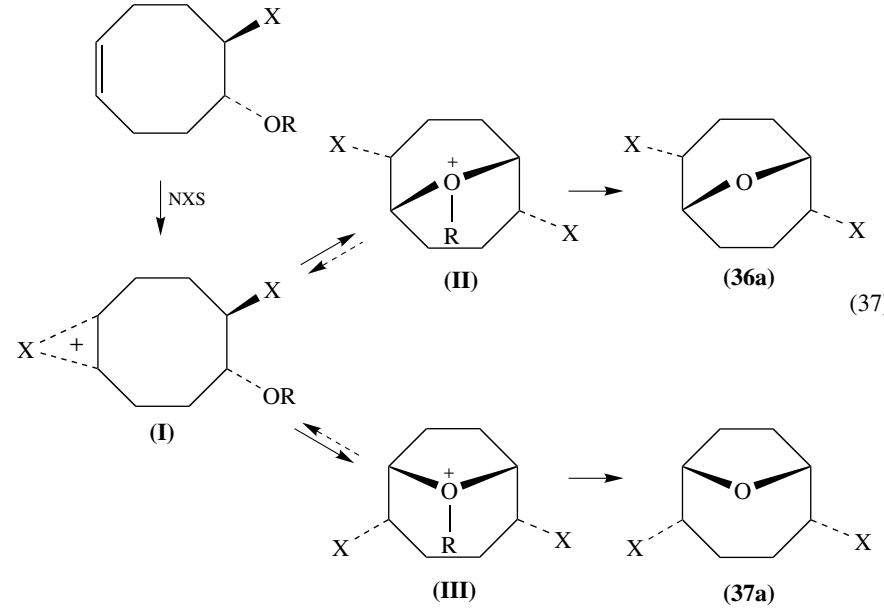
This latter compound, **36**, and the isomeric 9-oxabicyclo[4.2.1]nonane, **37**, were obtained as the sole products, in *ca* 13 : 87 ratio, by reaction of **3** with *N*-chlorosuccinimide (NCS) in protic solvents (methanol, dioxane–water mixtures)[72]. It is noteworthy that similar ratios of the two disubstituted bicyclononane derivatives were obtained, independently of the solvent, also by using *N*-bromosuccinimide (NBS) as electrophile, whereas a strongly solvent-dependent ratio was observed when *N*-iodosuccinimide (NIS) was used. Since these reactions should proceed through hydroxy- or alkoxyhalogenation of one of the double bonds, followed by transannular attack of the oxygen function on the cationic center which is formed on the other side of the ring by the reaction of another electrophile with the second double bond, the isomer ratio has been rationalized in terms of a different nature of the intermediates.

In the reaction of NCS, a weakly bridged chlorocarbenium ion is probably the intermediate. The positive charge is mainly on the carbons, and therefore the transannular cyclization of **I** is assumed to be irreversible independently of the leaving group R. As a consequence of the greater tendency to form a five-membered ring, the kinetically favored compound **37a** is formed preferentially. In the NBS reaction the intermediate should be more strongly bridged and the transannular step reversible so that the portion of the thermodynamically favored compound **36a** increases. In the case of the reaction with NIS, the charge is localized essentially on iodine and the transannular bridging step is considered reversible. Under these conditions, when R is not a good leaving group (Me, Et), intermediate **III** isomerizes to the thermodynamically more stable **II** from which **36a** is formed. When R is a better leaving group (R = *tert*-Bu), elimination is faster than isomerization and the kinetically favored **37a** is obtained (equation 37).

D. Bromine

1. Conjugated double bonds

Bromine addition to conjugated dienes gives 1,2- and 1,4-addition products (equation 38), with a stereochemical outcome which is strongly dependent on the diene structure and the reaction conditions.



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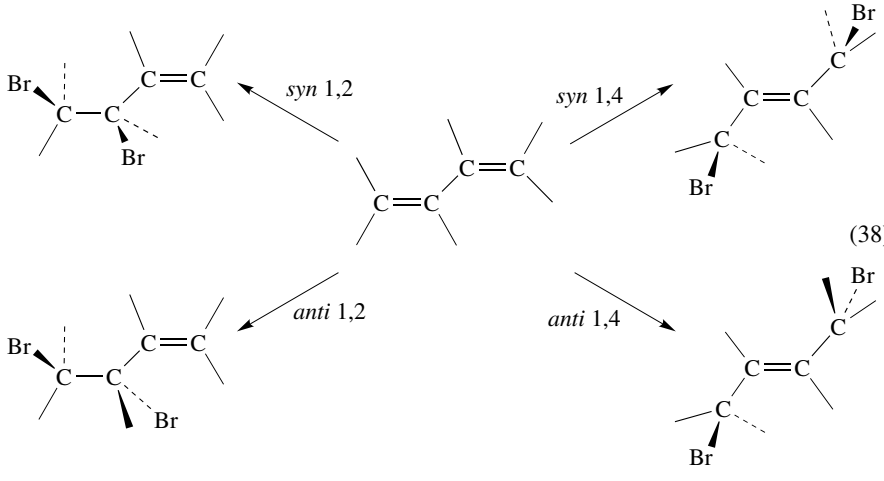


(38)

Generally, in bromine addition to carbon–carbon double bonds, bromine bridging, solvent dependent dissociation of the ionic intermediates, steric interactions between the counteranion and the first bonded halogen during the nucleophilic step, the possibility of carbon–carbon rotation in the carbenium ion intermediate, preassociation phenomena and nucleophilic assistance determine the stereochemical behavior of the reaction[3a,c,7d,8]. Several of these factors have been invoked to explain the stereochemistry of bromine addition to dienes, although others have been completely ignored or neglected. Bromine addition to cyclopentadiene, 1,3-cyclohexadiene, 2,4-hexadienes and 1,3-pentadienes has been examined repeatedly by Heasley and coworkers and the product distribution has been

compared to that of chlorine addition[13,15]. These studies have shown that, at variance with chlorine addition, cyclic dienes react with bromine, in solvents of different polarity, leading exclusively to *anti* 1,2-addition products. Although the different stereoselectivity of the two halogens could suggest the involvement of open ion intermediates in chlorine addition and bridged ions in that of bromine, considering that the 1,2-bromine addition to 2,4-hexadienes proceeds non-stereospecifically, it has been proposed[13,15] that in the reaction of bromine with cyclic dienes the ionic intermediates could, to a considerable extent, be open carbenium ions. Therefore, the absence of *syn* 1,2-addition products with these substrates has been attributed to the greater steric interaction of the counterion with the already bound halogen in bromine addition than in chlorine addition.

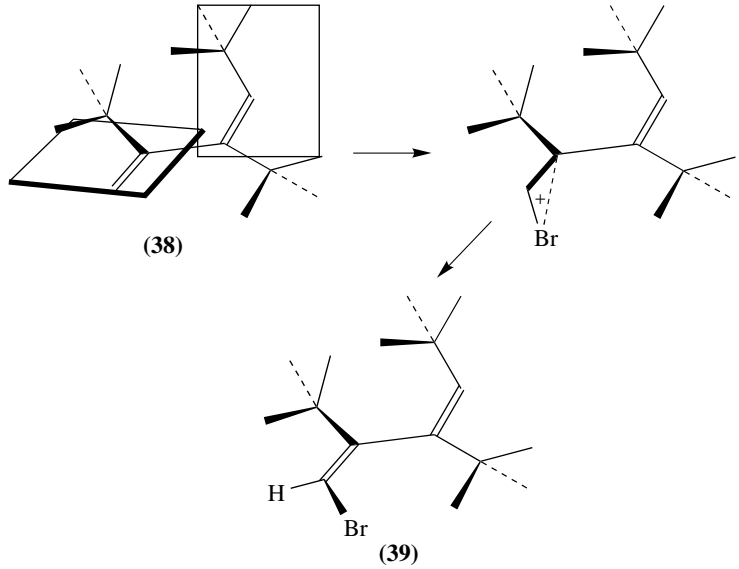
Furthermore, in the addition to the 3,4-bond of 1,3-pentadienes, the *anti* stereoselectivity observed with both bromine and chlorine has been attributed to a tightly bridged bromonium ion intermediate involving less charge dispersal in the vinyl group. In support of this hypothesis, it has been noted that bromine addition to the terminal double bond of the 1,3-pentadienes occurs without isomerization of the internal *cis* or *trans* double bond[15].

A mechanistic scheme involving weakly bridged intermediates, liable to undergo carbon–carbon bond rotation and counteranion translocation, analogous to that proposed for chlorination (see above), has been reported also for the bromination of dienes in order to rationalize the product stereochemistry.

The literature is more controversial concerning the relation between the bridging of the intermediate and the stereochemistry of the 1,4-addition. It has been suggested[15] that if 1,4-addition occurs via a bridged intermediate, an S_N2' process should be involved and the stereochemistry of the product should be completely *syn*. Alternatively, an increase in the amount of *anti* 1,4-addition would be expected when an open carbenium ion is involved[15]. Furthermore, the lack of any 1,4-product has been considered as evidence for an at least weakly bridged bromonium ion, and therefore the dependence of 1,4- vs 1,2-addition of bromine on the solvent polarity has been related to a solvent-dependent structure of the intermediate. However, it is noteworthy that although more bridging is expected in bromination than in chlorination intermediates, the amount of 1,4-addition, compared to 1,2-addition, is appreciably higher in brominations than in chlorinations. Furthermore, whereas chlorine addition occurs primarily via a *syn* addition process, the stereoselectivity of bromine addition is greatly variable, even if a strong preference for *syn* additions has been generally observed. Finally, both dependence and independence of this ratio on the solvent polarity have been claimed, although, with the exception of methanol and acetonitrile, a general trend toward greater 1,4-addition of bromine to 1,3-butadiene with increasing solvent polarity has been observed[60]. The latter results have been explained by assuming that Br_2 addition to butadiene in methanol occurs through an intermediate with little, if any, charge delocalization, whereas a delocalized carbenium ion should be involved in the bromine addition in chlorinated solvents. The weak solvating power of the medium should favor intramolecular charge stabilization. Once again, however, it must be stressed that in methanol, preassociation phenomena and nucleophilic solvent assistance, observed in the bromine addition to olefins, could affect the stereochemistry of the addition, which could therefore be determined by these factors but not by changes in the intermediate bridging[7d].

As observed with alkenes, bromine addition to sterically hindered dienes shows a peculiar behavior. Highly substituted dienes, existing predominantly in non-planar conformations, often present a chemical reactivity distinctly different from that of planar 1,3-dienes. (*Z*)-4-*tert*-Butyl-2,2,6,6-tetramethyl-5-methylene-3-heptene **(38)** reacts[73] with bromine in chloroform to give, instead of the expected 1,2- and 1,4-adducts, the monobromide **39**. The formation of this elimination product has been rationalized on the basis

of an initial bromine attack at the sterically less hindered side of the less hindered double bond of **38** to give an ionic intermediate. This intermediate, which cannot be captured by the usual back-side attack because of the extreme steric shielding, undergoes deprotonation to form **39** (equation 39). It has therefore been stressed that diene **38** behaves regeneratively, like a classical arene.



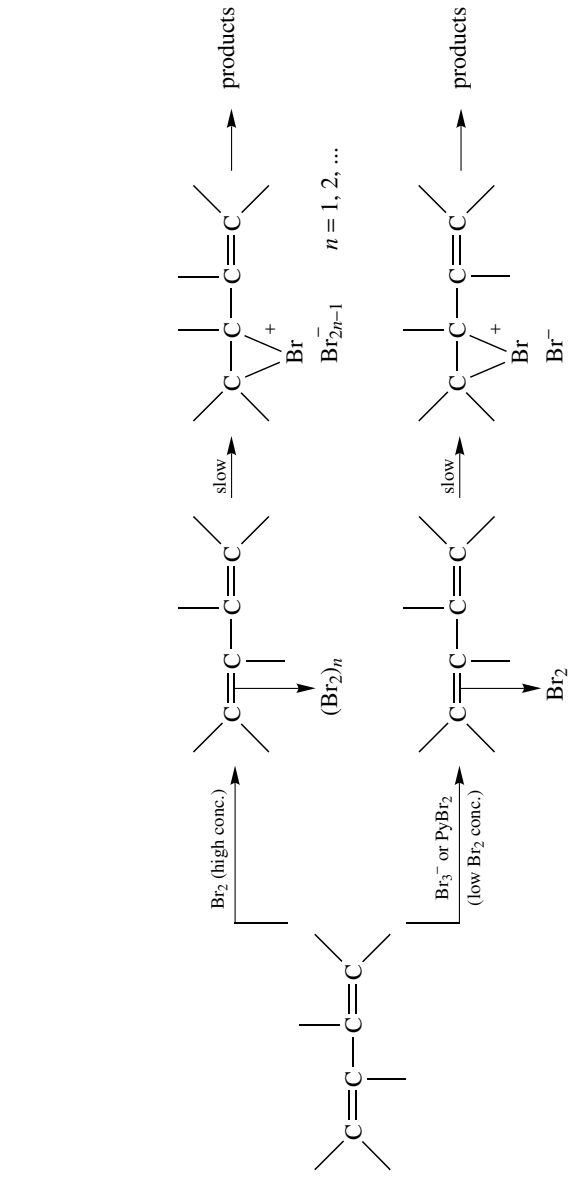
(38) **(39)** (39)

Bromination of dienes has been carried out also with pyridine–bromine complexes and tribromide ions as electrophilic reagents. Generally, they react with dienes to give much more 1,2 to 1,4 adducts and larger ratios of *anti* to *syn* adducts than those with molecular bromine. For instance, 2,4-hexadienes, which give non-stereospecific 1,2-additions with bromine, approach 100% *anti* addition when pyridine halogen complexes or tribromide are used as brominating agents[74]. Furthermore, the stereochemistry of 1,4-bromine addition with hexadienes and cyclopentadiene is mainly *anti* in the presence of an amine.

These results have been rationalized[74] by Heasley and coworkers by assuming that the primary function of the complexes is to limit the concentration of free halogen. In the reaction of free bromine where the reaction is second order in bromine, two or more molecules of halogen participate in the transition state while the halogen complexes with pyridine or amines impose a first-order mechanism by limiting the availability of free halogen (equation 40).

According to this hypothesis the structures of the counterions in the intermediates would therefore justify the differences between the mechanisms. Whereas in the presence of an excess of bromine the counterion is a tribromide or polybromide species, when the reaction is carried out with a tribromide salt or a pyridine bromine complex, the counterion would be a simple bromide ion. Because the latter should be unstable relative to Br_3^-, it has been suggested that the bromonium–bromide ion pair undergoes a fast collapse to the *anti* 1,2-adduct before the opening of the bromonium ion could occur. In contrast, the higher stability of polybromide anions would result in an ion pair of longer lifetime, thus permitting bromonium ion ring opening and the concurrent *syn* 1,2-addition.

However, attempts to test the hypothesis that the product distribution was affected significantly by the halogen concentration have not been encouraging. Only a very slightly


Br2 (high conc.)
slow
products
Br
Br2n−1
n = 1, 2, ...
(Br2)n
Br3− or PyBr2
(low Br2 conc.)
slow
products
Br
Br−
Br2

(40)

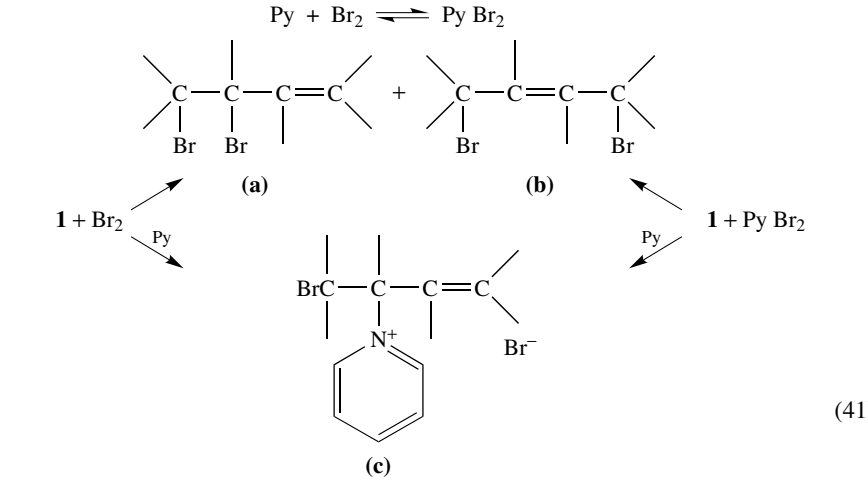
detectable effect of dilution was observed in methylene chloride or nitromethane. The alternative explanation of a change of mechanism from a stepwise Ad_EC_1 to a concerted Ad_EC_2 on going from free bromine to the $PyBr_2$ and Br_3^- reactions, which would account for some features of these reactions, was instead excluded[74] on the basis of the absence of a steric effect (reflected by a decrease in the relative amount of attack on the more substituted double bond) on the bromination of isoprene on going from BrCl to 2,6-lutidine-Br_2.

Subsequent kinetic and product distribution data on the reactions of 1,3-butadiene with molecular bromine, pyridine–bromine complex and tetra-*n*-butylammonium tribromide in chlorinated solvents have shown that pyridine-Br_2 and tribromide ion act as independent electrophiles, rather than as sources of molecular bromine[75].

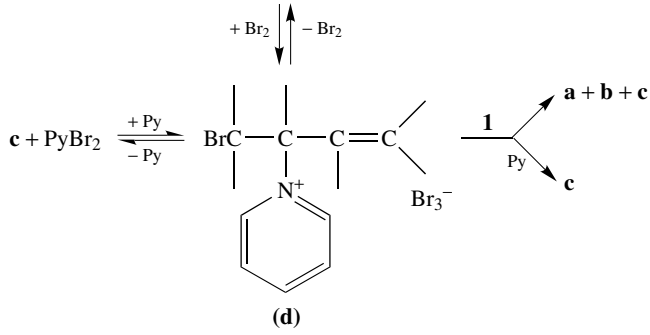
Whereas the reaction with Br_2 followed the usual third-order rate law (second order in halogen), those with the other two types of reagents were first order in the halogenating species. The solvent change from 1,2-dichloroethane to the slightly less polar dichloromethane produced a threefold decrease in the rate of the reaction with Br_2 and a fourfold increase in that with Br_3^-, showing that the reactions follow two different mechanisms. Indeed, if the only role of tribromide, as well as of $PyBr_2$, was to limit the concentration of free bromine, affecting the nature of the counterion of the ionic intermediate, a change from second to first order in the electrophile could occur, but the rates of the two processes involving the same cation as the intermediate should not exhibit an opposite trend to the solvent sensitivity[75]. Once again, significant differences in the ratios of 1,2- to 1,4-adducts on changing from molecular bromine to complexed bromine were found. Furthermore, in the reaction of $PyBr_2$ (and to a lesser extent in that with Br_3^- in the presence of pyridine) substantial amounts of *N*-(4-bromo-1-buten-3-yl)pyridinium bromide accompanied the expected dibromo adducts. This salt was converted into the corresponding tribromide as long as free Br_2 or $PyBr_2$ was present in the medium. The tribromide therefore remained the only brominating species during the later stages of the reaction. The reaction mechanism reported in equation 41 has been consequently proposed to rationalize the kinetic and product distribution data.

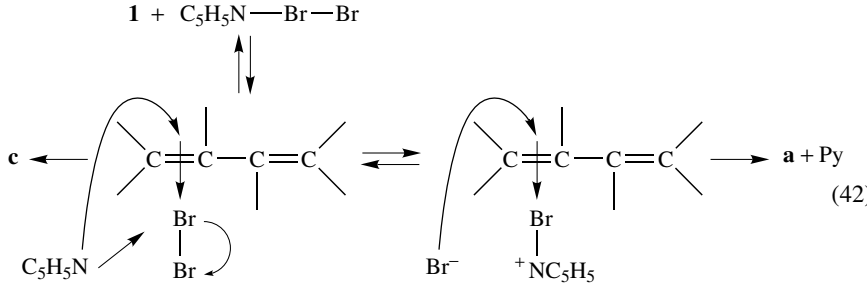
It is noteworthy that this mechanism implies an equilibrium between $PyBr_2$ and a diene-Br_2 charge transfer complex (CTC). Nucleophilic attack by pyridine at the carbon of the CTC with concerted Br−Br bond breaking gives the pyridine incorporation product (equation 42). On the other hand, the formation of a dibromo adduct requires a preliminary breaking of the Br−Br bond in the first formed CTC. Since under the reaction conditions there is no free bromine which is able to provide electrophilic assistance, it has been suggested that this breaking may be achieved through nucleophilic assistance by pyridine to give a new CTC and a bromide ion. The collapse of this latter compound would give the dibromo adduct. Finally, considering that the reaction of Br_3^- in the presence of pyridine proceeds also with a significant incoporation of pyridine, the mechanism reported in equation 43 has been proposed.

The diene-Br_2 complex is again in equilibrium with the reagents, and nucleophilic attack at carbon can be carried out either by the bromide of the ammonium bromide ion pair, formed at the moment of the electrophilic attack, or by the less nucleophilic pyridine added in excess in the reaction medium. It is noteworthy that this mechanism is characterized by a rate- and product-limiting nucleophilic step which should be quite insensitive to steric hindrance around the double bond. In agreement with a weak influence of the steric effects, pyridinium perbromide reacts[76] in chloroform and tetrahydrofuran with substituted conjugated and non-conjugated dienes to give selectively (>95%) bromine addition to the more alkylated double bond (equation 44).



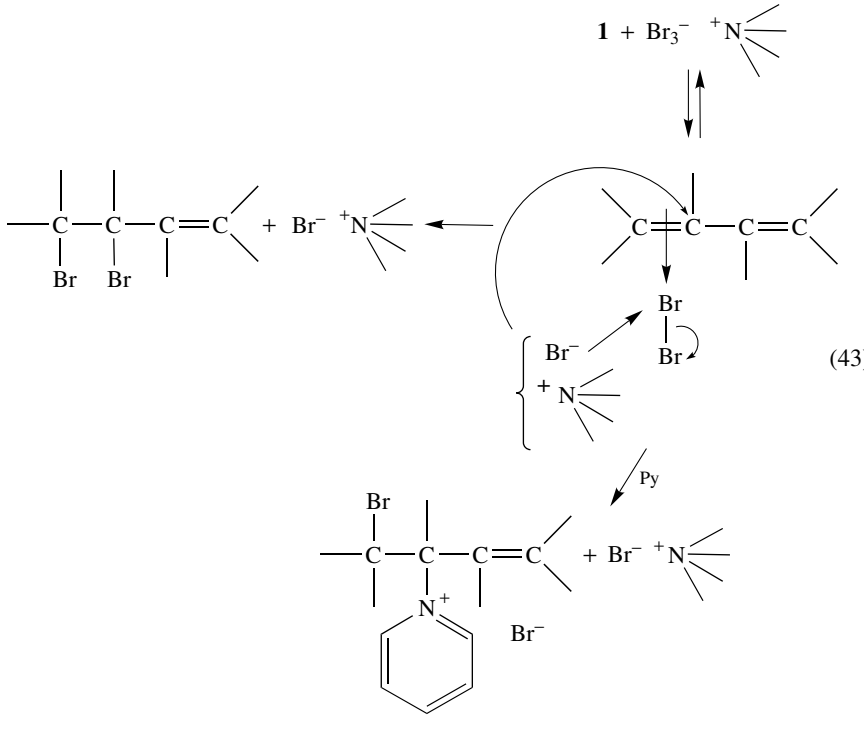
(41)



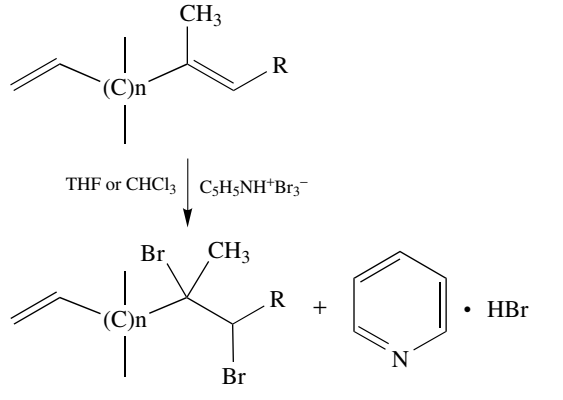


(42)

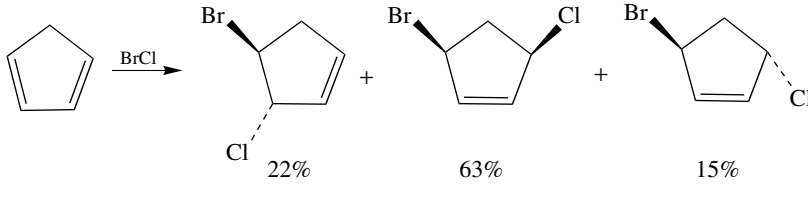
The addition of bromine chloride (BrCl) and amine–bromine chloride complexes to cyclopentadiene, isoprene and *cis*- and *trans*-1,3-pentadienes has been also investigated[74,77]. The amine–bromine chloride complexes react with these dienes to give mixtures of bromochlorides in ratios markedly different from those obtained with BrCl. In particular, in analogy with Br_2, BrCl gives significantly more 1,4-addition and the complexes give more *anti* 1,2-addition. Only Markovnikov 1,2-adducts have been reported for BrCl addition to these dienes. Furthermore, in the case of cyclopentadiene, 1,2-addition proceeds completely *anti* whereas 1,4-addition gives predominantly the *cis* adducts (equation 45).


1 + Br3−
Br
Br
Br−
Py
Br
Br−

(43)


CH3
(C)n
R
THF or CHCl3
C5H5NH+Br3−
Br
CH3
R
Br
HBr

(44)


BrCl
Br
Cl
Br
Cl
Br
Cl
22%
63%
15%

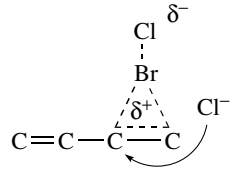
(45)

The stereochemical behavior observed in the addition of BrCl has been compared with that related to the Br_2 and Cl_2 additions to the same diene and discussed in terms of steric hindrance of the nucleophile approach (chloride ion with respect to bromide or tribromide ion) and different bridging in the bromonium or chloronium intermediates[77].

A completely different stereoselectivity, with respect to BrCl, has more recently been observed with tetrabutylammonium dichlorobromate as a bromochlorinating agent[78]. The reaction of this electrophile with 1,3-butadiene, isoprene, *cis*- and *trans*-1,3-pentadienes and cyclopentadiene gives selectively, in good yields, the corresponding 1,2-bromochloro adducts. Moreover, the addition to the 3,4-bond of pentadienes and to cyclopentadiene proceeds with a complete *anti* stereoselectivity. In the case of the unsubstituted butadiene the reaction gives a mixture of Markovnikov and anti-Markovnikov 1,2-adducts (equation 46).

$$H_2C{=}CH{-}CH{=}CH_2 \xrightarrow{BrCl_2^-} CH_2(Br)CH(Cl)CH{=}CH_2 + CH_2(Cl)CH(Br)CH{=}CH_2 \quad (46)$$

A mechanism involving a nucleophilic attack of chloride ions on a three-center π complex-type intermediate, with an unimportant delocalization of the positive charge across the system as shown below, has therefore been suggested to rationalize the stereochemical results.



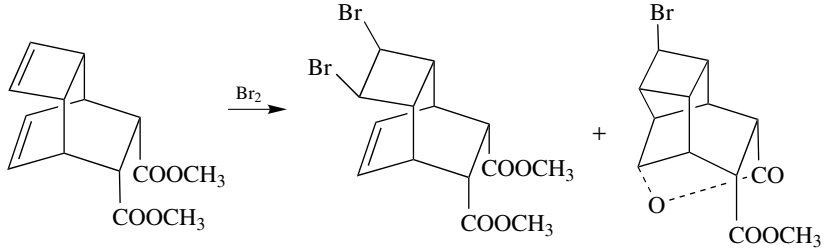
2. Non-conjugated double bonds

Dimethyl tricyclo[4.2.2.$0^{2,5}$]deca-3,7-diene-9,10-dicarboxylate adds bromine and iodine only to the less hindered double bond to give the *syn* 1,2-addition product of the cyclobutene moiety[79]. The product composition from this compound depends on the temperature and the solvent. At high temperatures, the 1,2-addition predominates over the transannular reaction, but this predominance is small in a solvent like chloroform and is lost in a protic solvent such as acetic acid (equation 47).

These results have been interpreted in terms of HOMO–LUMO interactions. As a result of the orbital perturbation, the interaction of the HOMO of the cyclohexene double bond with the LUMO of the developing cation may become effective. At the first stage of this interaction, an overlap of the LUMO of the cyclobutyl cation with the p lobe of the double bond located close to the cation center is probably important. However, when the reaction progresses, the interaction with the p lobe on the remote carbon atom has been assumed to increase significantly.

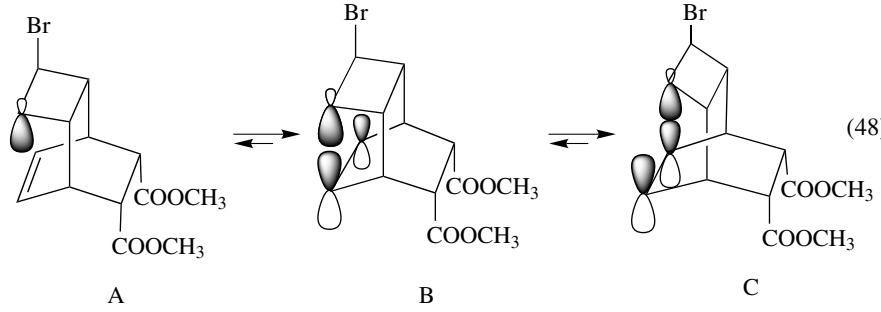
Therefore, when the reaction is carried out under conditions which facilitate the stabilization of the cationic intermediate, electrophilic attack on the cyclobutene double bond of A gives intermediate C, which on lactonization affords the cage compound. At higher temperature, cation B might be trapped by the counterion before the formation of C (equation 48). The attack of the bromide ion on this intermediate occurs from the

less-hindered and electronically favored side to give the *exo-cis*-adduct.



CCl_4	20 °C	14%	84%
CCl_4	77 °C	93%	–
$CHCl_3$	20 °C	–	quant.
$CHCl_3$	61 °C	68%	28%
AcOH	20 °C	–	quant.
AcOH	80 °C	37	63%

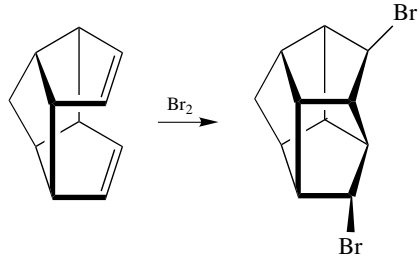
(47)



A B C

(48)

A transannular reaction involving a through-space interaction has been observed also when bromine was added to homohypostrophene **(40)**. The bromination proceeds straightforwardly by 1,4-addition to give exclusively the dibromo adduct **41** (equation 49)[80].

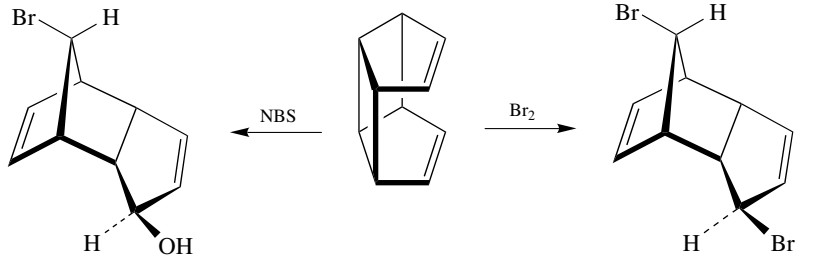


(40) **(41)**

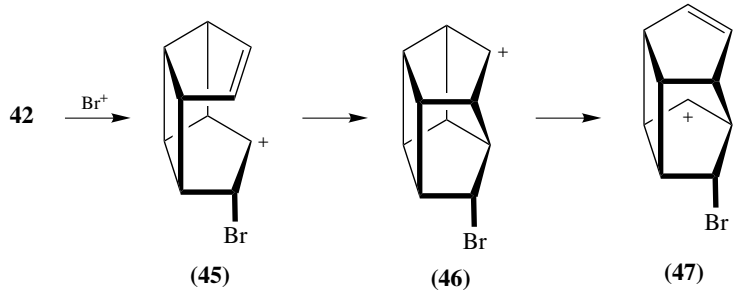
(49)

At variance with homohypostrophene, the related hypostrophene **(42)** reacts with bromine or with *N*-bromosuccinimide in wet dimethyl sulfoxide to give products arising from an extensive structural rearrangement, i.e. the *endo*-dicyclopentadiene derivatives

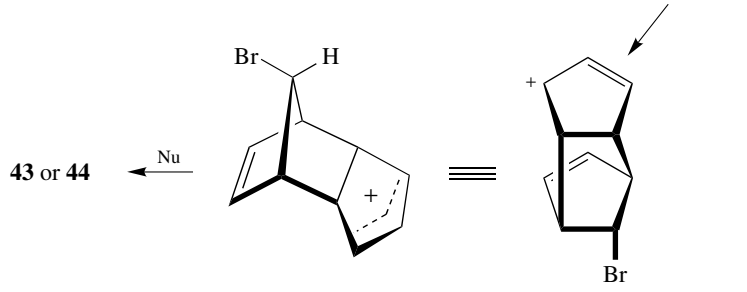
43 and **44**, respectively (equation 50)[80]. A striking feature of the conversion of hypostrophene into **43** and **44** is the involvement of *eight* of its ten carbon atoms in the skeletal rearrangement, which has been explained on the basis of an initial *exo* electrophilic attack to give the intermediate **45**, which should undergo transannular bonding with the normal kinetic preference for 5-ring closure to give **46** (equation 51). Two subsequent cyclobutane bond cleavages are suggested. The formation of **47** should be favored by the electron-rich nature of the lateral bond and controlled by strain release, while the further formation of **48** should be favored by the development of allylic resonance, and a further reduction of strain could also contribute. Nucleophilic attack at either allylic terminus would finally give compounds **43** or **44**. It is, however, possible that the conversion of **45** to **48** can occur through a concerted electronic reorganization since all attempts to intercept these intermediates, even with highly reactive electrophiles, have failed.



(43) (42) (44) (50)



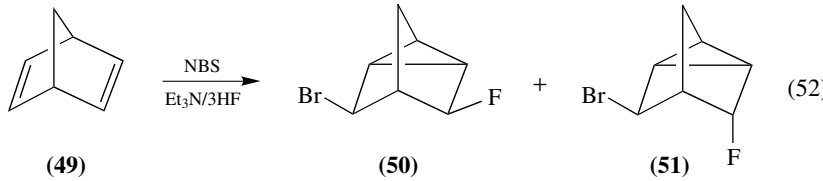
(45) (46) (47) (51)



(48)

Transannular cyclization has also been observed in the bromofluorination of norbornadiene **(49)** using NBS in the presence of Et_3N-3HF which led to a 3 : 2 mixture of

3-*exo*-bromo-5-*exo*-fluoronortricyclane **(50)** and 3-*exo*-bromo-5-*endo*-fluoronortricyclane **(51)**, arising from an exclusive *exo* attack of the Br^+ species on **49** (equation 52)[81].

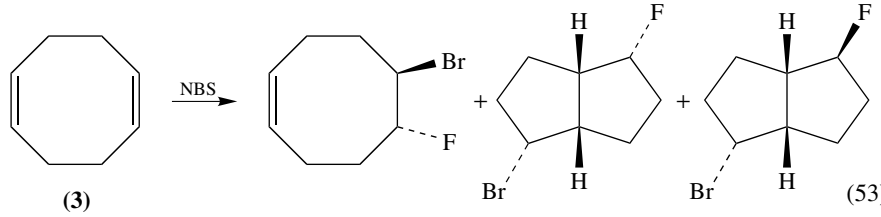


(52)

(49) **(50)** **(51)**

Although the possibility of an *endo* attack was considered[82] previously on the basis of the reported formation of 3-*endo*-bromo-5-*exo*-fluoronortricyclane as the major product in the bromofluorination of **49** with NBS and Olah's reagent (pyridine/10HF), it was subsequently shown[81] that this assumption arose from an incorrect assignment of the structure. With both reagents the minor compound is always the isomer **51**.

Nevertheless, a different selectivity has really been observed[83] in bromofluorination reactions of 1,5-cycloalkadienes with NBS/Et_3N–3HF or Olah's reagent. The reaction of 1,5-cyclooctadiene **(3)** with the former reagent yields mainly the 1,2-addition product **52**, but when the reaction is carried out with Olah's reagent only compounds **53** and **54**, arising from the usual transannular π-cyclization, are formed (equation 53).



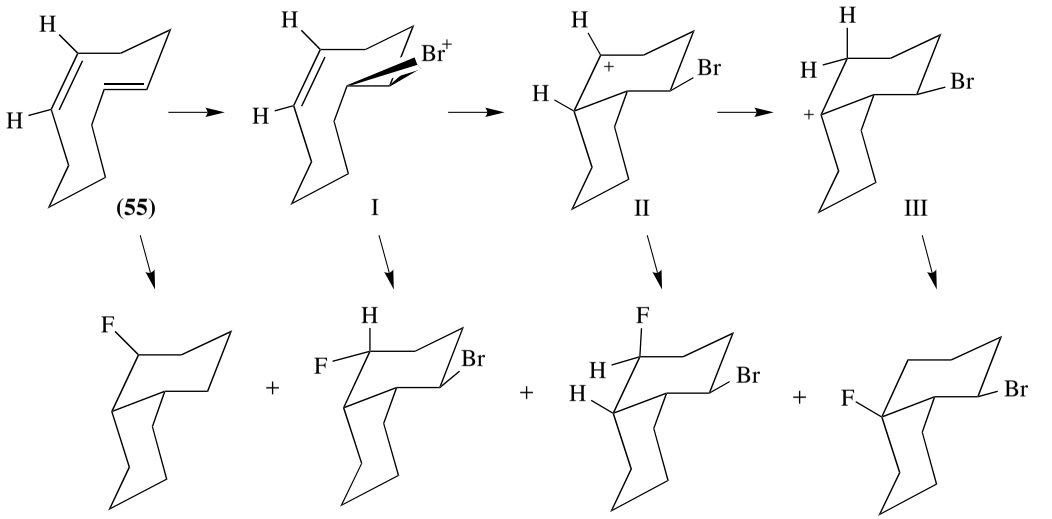
(53)

(3) **(52)** **(53)** **(54)**

Et_3N/3HF	92%	2%	6%
pyridine/10HF		26%	66%

Under similar conditions the reaction of (*E*,*Z*)-1,5-cyclodecadiene **(55)** with either reagent gives exclusively transannular cyclization products **56**–**59** (equation 54). In the reaction of diene **55** the initial formation of the cationic intermediate I, arising from the electrophilic addition to the *E*-double bond of the most stable chair–boat–chair conformation of **55**, has been suggested. A parallel transannular π-cyclization may lead either to the carbenium ion II, or preferentially to the main product **57** through concerted nucleophilic attack by the fluoride ion. With **55**, cyclization should be favored by the fact that one conformation of this diene resembles that of *cis*-decalin, so that carbons C(1) and C(6) are in close spatial proximity. On the other hand, the attack of fluorine on C(1) or C(2) is probably sterically hindered. The cation II is attacked by the nucleophile, producing the product **58** or, particularly under the stronger acidic conditions of the reaction with Olah's reagent, it undergoes a 1,2-shift to give the tertiary cation III from which **59** is obtained.

On the basis of these latter results, the bicyclic products derived from **3** have been explained by cross-transannular π-cyclization. The different behavior observed in the reaction of **55** with the two reagents has been attributed to the strong nucleophilicity of the fluoride ion, which competes with the internal double bond for the bromonium ion attack.

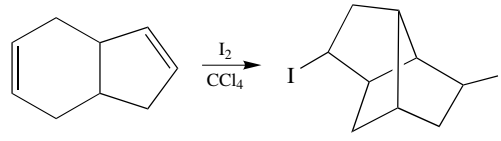


(54)

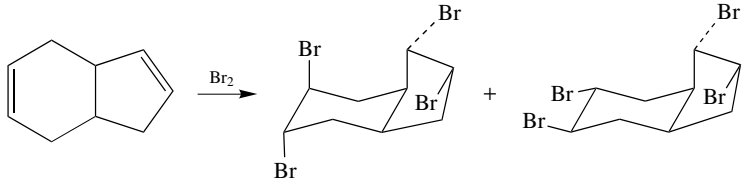
$Et_3N/3HF$	8%	78%	12%	1%
pyridine/10HF	17%	46%	19%	18%

It is noteworthy that Br_2 addition to **3** in aprotic and protic solvents gives exclusively the *anti* 1,2-addition product. For diene **55**, the intramolecular nucleophilic attack of the *Z*-double bond on the cationic center is exclusive, even in the presence of Et_3N-3HF. This has been ascribed to a large strain release in the formation of the *cis*-decalin system from the highly strained medium-sized system.

Although *cis*-bicyclo[4.3.0]nona-3,7-diene reacts with I_2 in CCl_4 or $CHCl_3$ through a regio- and stereoselective transannular cyclization to give *endo*-4-*exo*-8-diiodotricyclo[4.3.0.$0^{3,7}$]nonane (*endo*-4-*exo*-8-diiodobrexane)[84] (*vide infra*) (equation 55), the reaction of this diene with Br_2 at $-8\,^{\circ}C$ leads to a 2 : 1 mixture of the isomeric tetrabromides with the *trans*-diaxial and *trans*-diequatorial arrangements of the bromine atoms in the six-membered ring and with identical *trans* position for the bromine atoms in the five-membered ring (equation 56)[85]. Because of the conformational flexibility of the diene molecule and of the competition in the bromine addition to the cyclohexene and cyclopentene double bonds, the stereoselectivity has been explained in terms of steric factors, whereas no rationalization has been given for the halogen dependent product distribution.



(55)



(56)

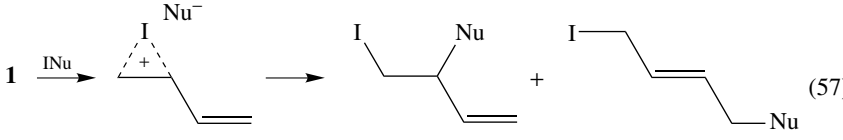
E. Iodine

1. Conjugated double bonds

The addition of iodine electrophiles, *tert*-butyl hypoiodite (*t*-BuOI) in the presence of BF_3, acetyl hypoiodite (AcOI), iodine monochloride (ICl) and iodine monobromide (IBr), to 1,3-butadiene gives always, under ionic conditions, mixtures of 1,2- and 1,4-Markovnikov adducts (equation 57). These mixtures are the kinetic products, since rearrangement to the thermodynamically stable products occurs under the appropriate conditions[86].

At variance with 1-hexene, no addition to the α-carbon (anti-Markovnikov, AM 1,2-addition) was observed when *t*-BuOI-BF_3 was used as the electrophile. Since steric factors in the iodonium ions from 1-hexene and 1,3-butadiene should be similar, the different regioselectivity of the nucleophilic attack has been attributed to the greater reactivity of the allylic β- (M 1,2-addition) and δ-carbons (1,4-addition) of the intermediate, although no extensive development of charge should be present on these carbon atoms. The positive charge is indeed mainly on iodine. An S_N2' attack has therefore been proposed to explain the formation of the 1,4-adducts. Furthermore, assuming that the charge distributions are the same in the iodonium ions, regardless of the anion, the differences in product distribution from *t*-BuOI to IBr have been attributed to differences in the stabilities of the ion pairs and in the rates of their collapse. The anions having lower nucleophilicity (Br^- and Cl^-) should have more time to migrate to the γ-carbon before collapse occurs. On

the other hand, the different product distributions observed in the reactions of the three *tert*-butyl hypohalites have been related to the relative bridging abilities of the halogens. The magnitude of bonding between the halogen and the β-carbon should decrease from iodine to chlorine with increasing charge dispersal into the allylic system, and apparently this shift of charge to the δ-carbon outweighs the influence of ion pair stability and leads to greater 1,4-addition.



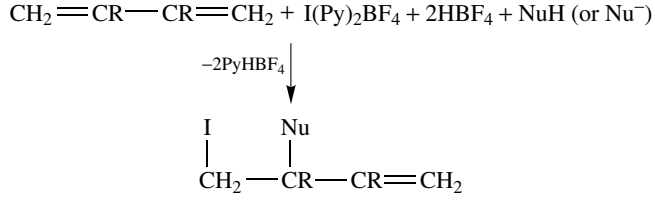
(57)

Nu = nucleophile M 1,2-adduct 1,4-adduct

Electrophile	M 1,2-	: 1,4-	Yield (%)
t-BuOI	92	8	82
AcOI	90	10	75
ICl	65	35	89
IBr	56	44	73
t-BuOBr	69	31	66
t-BuOCl	54	46	55

Bis(pyridinium)iodonium tetrafluoroborate [$I(Py)_2BF_4$] reacts readily with alkenes to afford 1,2-disubstituted products arising from addition of iodine and pyridine. Synthetically more important is, however, the reaction of unsaturated systems with $I(Py)_2BF_4$ in the presence of nucleophiles, which provides a general method for vicinal iodofunctionalization of alkenes. In this regard, the addition of a stoichiometric amount of tetrafluoroboric acid to the reaction medium is often required to avoid the competitive formation of products resulting from pyridine acting as a nucleophile.

Terminal dienes such as butadiene, isoprene and 2,3-dimethylbutadiene react regiospecifically with $I(Py)_2BF_4$, in the presence of a nucleophile, to give 1,2-iodofunctionalization (equation 58)[87]. In contrast, internal dienes such as (*Z*,*E*)-2,4-hexadiene and 1,3-cyclooctadiene yield the 1,4-addition products under similar conditions (equation 59).

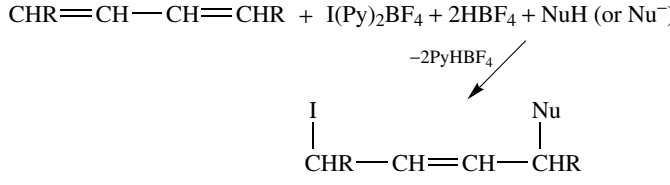


(58)

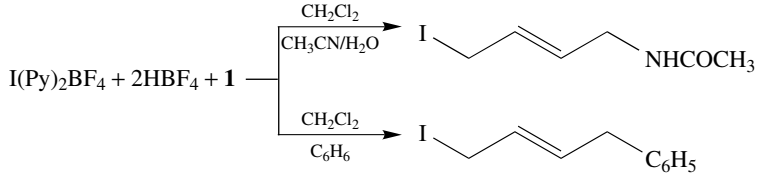
NuH = CH_3OH, HCl, DMF, CH_3CN, $HSiEt_3$; M $^+Nu^-$ = LiCl, $NaNO_2$

However, when the addition to butadiene is carried out in the presence of benzene or acetonitrile as nucleophiles, the iodofunctionalization leads to the *E*-1,4-regioisomers as the only product[14] (equation 60), unlike the previously reported 1,2-functionalization of

butadiene[87].



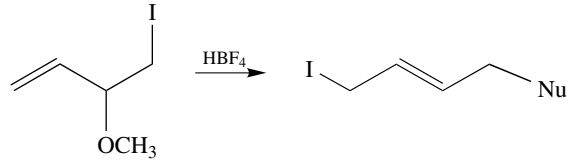
(59)



(60)

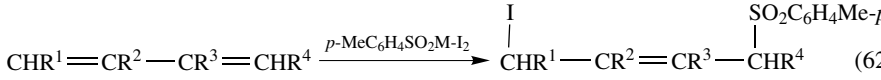
The latter results have been explained on the basis of the following reaction scheme. The 1,2-regioisomers derived from butadiene are obtained through a non-symmetrical iodonium ion intermediate. The subsequent nucleophilic attack on the allylic position gives, under kinetic control, 1,2-derivatives. Nevertheless, when poorer nucleophiles such as benzene or acetonitrile are employed, the conversion of the initially formed iodonium ion into the allylic cation has been suggested to give 1,4-products, under thermodynamic control. However, other alternatives like nucleophilic attack involving allylic participation have not been excluded for the formation of 1,4-derivatives.

To support the assumption of a kinetic or thermodynamic control, it has been underlined that treatment of a solution of 4-iodo-3-methoxy-1-butene with an etheral solution of HBF_4, in acetonitrile, benzene or methanol, affords the corresponding 1,4-iodofunctionalized substrates (Nu = $NHCOCH_3$, C_6H_5, or OCH_3) as the major product (equation 61).



(61)

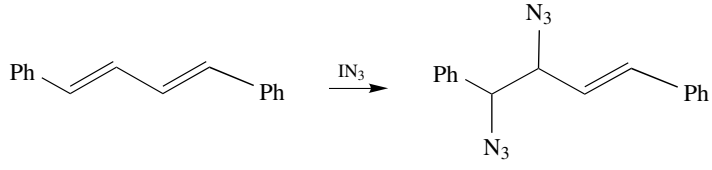
An exclusive 1,4-addition has also been observed[88] in iodosulfonylation of conjugated dienes with *in situ* generated tosyl iodide. With symmetrical acyclic dienes the corresponding δ-iodobut-2-enyl sulfones were obtained. In the case of asymmetrical acyclic dienes, with the exception of isoprene, mixtures of regioisomeric products were isolated (equation 62).



(62)

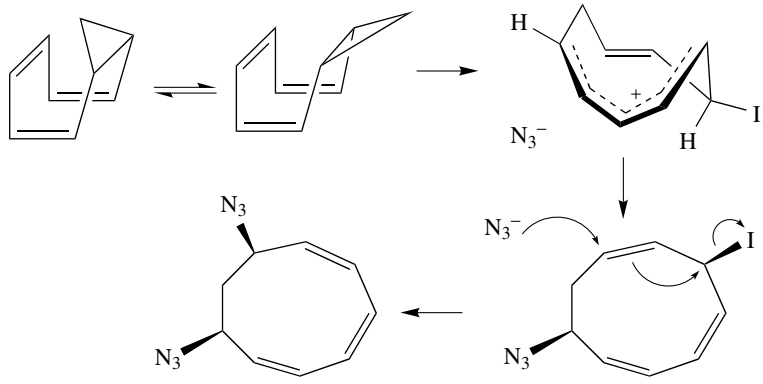
Finally, although only few data have been reported about the addition of halogen azides[14] to conjugated dienes, it has been shown that whereas BrN_3 addition affords 1,2- and/or 1,4-adducts, depending on temperature, the addition of IN_3 (generated *in situ* from NaN_3 and ICl) generally gives the corresponding diazide, arising from allylic displacement by azide ions on the initially formed adduct. This behavior has been observed in the

reaction of the acyclic 1,4-diphenyl-1,3-butadiene (equation 63)[89] as well as in additions to medium-size cyclic dienes and polyenes[90].



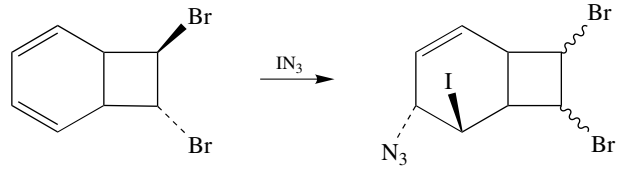
(63)

A diazide was obtained[91] as the sole product also by addition of IN_3 in acetonitrile to *cis*-bicyclo[6.1.0]nonatriene. In this case, however, at variance with the medium-size ring unsaturated compounds, the reaction did not afford a normal *vic*-diazide. A mechanism involving a bishomotropylium or cyclopentadienyl cation has been proposed (equation 64).

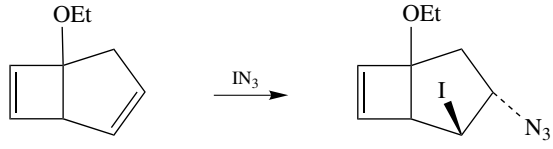


(64)

The reaction of IN_3 with *trans*-7,8-dibromobicyclo[4.2.0] (equation 65) and 5-ethoxybicyclo[3.2.0]hepta-2,6-dienes (equation 66) gives β-iodoazides as normal adducts[91].



(65)

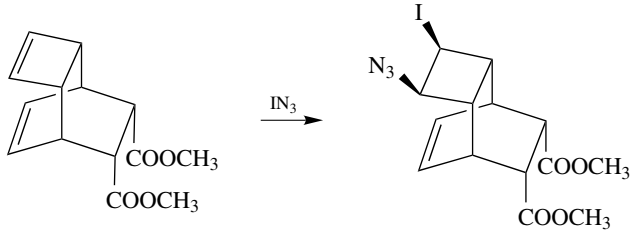


(66)

2. Non-conjugated double bonds

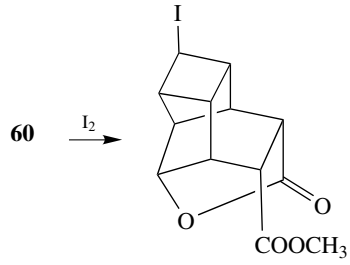
Electrophilic addition of IN_3 to the tricyclo[4.2.2.0^{2,5}]deca-3,7-diene derivative **60** has been reported[92,93] to give exclusively or predominantly the *syn* azido iodide **61**

(equation 67). The *syn* addition of IN_3 to the cyclobutene moiety has been explained by examination of the transition state in terms of the 'twist strain' theory. In contrast, it has been reported that I_2 addition to the same diene gives almost exclusively (94%), at least at room temperature, a transannular iodolactone (equation 68), whose formation has been rationalized, in analogy to the bromine addition, on the basis of HOMO–LUMO interactions[79].



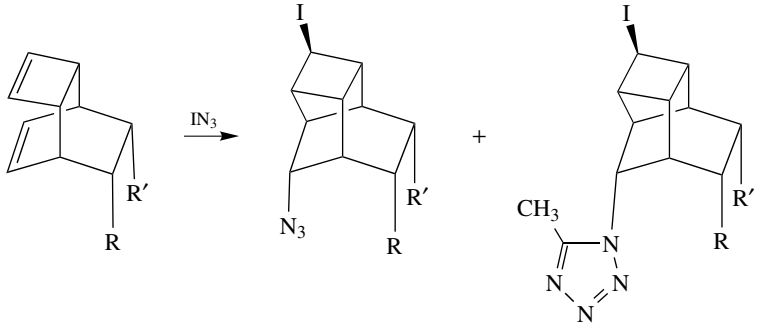
(67)

(60) **(61)**



(68)

A transannular solvent participation has instead been observed in the IN_3 addition in CH_3CN to tricyclo[4.2.2.0^{2,5}]deca-3,7-diene derivatives **62** and **63**, which give adducts **64** and **65** as well as tetrazoles **66** and **67** via Hassner–Ritter reaction (equation 69).



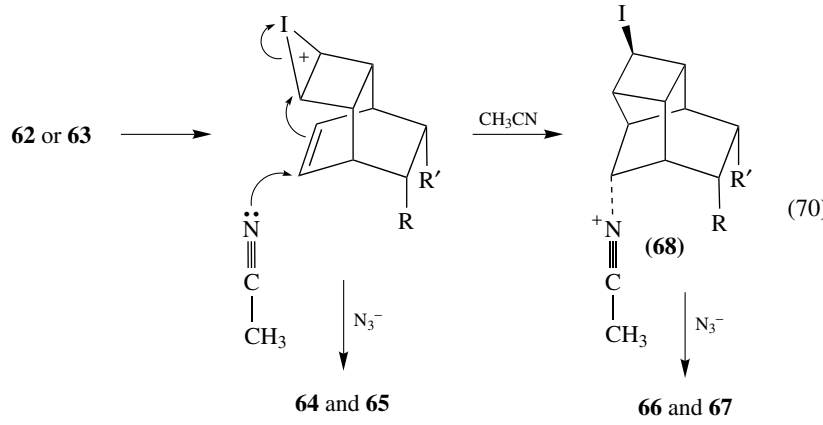
(69)

(62) R = R′ = CH_3 **(64)** R = R′ = CH_3 **(66)** R = R′ = CH_3

(63) RR′ = CH_2OCH_2 **(65)** RR′ = CH_2OCH_2 **(67)** RR′ = CH_2OCH_2

The formation of the tetrazoles **66** and **67** from **62** and **63**, respectively, has been rationalized on the basis of the solvent-assisted opening of the initially formed iodonium ion to give the Ritter reaction intermediate **68**, which undergoes cycloaddition with azide

ion to form the substituted tetrazoles. When the reaction is carried out in CH_2Cl_2, only the iodo azide (**64** or **65**) resulting from participation and nucleophilic capture by the azide ion is obtained (equation 70).

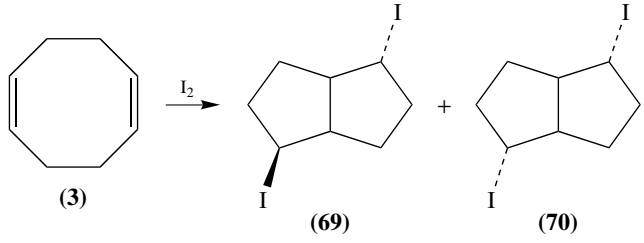


(70)

The difference in the stereochemical behavior of **62** and **63** as compared to that of **60** has been explained by assuming that the presence of the electron-withdrawing carbomethoxy substituents at C(9) and C(10) in the latter markedly decreases the availability of electrons from the participating C(7)−C(8) double bond, thus forcing the reaction to proceed mainly via the iodonium ion.

The electrophilic addition of iodine donors to 1,5-cyclooctadiene **(3)** gives, analogously to those of BrX, a product distribution which is strongly dependent on the nature of the nucleophile and reaction conditions.

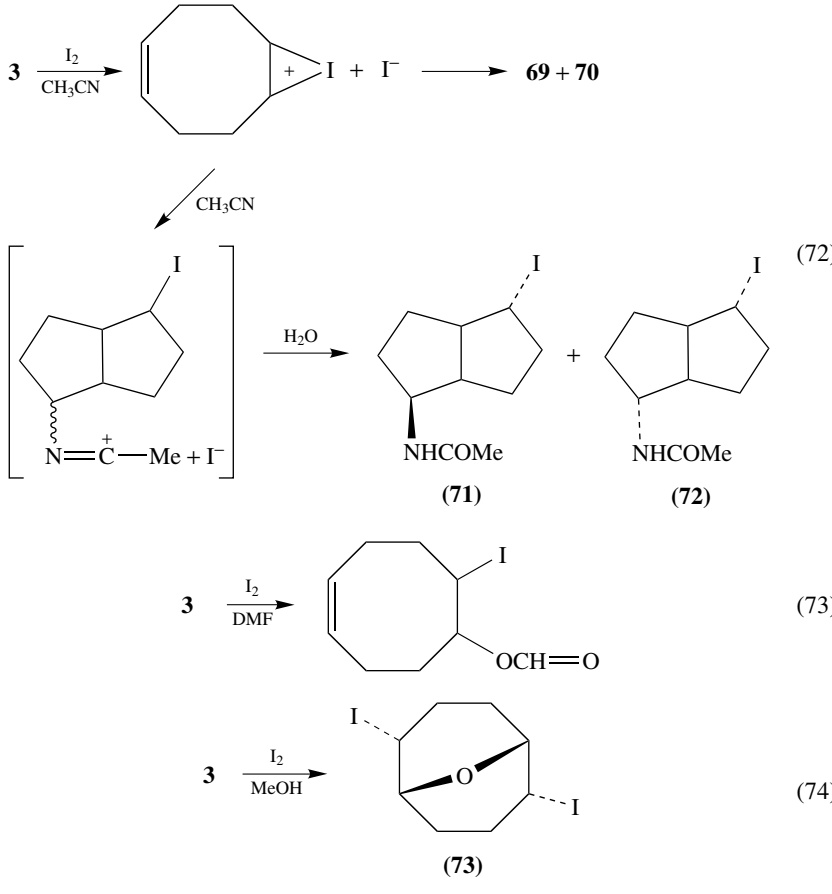
The I_2 addition to **3** in chlorinated solvents yields a mixture of isomeric 2,6-diiodobicyclo[3.3.0]octanes (*endo*,*exo*-**69** and *endo*,*endo*-**70**) (equation 71)[22]. When the reaction was carried out in aqueous acetonitrile under similar conditions, the formation of a mixture of acetamido derivatives **71** and **72**, arising from iodocyclization followed by the capture of the iodonium ion by the solvent to give a Ritter reaction intermediate, accompanied the formation of products **69** and **70** (equation 72)[22].



(71)

In *N*,*N*-dimethylformamide, the 1,2-addition product was obtained as the main product (60% yield) (equation 73) together with small amounts of **69** and **70**. Small amounts of 1,2-adducts were also obtained in acetic acid, the main products being again **69** and **70**[22].

In methanol, only the oxa bridged compound **73** was instead isolated in a yield of 28% (equation 74)[22].

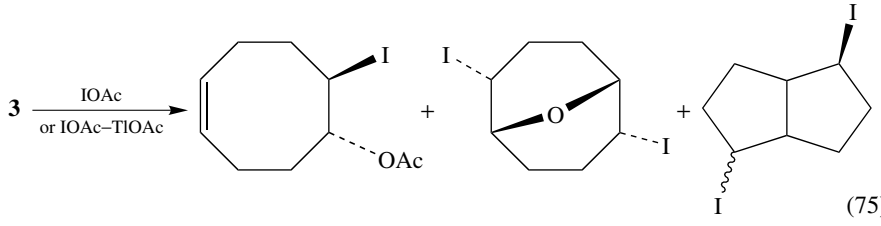


Higher yields of disubstituted 9-oxabicyclo[4.2.1]nonane and 9-oxabicyclo[3.3.1]nonane derivatives from **3** have been obtained using *N*-halosuccinimides as reagent[72] (*vide supra*). In this case, a solvent dependent isomer ratio has been observed only with *N*-iodosuccinimide and the different dependence on the solvent shown by the three *N*-halosuccinimides has been explained again in terms of the different nature of the intermediates (*vide supra*).

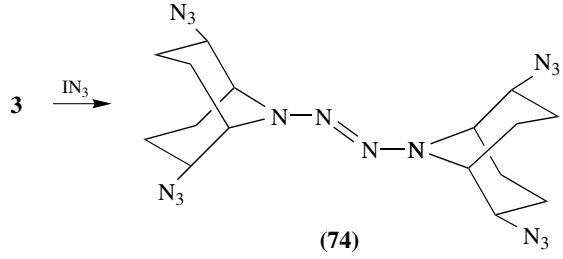
Significant amounts of the bicyclo[3.3.1]nonane adduct and of the octahydropentalenes were isolated also from the reaction of **3** with preformed iodine acetate and iodine acetate thallium (equation 75)[94] whereas only the monocyclic 1,2-adducts were obtained from treatment of **3** with iodine azide, iodine isocyanate or iodine nitrate[95]. The different propensity to give transannular products with these latter reagents has been related to the different positive charge density on carbons in the corresponding iodonium ion intermediates.

Finally, it is noteworthy that the addition of iodine azide to **3** leads mainly to the surprisingly stable tetrazido-substituted 2-tetrazene **74** (equation 76)[96]. The formation of **74** should start with the addition of IN_3 to the double bonds of **3**, giving four possible isomers. Under the applied conditions these compounds seem to be unstable.

Elimination of HI, which in the presence of an excess of IN_3 can form hydrazoic acid, followed by its addition to the vinyl azides can give an intermediate triazide **75**. The same compound could arise directly by substitution of one iodine atom by an azido group. The intermediate **75** has been considered to undergo a transannular reaction with homolytic cleavage of the weak C−I bond to form the radical **76**, which loses a nitrogen atom to a radical **77**. Combination of the two radicals leads to the 2-tetrazene **74** (equation 77).



(75)



(74)

(76)

Recent studies on iodination and iodochlorination of bicyclo[4.3.0]nona-3,7-diene **(78)** and its derivatives have shown that the reactions depend strongly on the presence and position of the methyl groups on the cyclohexene double bond and on reaction conditions. When I_2 reacted with *cis*-bicyclo[4.3.0]nona-3,7-diene the only product was *endo*-4-*exo*-8-diiodobrexane[84]. The addition of ICl or IBr to the same diene gives exclusively unrearranged products in an identical conformation, with the substituents in the six-membered ring in *trans*-diequatorial position (equation 78)[85].

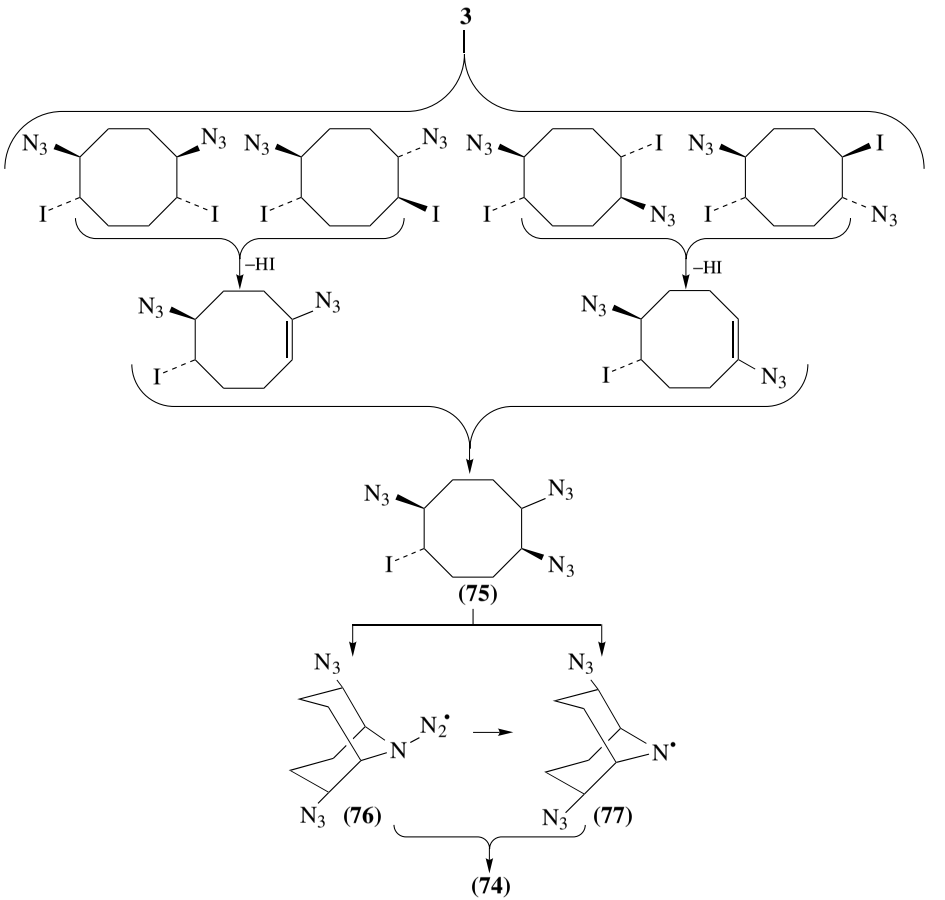
The presence of two methyl groups on C(3) and C(4) in **79** completely changes the product distribution. The addition of I_2 in CCl_4 leads to the tricyclic monoiodides *exo*-5-iodo-*exo*- and *exo*-5-iodo-*endo*-1,9-dimethylbrexanes (**80a** and **80b**)[97], differing in the configuration of the methyl group at C(9) (equation 79).

Since similar compounds are found in the reaction of the same diene with hydroiodic acid, it has been assumed that the monoiodides were formed by electrophilic addition of HI, which may be due to proton elimination from the first formed ion pair intermediate (equation 80).

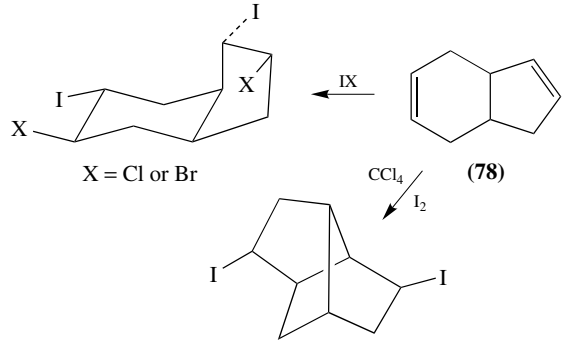
Steric factors during the nucleophilic attack have been invoked to explain the absence of addition products and the high tendency to undergo proton elimination.

The predominance of steric over electronic factors has been also used to explain the product distribution obtained by addition of I_2 in pyridine which takes place exclusively at the least substituted cyclopentene double bond of **79**. Under similar conditions the reaction of the unsubstituted diene **78** occurs by direct addition at the cyclohexene double bond[98].

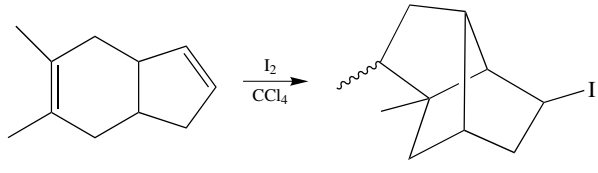
It is noteworthy that iodine addition in pyridine to **79** takes place regioselectively, with the iodine atom located exclusively in the product at C(7). Steric factors have been invoked again to explain the selectivity of the nucleophilic attack (equation 81).



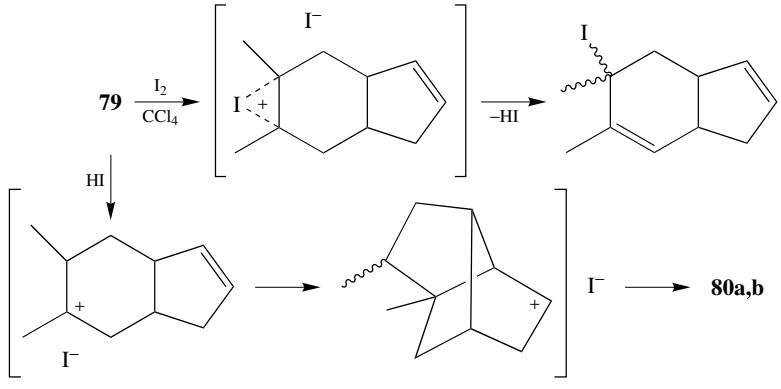
(77)


I
X
I
X
IX
X = Cl or Br
CCl4
I2
(78)

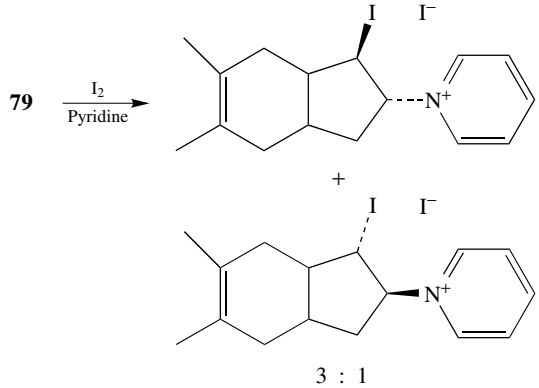
(78)


I2
CCl4
I
(79)
(80a,b)

(79)


79
I2
CCl4
I−
I
+
–HI
I
HI
+
I−
+
I−
80a,b

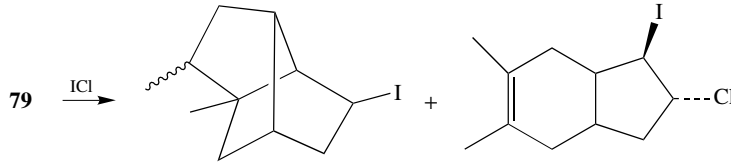
(80)


79
I2
Pyridine
I
I−
N+
+
I
I−
N+

(81)

3 : 1

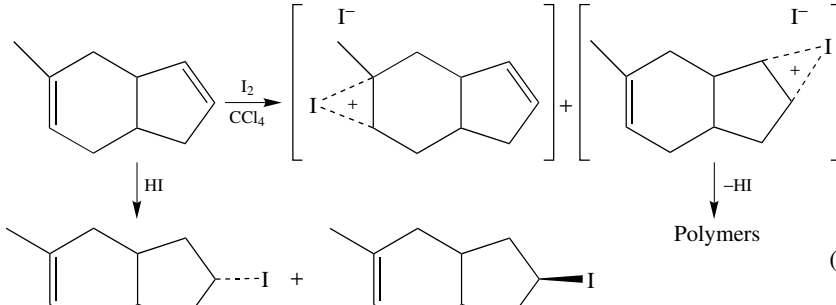
Finally, the addition of ICl gives a mixture of the tricyclic monoiodides **80a** and **80b** and of the product from addition of iodine and chlorine at the cyclopentene double bond (equation 82).



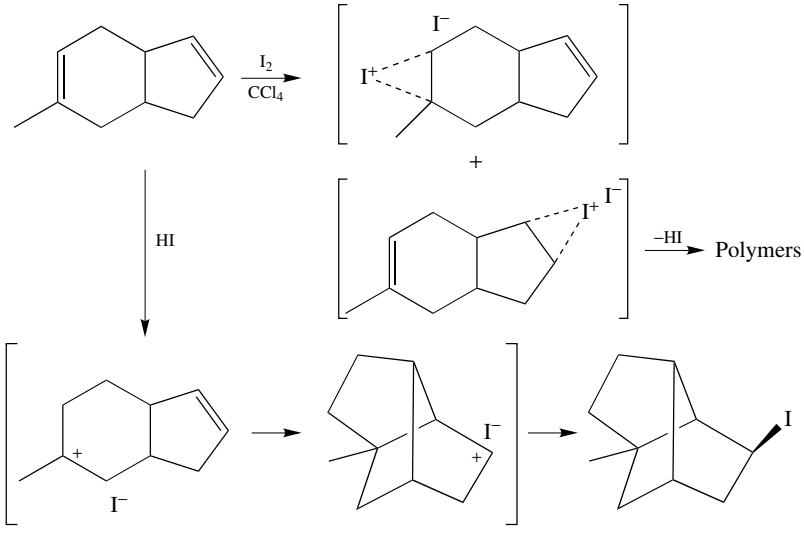
(82)

(80a,b)

By comparison, the direction of halogenation of monomethyl-substituted bicyclo[4.3.0] nona-3,7-dienes depends[99] considerably on the position of the methyl group. For a diene lacking a substituent at C(3), the reaction proceeds with retention of the initial structure (equation 83), whereas in the case of the 3-methyl substituted diene, it occurs through transannular cyclization giving a brexane type monoiodo derivative (equation 84).



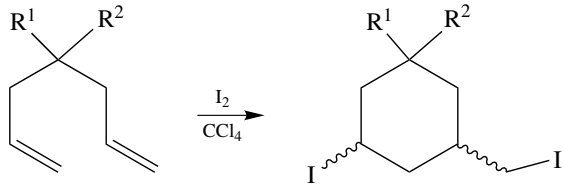
(83)



(84)

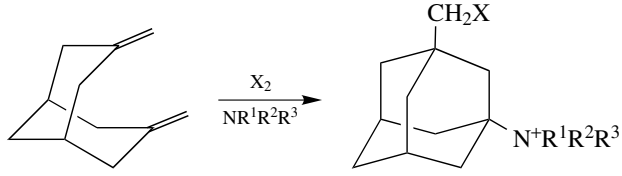
In both cases the electrophilic addition of HI, formed during the course of the reaction, is however the main pathway.

Reaction of iodine with non-conjugated dienes has been applied to the synthesis of cyclic compounds[100]. Although the reactions of 1,5-hexadiene, 1,6-heptadiene and 1,7-octadiene with I_2 in CCl_4 gave exclusively products arising from addition to the two double bonds, the introduction of dialkyl substituents into the 4-position of 1,6-heptadiene completely changed the reaction course in favor of cyclization (equation 85).



(85)

An easy cyclization arising from the intramolecular nucleophilic attack of the second double bond on the first formed intermediate has been also observed[101] in the reaction of 3,7-dimethylenebicyclo[3.3.1]nonane with iodine or bromine in the presence of amines. A series of halogenoadamantylammonium salts have thus been prepared in high yield and purity (equation 86).



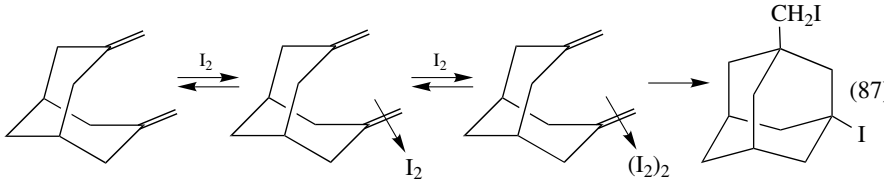
(86)

X = Br or I

$NR^1R^2R^3$ = pyridine, 2-methylpyridine, quinoline

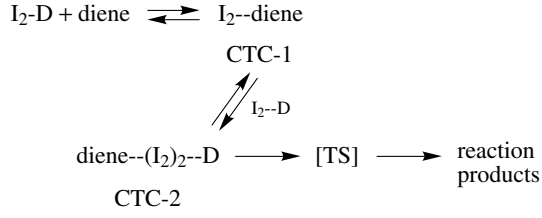
Although I_2 addition in non polar solvents generally follows a fourth-order rate law (third-order in iodine), the iodine addition in CCl_4 to this unconjugated diene is an overall third-order process (second order in halogen)[102–104]. Furthermore, a charge transfer band has been observed on mixing the reagents and the reaction rate is characterized by a negative temperature dependence and a large negative entropy of activation.

All these features have been initially interpreted[102–104] in terms of a molecular mechanism involving two successive alkene–iodine complexes of 1 : 1 and 1 : 2 stochiometries, the second of which evolves by internal nucleophilic attack of the uncomplexed double bond to the diiodo derivative (equation 87). The intramolecular attack of the second double bond has been regarded as rate determining, owing to the fact that the overall rate law is second order in iodine rather than the usual third order. Nevertheless, more



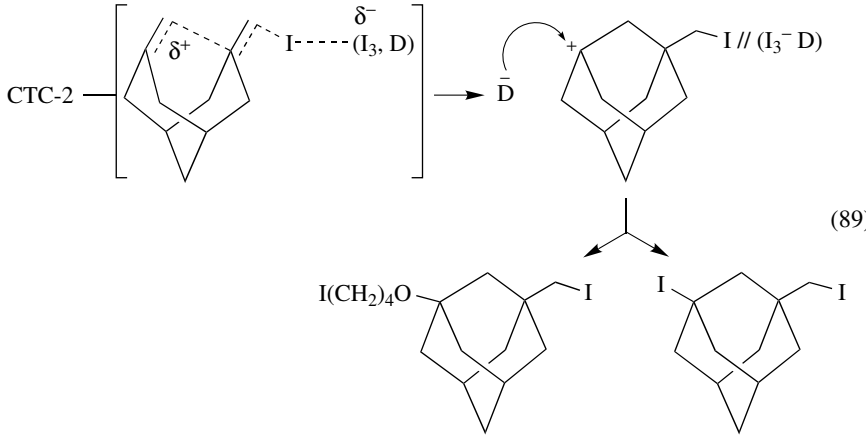
(87)

recently a molecular-ionic mechanism, characterized by a rate-limiting formation of an ion pair, has been suggested[105], in particular for transannular addition of iodine to 3,7-dimethylene- and 3-methylene-7-isopropylidenebicyclo[3.3.1]nonane in benzene, toluene, dioxane, diethyl ether and tetrahydrofuran. In all these solvents the reactions indeed follow a third-order rate law of the form $r = k_3[\text{diene}][I_2]^2$, with a reaction rate which is sensitive to both the electrostatic and electron-donor parameters of the medium. A reaction scheme involving the charge-transfer complexes CTC-1 and then CTC-2 which is additionally stabilized by one molecule of a donor solvent, D, has been proposed (equation 88).



(88)

The existence of an ion pair stabilized by a solvent molecule in the product-determining step of the reaction has been established by calculations and also supported by the product composition (equation 89). While the formation of the diiodo derivative is characteristic of all the cited solvents, in tetrahydrofuran this iodination takes place with the predominant formation of 1-iodomethyl-3-(4-iodobutoxy)adamantane (equation 89).



(89)

V. ELECTROPHILIC SULFUR AND SELENIUM

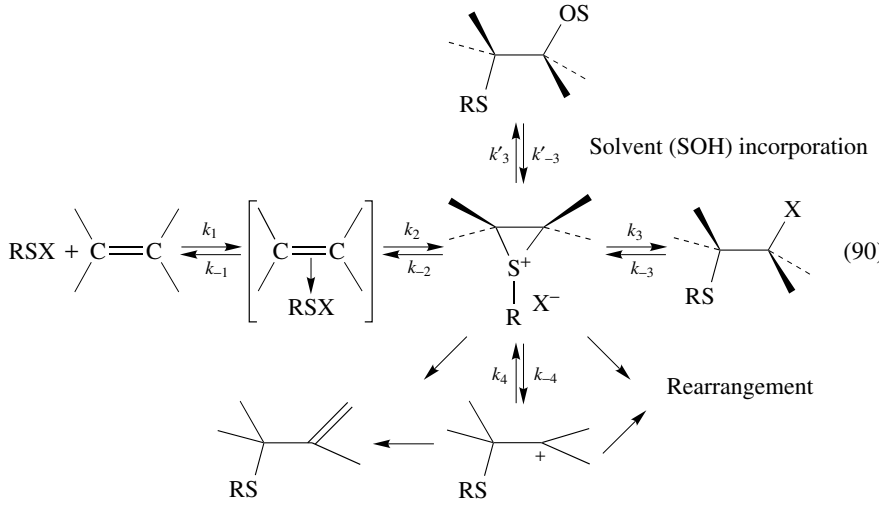
A. Sulfenyl Halides and Related Compounds

1. General aspects

Electrophilic addition of sulfenyl compounds at carbon–carbon double bonds, extensively studied and reviewed[2,4,7b,106], finds numerous synthetic applications owing to the regio- and stereoselectivity of the addition[2b]. The most common types of agents for the electrophilic addition of sulfur to double and triple bonds are sulfenyl halides (RSX,

ArSX), and among these the most used anionic carrier of the sulfenylium ions is the chloride anion[7b]. However, sulfenyl bromides have been also used[107] whereas iodides and fluorides are unstable although they can be prepared *in situ*[108,109]. Other sulfenylating agents include mixed anhydrides of the sulfenic acid such as sulfenyl sulfonates[110,111], triflates[112] and carboxylates[113]. Furthermore, the sulfenylium ion may be associated with basic anionic nucleophiles, such as in sulfenamides, disulfides, thiosulfinates, thiosulfonates and sulfenic esters[114]. Finally, the sulfenylium ion may be linked to a neutral and poorly nucleophilic sulfide or disulfide. Thiosulfonium and bis-thiosulfonium ions have been widely used as excellent sulfenylating agents[115].

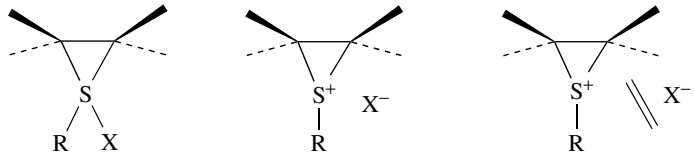
Sulfenyl chlorides and most of the other sulfenyl derivatives react with alkenes to give generally *anti* addition products with a high stereoselectivity. Although the mechanism of these reactions is still under study, it is usually accepted that sulfenyl transfer from the carrier to nucleophilic double bonds is consistent with the multistep mechanism reported in equation 90[7b].



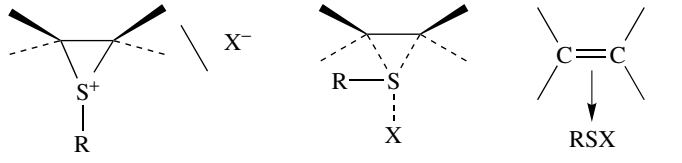
The regio-, stereo- and chemoselectivity of electrophilic additions of sulfenyl halides to alkenes, or reactions of preformed thiiranium ions with nucleophiles, as well as the role of solvent and 'doping' effect, have been interpreted by assuming the formation of a bridged intermediate characterized by different degrees of polarization of the S−Cl bond, depending on the reaction conditions[106]. In a general way it has been assumed that a continuum exists ranging from a completely covalent species, the sulfurane **81**, to the free ion **84**. Between these limits intimate and solvent-separated ion pairs (**82** and **83**, respectively) have been distinguished[2d].

The formation of the bridged intermediate has been represented as an S_N2-like displacement of the leaving group from the sulfenyl sulphur of **85**[116], or alternatively, as reported in equation 90 in agreement with the addition of other electrophiles to alkenes, it has been proposed that the reaction involves the initial formation of π-complex **86** in a rapid equilibrium with the reagents[7b].

As for the nature of the ionic intermediates, it is noteworthy that, independently of their representation, the bridged ions are not necessarily symmetrical species. The substituents at the ring carbons as well as at sulfur determine the amount of positive charge

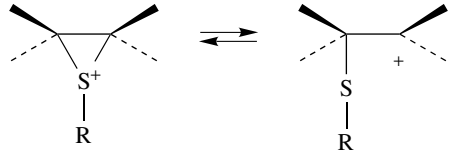


(81) **(82)** **(83)**



(84) **(85)** **(86)**

at this center and consequently on the ring carbons. Furthermore, the possibility of an equilibration of the bridged species with the open carbenium ion (equation 91) has been suggested[117].



(91)

As shown in equation 90, the ionic intermediate can follow several reaction routes. The product distribution is therefore controlled not only by the nature of the intermediate, whether bridged or weakly bridged, but also by association with its nucleophilic partner and by the rate ratios derived from the different reaction paths. All these factors depend on the alkene structure, the electrophile and the reaction conditions (solvent, added salts, temperature).

In agreement with the mechanism reported in equation 90, the reaction generally follows a second-order rate law (equation 92), first order in the sulfenyl halide and in the alkene, respectively.

$$dp/dt = k_{\text{obsd}}\ [\text{RSX}]\ [\text{Alkene}] \tag{92}$$

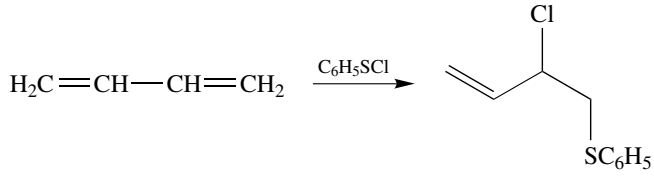
The alkene structure and the solvent polarity markedly affect the reaction rate. However, these effects are not easy to rationalize since, as shown in equation 90, one or more intermediates may be involved and each factor can influence the individual rate constants in a different way. It follows that only when the first step is rate determining can the observed rate constant k_{obsd} be interpreted straightforwardly.

2. Conjugated double bonds

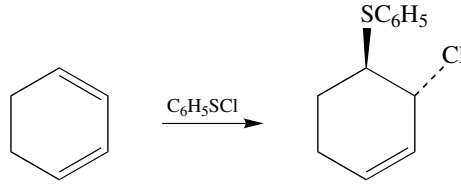
The sulfenylation of dienes as a distinct class of compounds has not been specifically reviewed, although several examples have been reported in early papers[2a,7b].

Generally, the addition of sulfenyl halides to conjugated dienes occurs, under kinetic control, at either double bond with *anti* stereospecificity to give 1,2-adducts with either

Markovnikov (M) or anti-Markovnikov (AM) regiochemistry (equation 93 and 94)[12]. A preferential attack of the electrophile on the least substituted double bond has often been observed[13]. The M adduct is the only one formed when the ionic intermediate has a high carbocationic character, and may be formed from bridged species when the nucleophilic step has a substantial S_N1 character. The AM product arises from an S_N2 process on the bridged intermediate.

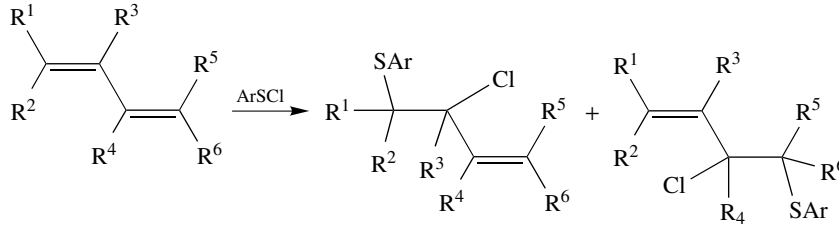


(93)



(94)

Except for the addition products to 1,3-butadiene, the initial products isomerize slowly to the 1,4-adducts[13]. Although small amounts of these compounds have been found among the addition of 4-chlorobenzenesulfenyl chloride to methyl substituted 1,3-butadienes (equation 95), it was not possible to establish whether they were formed under kinetic control or resulted from isomerization of the initially formed adducts. Therefore it is generally reported that arenesulfenyl chlorides react with dienes to give exclusively 1,2-adducts.

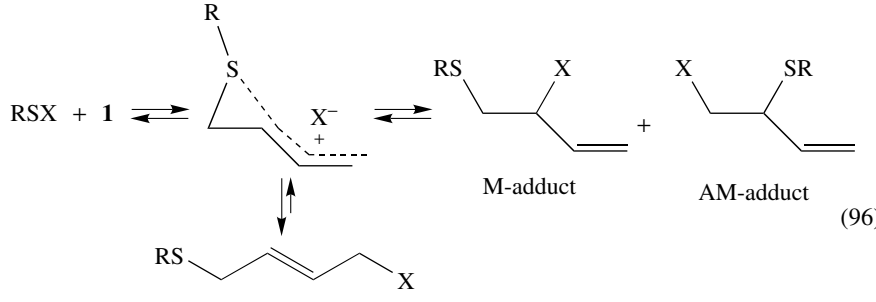


(95)

Kinetic studies carried out[12] on 1,3-butadiene and eleven of its methyl-substituted derivatives have shown that the addition of 4-chlorobenzenesulfenyl chloride in 1,1,2,2-tetrachloroethane to dienes follows the second-order rate law of equation 92. Furthermore, although substituent effects on rates and products are difficult to analyze quantitatively, owing to the presence of two possible sites of electrophilic attack, the authors concluded that the addition of arenesulfenyl chloride to 1,3-butadienes occurs through rate- and product-determining transition states resembling a thiiranium ion. The increase in rate caused by a methyl substituent on the β-double bond suggested charge delocalization in the rate-determining transition state and has therefore been considered as evidence for an unsymmetrically bridged transition state.

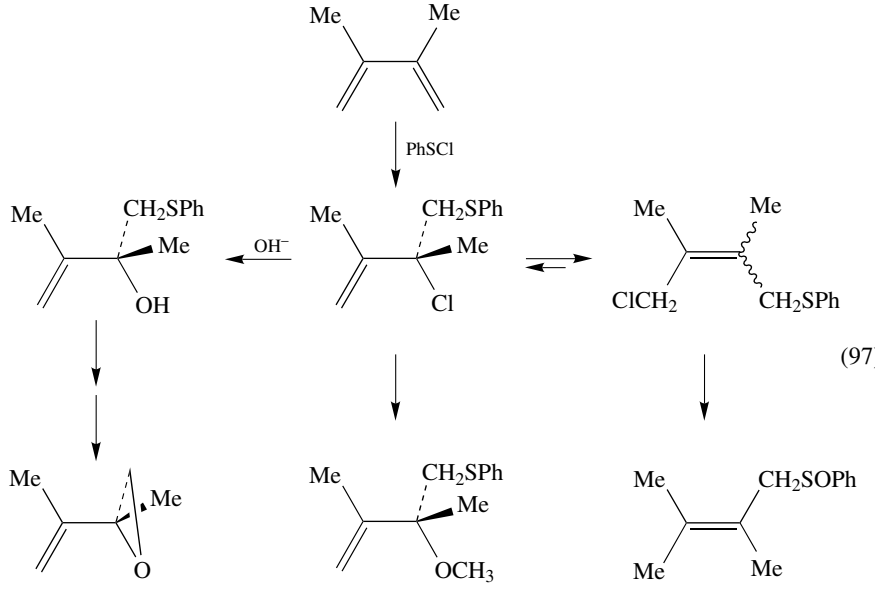
Finally, the possibility of obtaining 1,2- or 1,4-adducts, depending on reaction conditions, has been interpreted[2a], in agreement with the accepted mechanism of addition of

sulfenyl chlorides to alkenes, as reported in equation 96, as a classical example of kinetic vs thermodynamic control. The initially formed bridged but unsymmetrical ionic intermediate rapidly collapses to the 1,2-addition products. These compounds are, however, in equilibrium with the thiiranium chloride from which, through a slower reaction, the thermodynamically more stable 1,4-adduct may be formed.



(96)

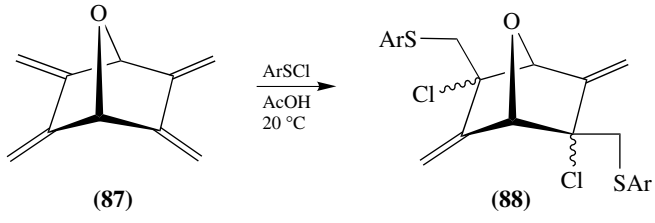
The possibility of obtaining, under kinetic control, a selective transformation of only one of the double bonds present in a dienic system, as well as the formation of 1,4-adducts under thermodynamic control, may find interesting applications. These two adducts may indeed be transformed into attractive synthetic intermediates, as shown in equation 97[118].



(97)

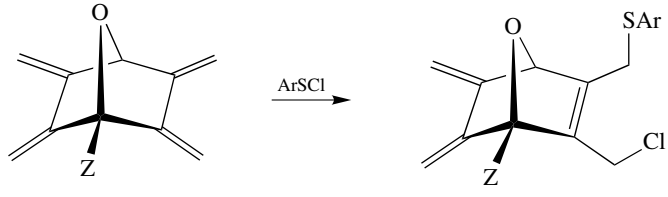
As far as the reactivity of polyenes is concerned, it is noteworthy that the stereochemistry of the addition of arenesulfenyl chloride to exocyclic tetraenes of type **87** depends on the substituent on the bridgehead carbon. The addition of arylsulfenyl chloride to the unsubstituted compound **87** proceeds with a high regio- and stereoselectivity[119]. This tetraene adds 2-nitrobenzenesulfenyl chloride to give exclusively the unstable bisadduct **88**, arising from a double 1,2-addition (equation 98)[120,121]. The regioselectivity of this

double addition has been interpreted in terms of either kinetic or thermodynamic control. The selectivity has been attributed in the former case, to a long-range effect of the monoadduct on the second electrophilic addition, and in the latter case it was attributed to the preferential stability of the bisadduct.



(87) **(88)** (98)

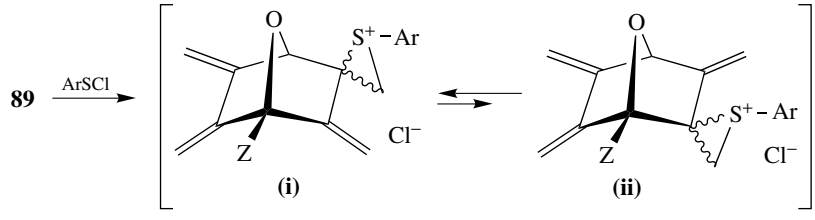
When an acetal moiety is introduced at one of the bridgehead centers, the reaction leads exclusively to a monoadduct[119]. In particular, in the presence of 1.5 equivalents of 2-nitrobenzenesulfenyl chloride, tetraene **89** gives a single derivative **90** corresponding to a 1,4-addition product (equation 99).



(89) **(90)** (99)

$Z = CH(OMe)_2$

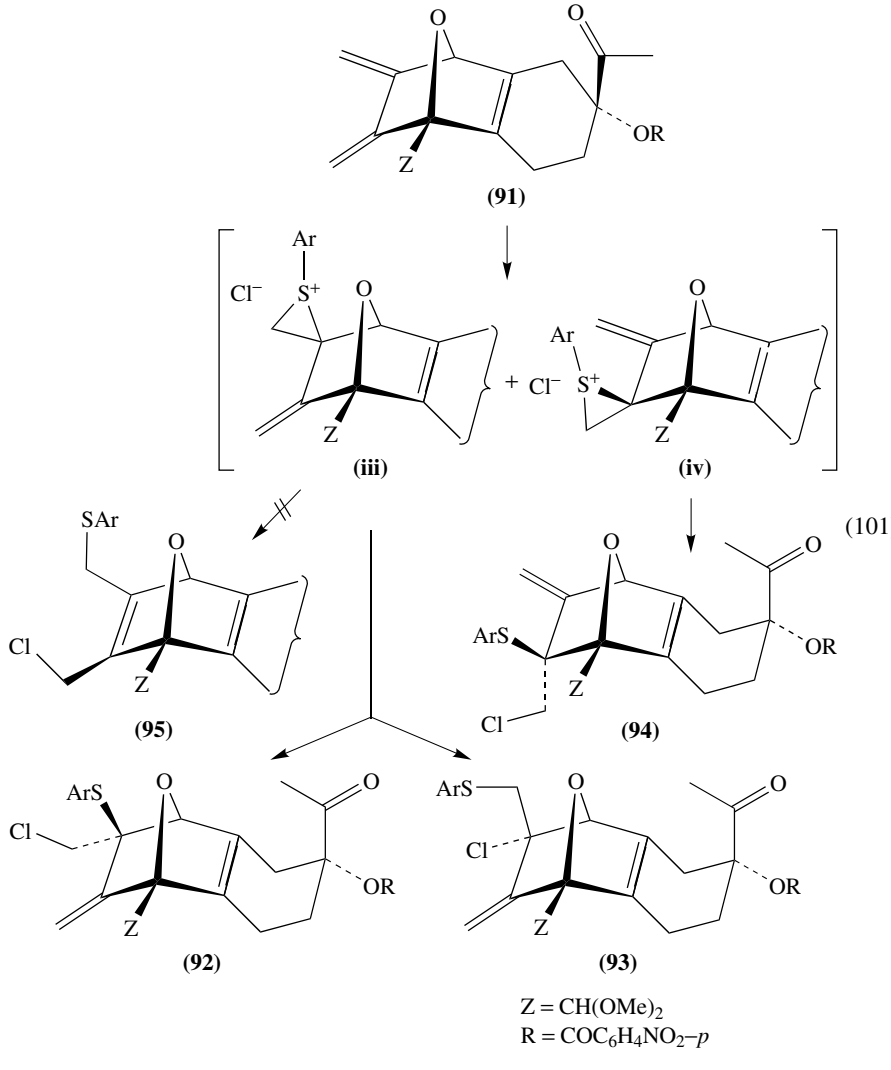
Although it was not possible to verify whether this product is formed under kinetic or thermodynamic control, the authors suggest[119] that if **90** arises from a kinetically controlled reaction, its formation could be rationalized on the basis of the stability of the involved intermediate. The bridged intermediate **i** is expected to be more stable than **ii** (equation 100) owing to the effect of the dimethoxymethyl substituent.



(100)

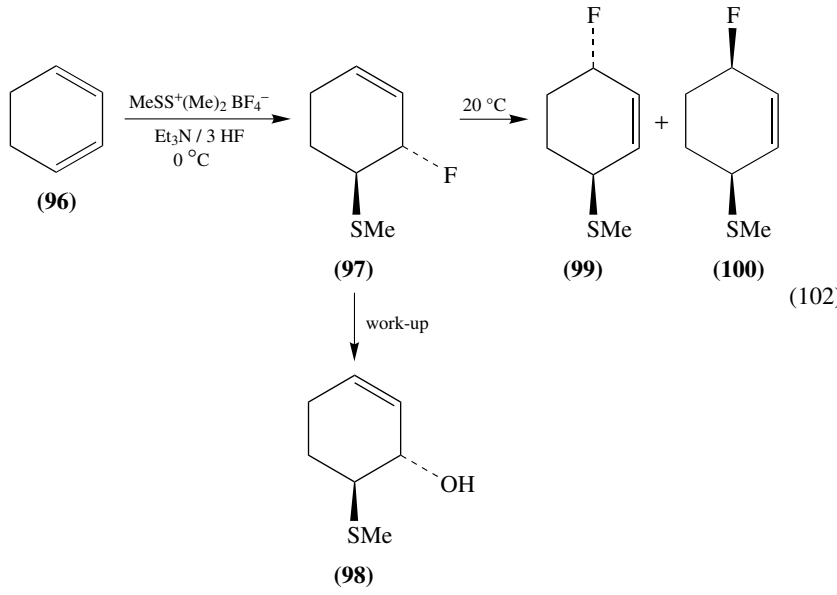
At variance with **89**, triene **91** gives a 17 : 51 : 31 mixture of monoadducts **92**, **93** and **94** (equation 101). This ratio does not change during the course of the reaction, indicating that these adducts are formed under kinetic control. The regioisomers **92** and **93**, corresponding to AM and M additions, may arise from a preferential electrophilic attack at the center remote from the electron-withdrawing acetal group, leading to the corresponding bridged thiiranium ion intermediate **(iii)** which is trapped by the chloride anion at the primary (giving **92**) or tertiary (giving **93**) carbon atom. Adduct **94** should

instead arise from the nucleophilic attack on the less stable intermediate **iv**. It is interesting to note that no 1,4-adduct **95** has been detected, in contrast with the stereochemical behavior of the reaction of tetraene **89**. This latter observation has been interpreted[119] in terms of enhanced strain, larger in bicyclo[2.2.1]hepta-2,5-diene derivatives than in 5,6-dimethylidenebicyclo[2.2.1]hept-2-ene systems. The increased strain could reduce the rate of transformation of intermediate **iii** into **95**, or make it unstable.



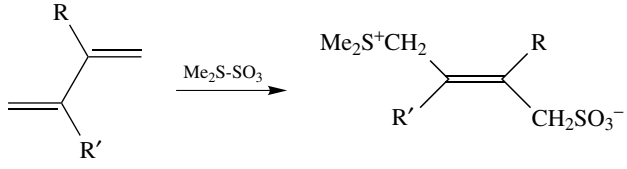
Sulfenyl fluorides are extremely unstable and therefore only few perhalosulfenyl fluorides have so far been reported[122]. The formal addition of the elements of methanesulfenyl fluoride to carbon–carbon double bonds has been obtained[123] by a one-pot reaction with dimethyl(methylthio)sulfonium tetrafluoroborate and triethylammonium tris(hydrofluoride). With this system also the addition to double bonds is highly stereoselective, at least

under kinetic control. With 1,3-cyclohexadiene **(96)**, *trans*-3-fluoro-4-(methylthio)cyclohexene **(97)** was found as the sole fluorinated product after 40 min at 0 °C, accompanied by 20% of **98**, which was formed during the work-up. Allylic rearrangement, giving the 1,4-adducts **99** and **100**, was reported only as a minor process when the reaction was continued for 4 h at 20 °C (equation 102).



(96) **(97)** **(99)** **(100)** **(98)** (102)

The complexes of sulfur trioxide with various nucleophiles (dioxane, pyridine etc.) are mild sulfonating reagents. Unlike other complexes of sulfur trioxide, dimethyl sulfide–sulfur trioxide readily adds to conjugated multiple bonds. Consequently, not only the sulfo group but also the dimethyl sulfide group add at the multiple bond. The reactions of dimethyl sulfide–sulfur trioxide complex with butadiene, isoprene and 2,3-dimethylbutadiene take place as conjugated 1,4-*E*-additions of dimethyl sulfide and sulfonate groups at the double bonds of the diene (equation 103).[124]

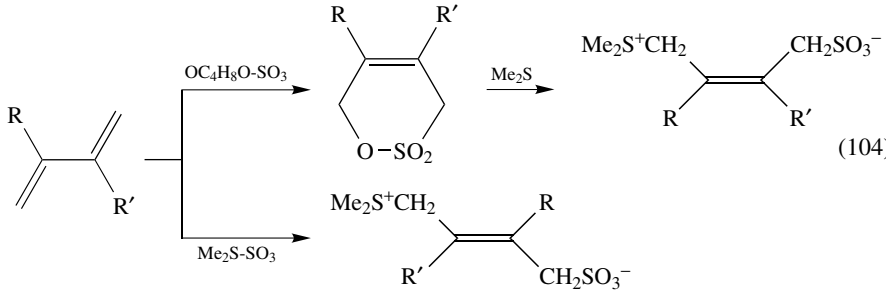


(103)

Cyclopentadiene forms a mixture of the 1,2- and 1,4-adducts in equal proportions. However, the 1,2-isomer rearranged completely into the thermodynamically more stable 1,4-isomer after prolonged standing in the solvent (alcohol or dichloroethane).

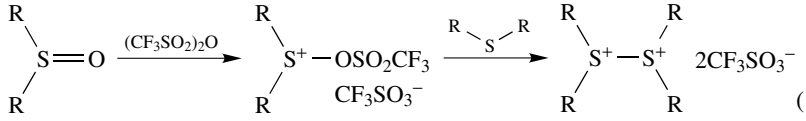
The different stereochemical outcome observed in the opening of sultones by the action of dimethyl sulfide and by that of $Me_2S–SO_3$ complex with the conjugated alkadienes has been considered as evidence against the intermediate formation of the sultones in the

latter reaction (equation 104).



(104)

Unusual electrophilic compounds containing sulfur are the S^+-S^+ dications[125]. The reaction of dimethyl sulfide ditriflate with dimethyl sulfide leads to the formation of tetramethyldisulfonium ditriflate **(101a)**. The same procedure starting from tetrahydrothiophene ditriflate gives by reaction with tetrahydrothiophene the corresponding dication **101b** (equation 105).

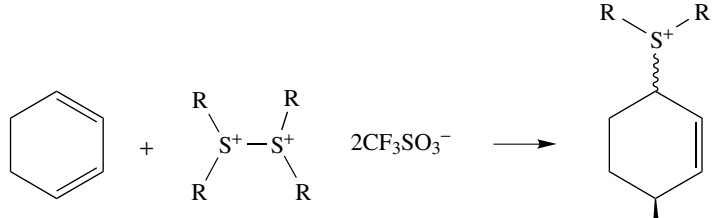


(105)

(101a,b)

(a) R = CH_3; **(b)** RR = $-(CH_2)_4-$

These dications react with alkenes to give 1,2-disulfonium salts, and with conjugated dienes to afford 1,4-adducts. Furthermore, while 1,4-disubstituted linear dienes yield complex mixtures of unidentified substances, 1,3-cyclohexadiene **(96)** produces a moderately stable salt **102** (equation 106). The formation of the kinetically controlled 1,2-addition product has never been observed.

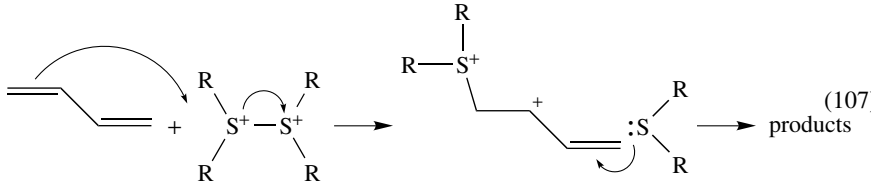


(96) **(101a,b)** (106)

(102)

In view of the stereochemical behavior in the additions to alkenes and dienes, the authors suggest that the reaction proceeds via a stepwise electrophilic addition[126]. However, in this case the two sulfur atoms of the dithioether dication are positively charged. In the reaction with multiple bonds, therefore, one of these sulfur atoms should be an electrophilic center whereas the other one should simultaneously be a nucleophilic center. In

agreement with the generally accepted mechanism for an Ad_E path, this reaction should be a conjugated addition of a doubly charged sulfur electrophile (S^{+2}) and of a sulfide acting as nucleophile. The authors, however, believe that it is more correct to view this reaction as a nucleophilic substitution at the sulfur atom. The first step should therefore be the substitution of the sulfide moiety by the double bond to give a carbocation intermediate, followed by the trapping of the carbocation by the formed sulfide (equation 107).

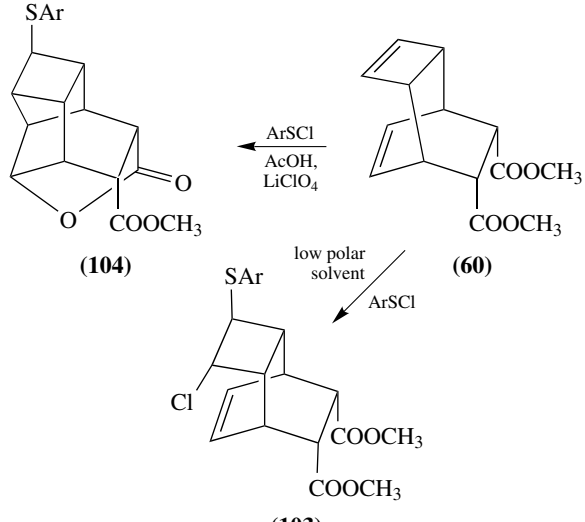


(107)

The possibility of trapping of the carbocation by a triflate anion followed by substitution of the triflate group by sulfide has also been suggested[126], at least for the addition of bicyclic dithioether dications to alkenes and alkynes.

3. Non-conjugated double bonds

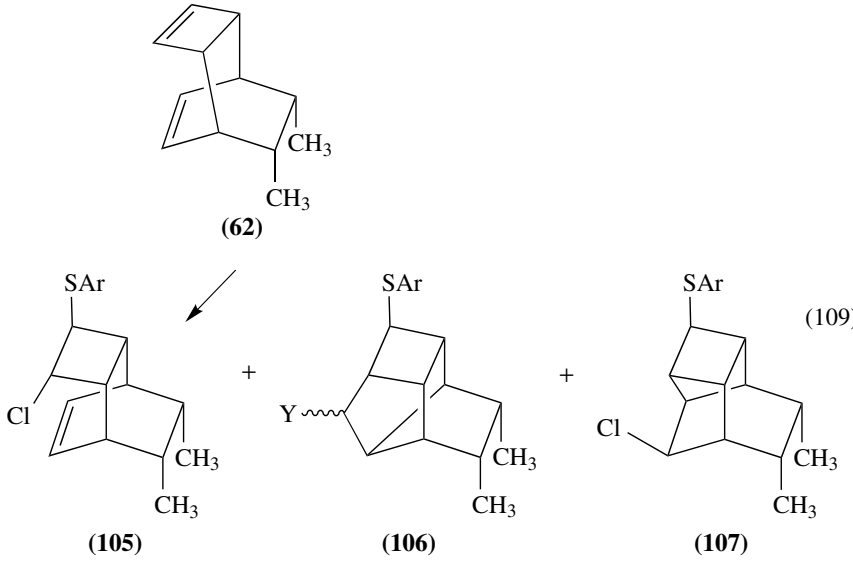
The addition of electrophilic reagents to tricyclo[4.2.2.0^{2,5}]deca-3,7-diene derivatives can give, depending on the electrophile or reaction conditions, products arising exclusively from *syn* or *anti* addition to the strained cyclobutene double bond, or involving transannular cross type participation of the second carbon–carbon double bond[127,128]. In particular, the addition of methanesulfenyl or aryl sulfenyl chlorides to diester **60** in non-polar solvents leads to the formation of the *anti* 1,2-addition product **103**, whereas the addition under 'doping conditions' ($AcOH + LiClO_4$) produces the cage δ-lactone **104** (equation 108)[128].



(108)

The addition of arylsulfenyl chlorides under doping conditions has also been investigated[127] with other compounds of this series where structural features did not permit lactone ring closure and therefore allowed other skeletal transformations.

Compound **62** on treatment with 2,4-dinitrobenzenesulfenyl chloride in acetic acid gave a mixture of compounds **105**, **106a**, **106b** and **107**, but in the presence of $LiClO_4$ only compounds **106a** and **106b** were isolated. On the other hand, the addition of ArSCl in an apolar solvent (CCl_4) yielded exclusively the *anti* addition product **105** (equation 109).



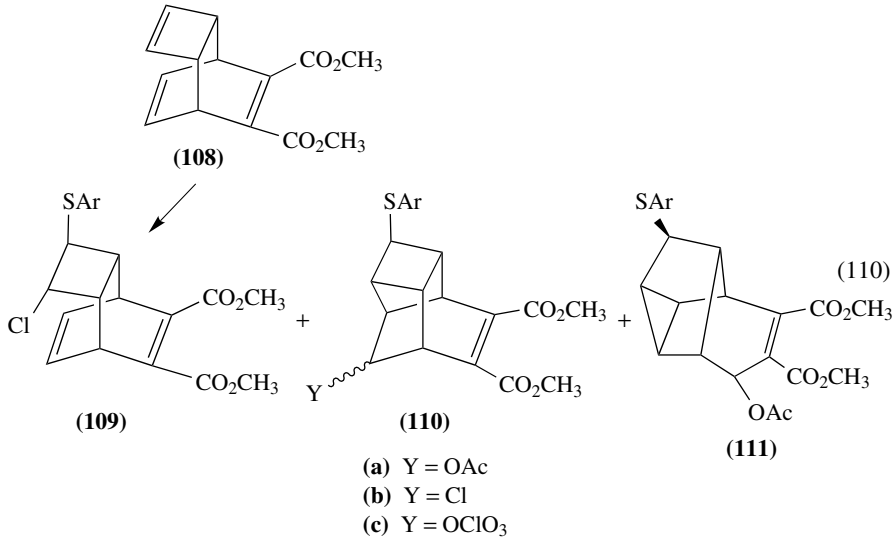
Ar = 2,4-$(O_2N)_2C_6H_3SCl$ **(a)** Y = OAc **(b)** Y = Cl

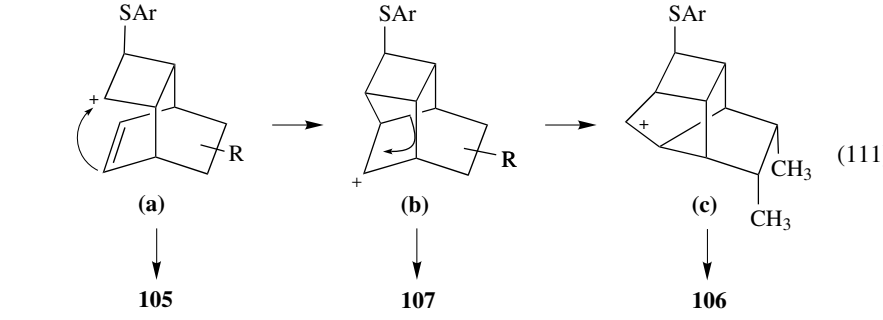
Similarly, compound **108** gave only the *anti* addition product **109** in CCl_4 and a mixture of compounds **109**, **110** and **111** in AcOH (equation 110). In the presence of $LiClO_4$ once again the 1,2-addition product was absent.

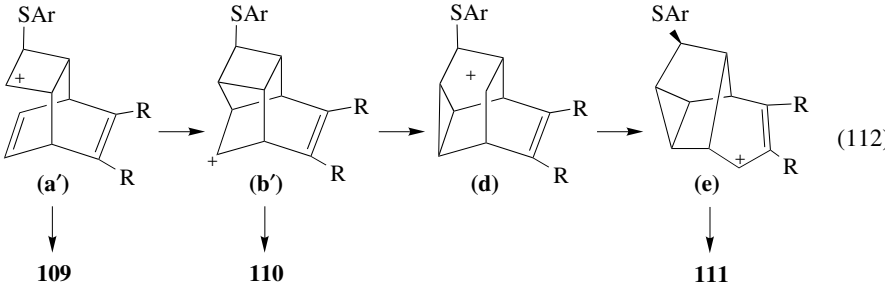
The change in solvent polarity thus leads to an appreciable variation in product composition, which is further changed under doping conditions. In the presence of $LiClO_4$ the products indeed arise exclusively from skeletal rearrangements and incorporation of external nucleophiles, solvent and perchlorate anion. The formation of ClO_4^--incorporated products can be increased by carrying out the reaction in non-nucleophilic solvents[129].

Skeletal rearrangements and incorporation of external nuclophiles were interpreted in terms of an ionic mechanism involving carbenium ions. Taking into account the structural features of the rearranged products, the authors propose[127] a reaction course involving an initial *exo* attack of the electrophile on the cyclobutene double bond. The primarily formed carbenium ions **a** or **a′**, arising respectively from **62** or **108**, which for the sake of simplicity are represented in the original work and in this review as pure carbenium ions, interact in a transannular fashion with the proximal double bond of the six-membered ring to give new cationic species, **b** or **b′**. The trapping of the latter intermediates gives **105**, **109** and **107** and **110**, respectively. However, both **b** and **b′** may undergo additional rearrangements, 1,2-shift of the C(2)−C(7) bond in diene **62** to give a cationic structure

of type **c**, affording compound **106**, or two subsequent 1,2-shifts of the C(8)−C(10) and C(5)−C(6) bonds in triene **108** which give, through intermediate **e**, compound **111** (equations 111 and 112).



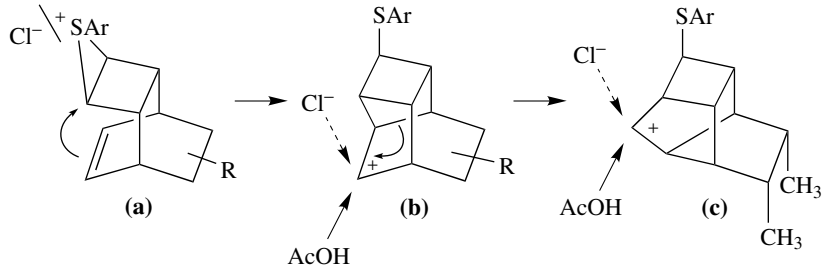




The different pathways followed by the two intermediates **b** and **b′** have been rationalized by assuming a possible participation of the third substituted double bond in the stabilization of the developing cationic center at C(10) in **d**.

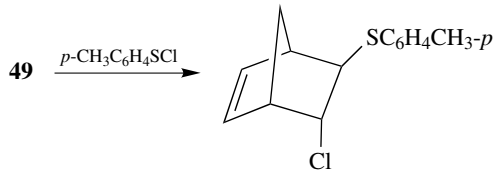
With this mechanistic scheme, the chemoselectivity of the addition and the formation of rearranged chlorides (but not acetates) have been chosen as criteria to differentiate the ion pair mechanism from the purely ionic one and, on the basis of both criteria, the authors suggest the involvement of a tight ion pair for the addition of ArSCl in AcOH to diene **62** and of solvent separated ion pairs to triene **108**. The effects related to the presence of added electrolytes, which favor the formation of rearranged acetates, have been considered in this work[127] as evidence that even a larger separation of ions, which should lead to more electrophilic species, is possible.

The involvement of ion pairs in the addition process has also been related to the stereochemical behavior. The remarkable difference in configuration between the rearranged chlorides and acetates has been rationalized, as shown in equation 113, on the basis of a *syn* internal attack of Cl^- on ion **c** and *anti* external attack of AcOH from the solvent pool.



(113)

The concept of stereocontrol by the ion pair mechanism in the electrophilic additions of sulfenyl chlorides has been further discussed[127] by Zefirov, using norbornadiene **(49)** as a substrate. The addition of sulfenyl chlorides to **49** has been reported to give a product distribution markedly dependent on the sulfenylating agent. In particular, it has been observed[129] that the addition of *p*-toluenesulfenyl chloride gives only the *anti* 1,2-addition product **112** (equation 114), whereas the addition of 2,4-dinitrobenzenesulfenyl chloride (DNBSC) yields, beside the 'normal' and 'inverted' *trans*-1,2-adducts, **112** and **113**, the single nortricyclic chloride **114** through homoallylic participation. Furthermore, when the reaction is carried out in the presence of $LiClO_4$, the addition of nitro- or dinitrobenzenesulfenyl chloride proceeds with the participation of the second double bond, giving the isomeric acetates **115** and **116** (equation 115).

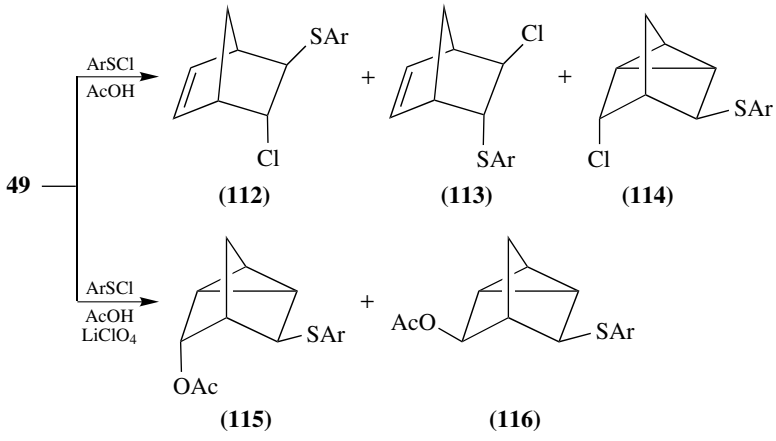


(112)

(114)

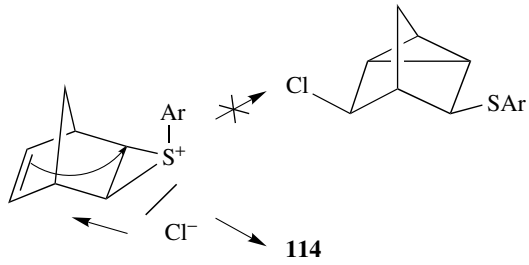
The non-stereospecific attack by nucleophiles has been regarded[127] as evidence for the involvement of a carbocation-like intermediate. The *endo* configuration of **114** has been attributed to the ion pair mechanism reported in equation 116, which should preclude the

formation of the product arising from an *exo* attack of the chloride anion.



(115)

Ar = 2,4-$(O_2N)_2C_6H_3SCl$

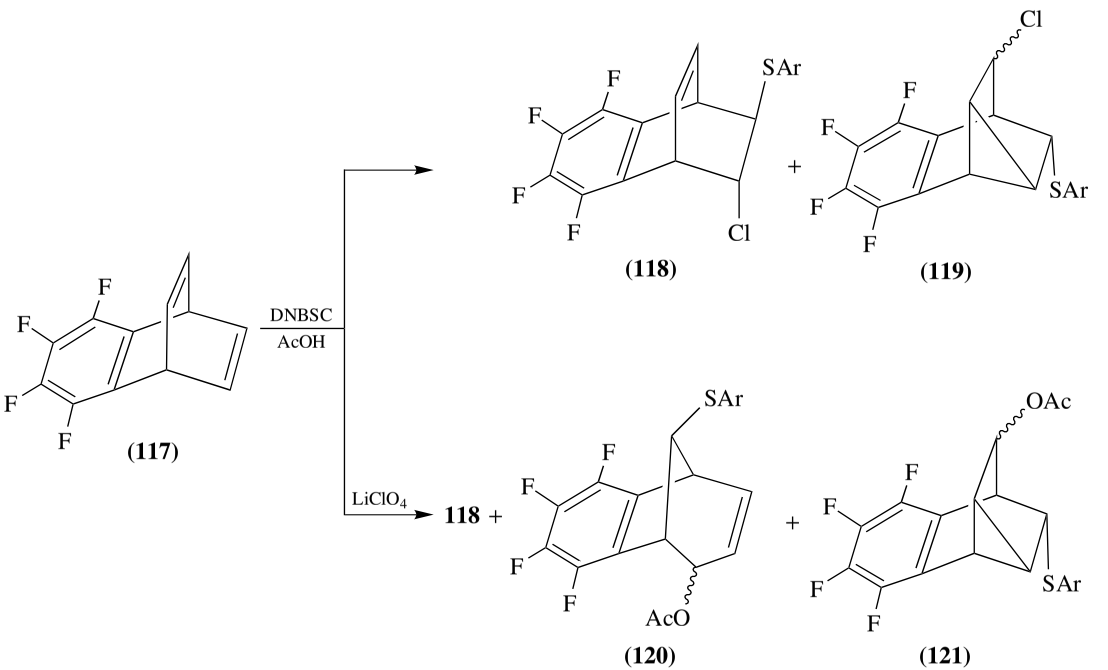


(116)

A dependence of the product distribution on $LiClO_4$ concentration has also been observed[130] in the addition of DNBSC to tetrafluorobarrelene (**117**). In the absence of added $LiClO_4$ this reaction gives the adduct **118** accompanied by a small amount of **119** (<2% yield). In the presence of $LiClO_4$ the products are chloride **118**, a mixture of the two isomeric acetates **120** and the tricyclic acetates **121** (equation 117). At high salt concentrations (0.2–0.25 M), the formation of the acetates **120** is dominant. Furthermore, a sharp non-linear increase in the content of doping-addition products at low concentrations of salt, followed by a more moderate increase at higher concentrations, has been observed[130].

Although the influence of $LiClO_4$ on the product distribution could be interpreted, in analogy with solvolysis, in terms of a 'special salt effect' which could be shown by internal return suppression at the stage of solvent separated ion pairs resulting from exchange between the ion pair counterion and ClO_4^-, the authors reject this interpretation on the basis of kinetic measurements. The addition of $LiClO_4$ indeed produces a significant acceleration of the reaction, which follows the equation for 'normal salt effect'. While underlining that the 'special salt effect' is kinetic in nature, whereas the 'doping addition' emphasizes products, the authors propose[130] a very similar mechanism (equations 118 and 119) for the doping effect to that reported for the special salt effect.

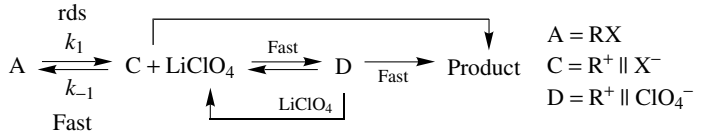
In both cases the product distribution is affected by the trapping of the first formed intermediate by the salt, but this trapping in the case of doping addition does not influence


F
F
F
F
(117)
DNBSC
AcOH
LiClO4
118 +
F
F
F
F
SAr
Cl
(118)
+
F
F
F
F
Cl
SAr
(119)
F
F
F
F
SAr
AcO
(120)
+
F
F
F
F
OAc
SAr
(121)

(117)

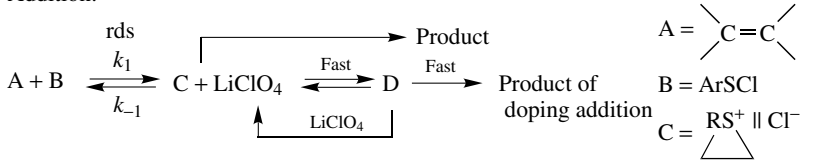
the total rate. The absence of the 'special' increase in rate therefore leads the authors to conclude that the reverse process, measured by k_{-1}, is relatively unimportant and the $A + B \rightarrow C$ transformation may be regarded as a non-reversible rate-limiting step. As remarked by the same authors, however, it is not possible to generalize this latter statement since the olefin structure and other factors can indeed markedly affect the return.

(a) Solvolysis:



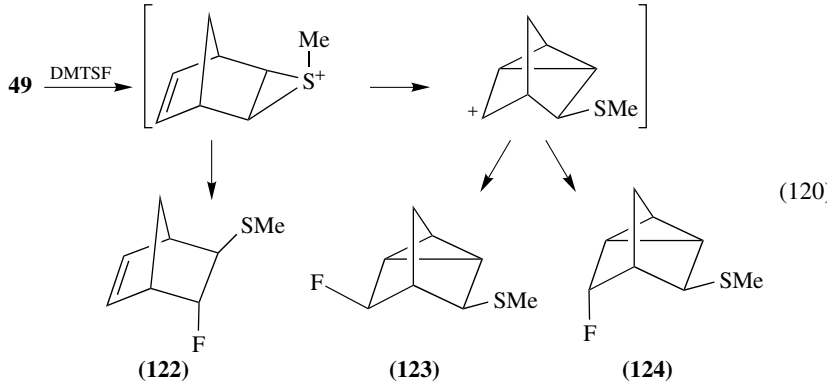
(118)

(b) Addition:



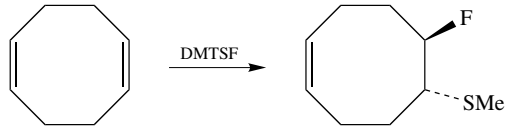
(119)

Finally, in contrast to the reactions reported above, **49** reacts[131] with dimethyl(methylthio)sulfonium fluoroborate (DMTSF) and triethylamine tris(hydrofluoride) in dichloromethane to give only 5% of the 1,2-addition product **122**. The main products, present in 73 : 27 ratio, are the *exo-exo* and *endo-exo* adducts **123** and **124**, formed by exclusive *exo* attack of the electrophile on the double bond, followed by transannular π-participation in the intermediate bridged cation and final addition of fluoride to the nortricyclic cation from both the *exo* or *endo* side (equation 120).



(120)

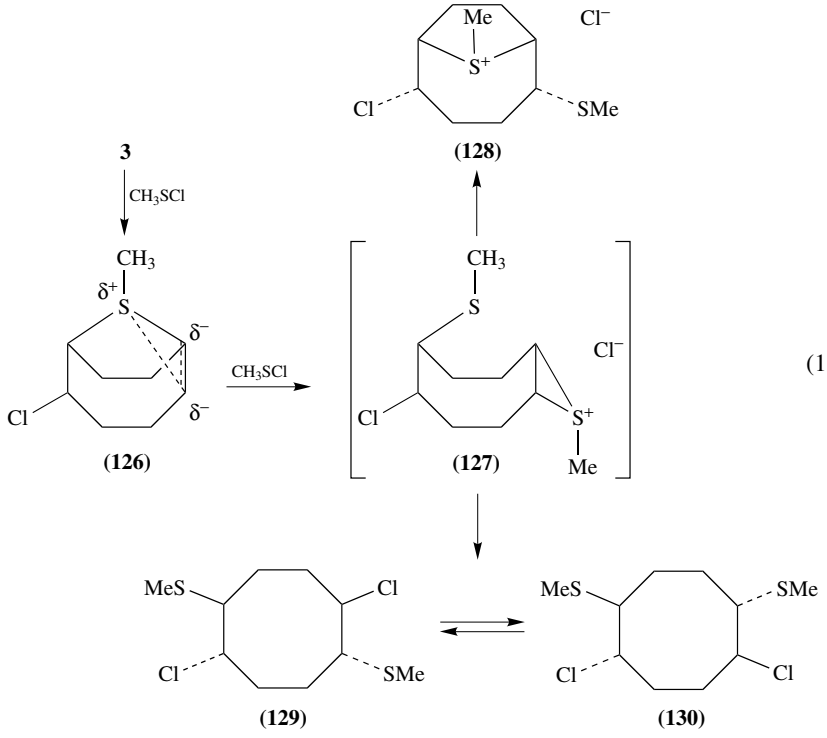
On the other hand, the addition of the same reagent to 1,5-cyclooctadiene **(3)** yields *trans*-5-fluoro-6-(methylthio)cyclooctene **(125)** as the sole product, without participation of the second double bond (equation 121).



(3) (125) (121)

Simple 1,2-additions to this compound have been observed[123,131,132] also in other sulfenylation reactions, and in other electrophilic additions involving strongly bridged intermediates. Although these results have been interpreted as evidence that additions of sulfenyl halides to symmetrical alkenes do not involve open carbenium ions before the product-determining step, the different behavior observed in the case of **49** suggests[123] that close proximity is necessary to have transannular participation of π-bonds, at least in additions of sulfenyl derivatives and of some other electrophiles carried out in the presence of efficient nucleophiles.

Finally, it is noteworthy that the reaction of methanesulfenyl chloride with **3** gives about 80–90% of the diadducts **128**–**130**, and only 8–13% of monoadduct **126**[20]. The remarkable propensity of **126** for diadduct formation has been attributed to the activation of the second double bond through a transannular overlapping of the sulfur orbitals with the π bond. Addition of the second mole of methanesulfenyl chloride probably involves an intermediate of type **127**. Attack by chloride ion on **127** gives compounds **129** and **130**. More interestingly, intramolecular ring opening by the methylthio group produces salt **128** (equation 122).



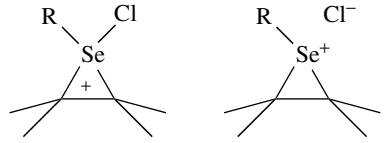
(122)

B. Selenenyl Halides and Related Compounds

1. General Aspects

The reaction of electrophilic selenium reagents with alkenes and alkynes has already been the subject of several reviews and mechanistic studies[2a,133]. Generally, the reactions involve selenic (Se^{II}) compounds; reactions of Se^{IV} were less extensively studied. Aryl, rather than alkyl, selenium derivatives are used in electrophilic reactions because of their lower volatility and toxicity. Diphenyl selenide (PhSeSePh) can be readily converted into benzeneselenenyl chloride or bromide by reaction with chlorine or bromine. These reagents can be further converted into useful Se^{II} electrophiles such as PhSeOAc, $PhSeN_3$, PhSeCN and $PhSeSO_2Ar$. In some cases these reagents can be isolated; in others they have been prepared and used *in situ* (PhSeF). The least reactive derivatives, such as PhSeSePh or $PhSeSO_2Ar$, require an appropriate coreagent such as strong protic or Lewis acids.

Areneselenenyl halides react with double bonds similarly to sulfenyl derivatives: 1,2-additions are generally *anti* stereospecific, in agreement with the involvement of a bridged intermediate [episelenurane **(a)** and/or seleniranium ions **(b)**], prior to the product-forming step.



(a) **(b)**

The regiochemistry of the addition depends on temperature and solvent. At low temperatures, under kinetic control, the AM products are favored while at room temperature or above, under thermodynamic control, the M adducts are generally formed.

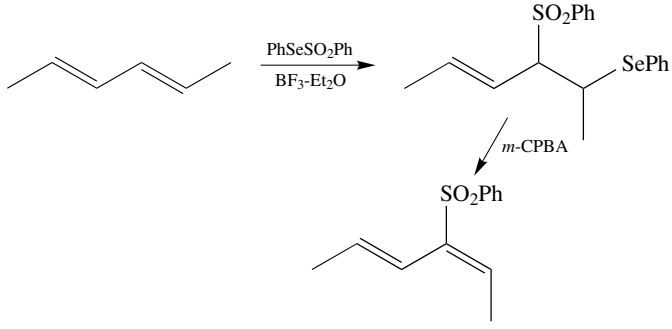
2. Conjugated double bonds

The addition of selenenyl derivatives to olefins has been shown to be of mechanistic interest and synthetic utility because of the versatility of the selenium functionalities[2a,133]. The possibility of modifying double bonds with seleno derivatives has been applied also to conjugated systems in order to obtain arylseleno dienes, or electron-deficient dienes, both being useful synthetic intermediates or building blocks.

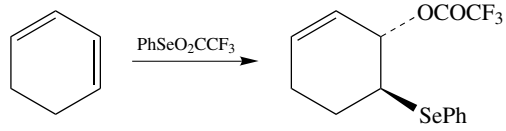
Selenosulfonylation of olefins in the presence of boron trifluoride etherate produces chiefly or exclusively M products arising from a stereospecific *anti* addition, from which vinyl sulfones can be obtained by stereospecific oxidation–elimination with *m*-chloroperbenzoic acid[134]. When the reaction is carried out on conjugated dienes, with the exception of isoprene, M 1,2-addition products are generally formed selectively from which, through the above-reported oxidation–elimination procedure, 2-(phenylsulfonyl)-1,3-dienes may be prepared (equation 123)[135]. Interestingly, the selenosulfonylation of butadiene gives quantitatively the 1,4-adduct at room temperature, but selectively 1,2-adducts at 0 °C. Furthermore, while the addition to cyclic 1,3-dienes, such as cyclohexadiene and cycloheptadiene, is completely *anti* stereospecific, the addition to 2,4-hexadienes is non-stereospecific and affords mixtures of *erythro* and *threo* isomers. For both (*E*,*E*)- and (*E*,*Z*)-2,4-hexadienes, the *threo* isomer prevails if the reaction is carried out at room temperature.

An *anti* stereospecific addition to 1,3-cyclohexadiene **(96)** has been observed also with benzeneselenenyl trifluoracetate (prepared by treatment of benzeneselenenyl bromide or

chloride with silver trifluoroacetate) which gives predominantly the *trans*-1,2-addition product **131** (equation 124). The small amount of a 1,4-adduct formed under these conditions[136] has been attributed to the lability of the first formed 1,2-adduct **(131)**.



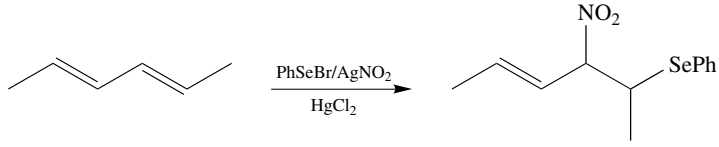
(123)



(124)

(96) **(131)**

The stereo- and regiospecific nitroselenylation of one of the double bonds of conjugated dienes was instead achieved by the addition of $PhSeBr/AgNO_2$ in the presence of $HgCl_2$ (equation 125)[137]. In all the examined cases 1,2-monoadducts with selenium in the 1-position were formed, the addition to (*E*,*E*)- and (*E*,*Z*)-2,4-hexadiene affording *erythro*- and *threo*-adducts respectively, showing that with this reagent the reaction exhibits a complete *anti* stereospecificity. Cyclic dienes, of course, give *trans*-adducts.



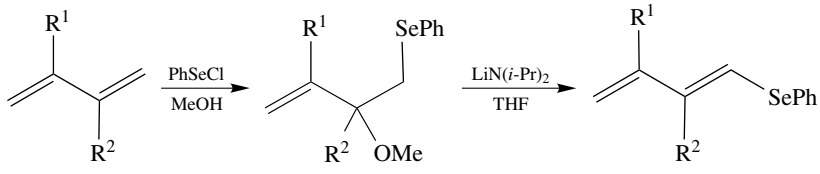
(125)

At variance with selenosulfonylation, however, attempts to prepare 2-nitro-1,3-dienes by oxidative elimination of selenium from the nitroselenylated products failed, probably owing to the lability of the products, which easily undergo further transformations. The expected 2-nitro-1,3-dienes have indeed been trapped as monoepoxy derivatives.

Finally, it has been shown that methoxyselenylation of conjugated dienes followed by treatment with lithium di-isopropylamide can be a convenient method for the preparation of 1-phenylseleno-1,3-dienes and their methyl-substituted homologues **134** (equation 126)[138].

With benzeneselenenyl chloride in methanol, Markovnikov-type 1,2-addition products **133a–d** are obtained in excellent yields. When isoprene is used as the conjugated diene, a mixture of two regioisomers **133b** and **133c** is formed. The main product is **133b** in the reaction at room temperature for 2 h, and **133c** when triethylamine is added to the reaction mixture. It is noteworthy that, as the above reported data show, although selenenyl halides react with alcohols to give the corresponding esters, the reaction of selenenyl chloride with methanol is generally much slower than its addition to a double bond. The comparison of

the rate constant $k_2 = 0.011\ M^{-1}\,s^{-1}$ for the reaction of benzeneselenenyl chloride with methanol with the rate constant $k_2' = 489\ M^{-1}\,s^{-1}$ for its reaction with ethylene gives a quantitative measurement of this reactivity difference, and indicates that the π orbital of a carbon–carbon double bond is a more efficient nucleophile than the oxygen of an alcohol in the nucleophilic displacement at bivalent selenium.

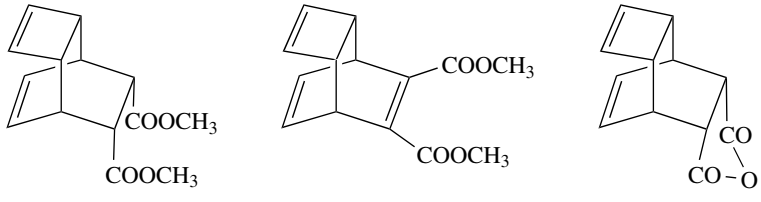


(132) **(133)** **(134)** (126)

(a) $R^1 = R^2 = H$
(b) $R^1 = Me$, $R^2 = H$
(c) $R^1 = H$, $R^2 = Me$
(d) $R^1 = R^2 = Me$

3. Non-conjugated double bonds

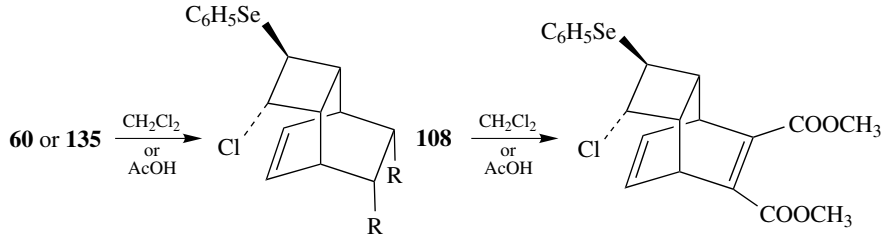
The addition of benzeneselenenyl chloride to strained tricyclo[4.2.2.0^{2,5}]deca-3,7-dienes **60**, **108** and **135** has been investigated in four media: methylene chloride, acetic acid, acetic acid/$LiClO_4$ and methanol[139]. Under conditions of kinetic control, only products of *exo-anti* attack, **136**–**138**, on the cyclobutene moiety are found both in methylene chloride and in acetic acid (equation 127), although during the course of the reaction of benzeneselenenyl chloride with **135** an *exo-syn* adduct, **139**, was observed as a transient product. The same results have also been obtained in acetic acid in the presence of $LiClO_4$, under 'doping conditions', except when the reaction was carried out on the tricyclotriene **108**, which gave as major product the cross-bonding adduct **140** arising from solvent incorporation (equation 128).



(60) **(108)** **(135)**

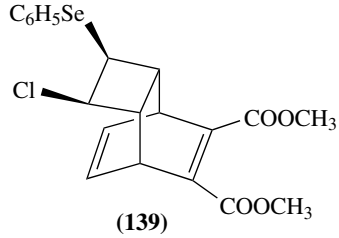
It is noteworthy that **108** reacts in AcOH with benzenesulfenyl chloride to give a 1 : 1 mixture of the sulfur analogues of **138** and **140**, but when the reaction is carried out in the presence of $LiClO_4$ a complex mixture of at least five products was detected. From this comparison the authors suggest that areneselenenylation is much less affected by the solvent than arenesulfenylation, and if the reaction profiles for the two product-forming processes are assumed to be similar, the difference in product distributions can be interpreted in terms of a more efficient bridging ability of selenium than that of sulfur. In the addition of selenenyl derivatives, the solvent-dependent product distribution has also

been rationalized in terms of an ion pair mechanism. A solvent polarity-dependent competition between bridged ionic intermediates, such as the seleniranium intimate ion pair **141**, which should give the *anti* 1,2-addition products by collapse before π-transannular participation, and a more loosely associated species, such as solvent-separated ion pairs **142**, the dissociated species **143** and the free carbenium ions **144**, more susceptible to give rearranged products, has been proposed (equation 129).

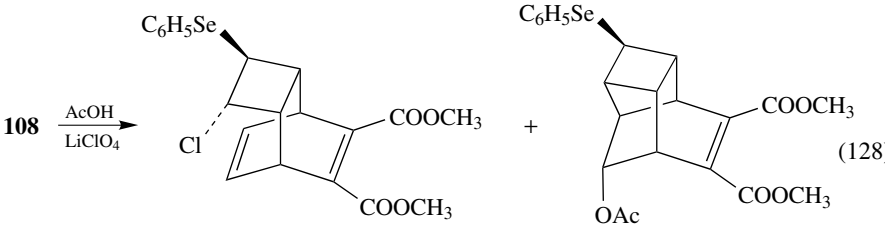


(136) R = $COOCH_3$
(137) RR = COOCO

(138) (127)



(139)

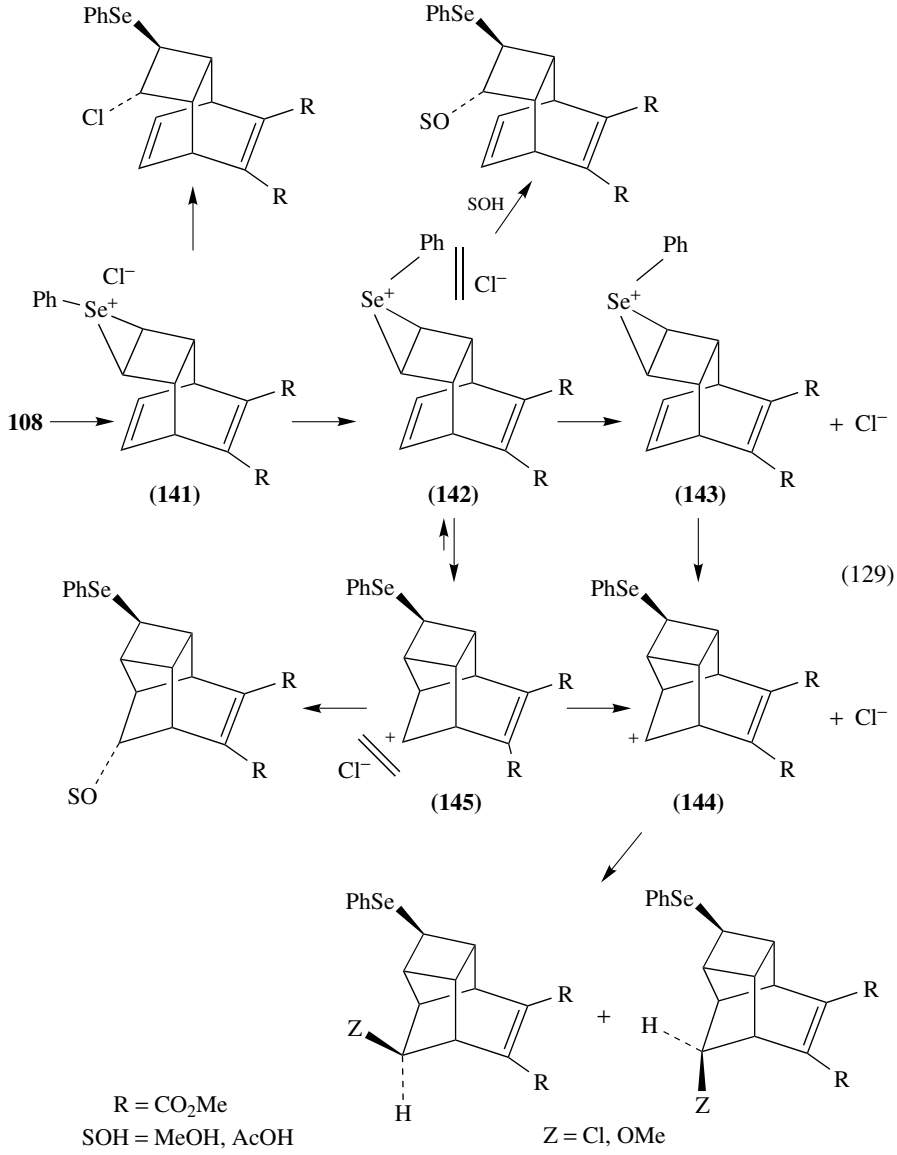


(138) **(140)** (128)

37 : 63

The same reaction scheme can also explain the stereochemical behavior of the addition of benzeneselenenyl chloride to **108** in methanol, which gives, in addition to the *trans* adduct **138**, the analogous methoxy derivative **146**, the cross-bonded chlorides **147** and **148**, and the analogous epimeric methoxy adducts **149** and **150** (equation 130).

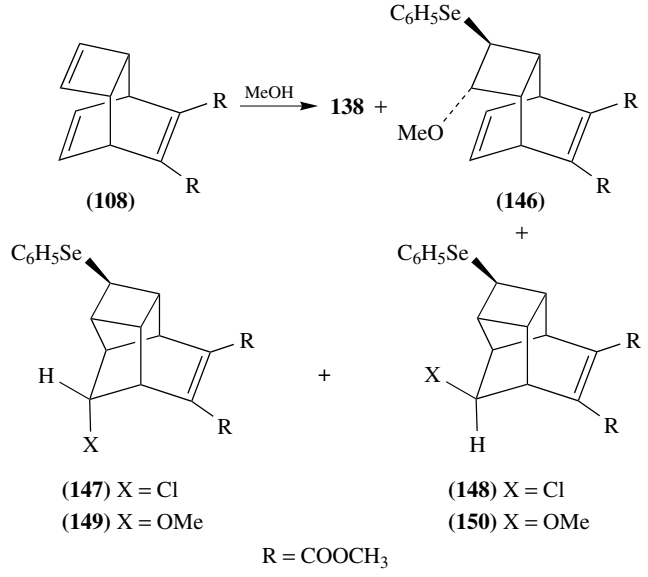
The formation of both isomeric chlorides **147** and **148** and the corresponding methoxy adducts **149** and **150** in methanol is at variance with the behavior observed in AcOH/$LiClO_4$, where only the acetoxy species **140** is formed. This has been interpreted by taking into account the possible role of a specifically solvated carbenium ion pair, such as **145**, prior to the formation of a free carbenium ion of type **144**.



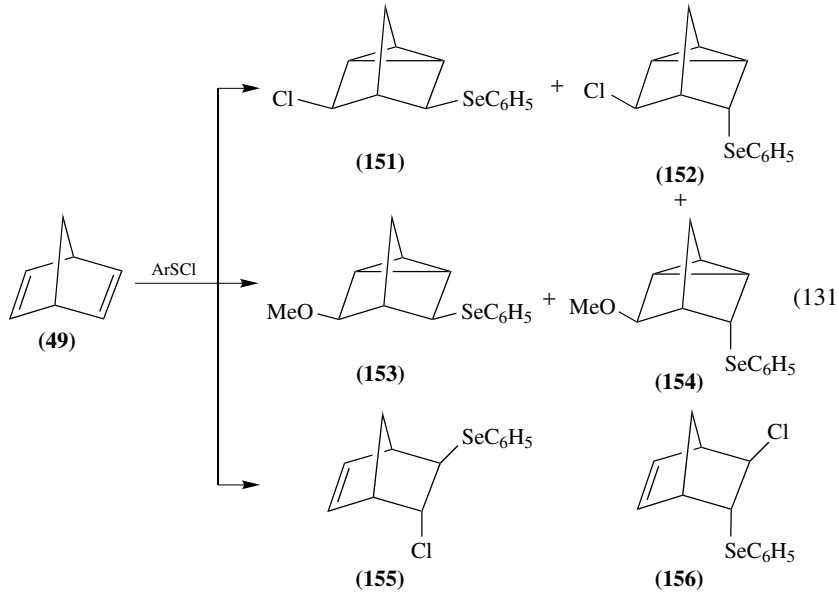
(129)

The involvement of at least three different forms of the seleniranium ion intermediate, i.e. tight and solvent-separated ion pairs and free ions, has been invoked also to rationalize the different chemical behavior observed in the addition of benzeneselenenyl chloride to bicyclo[2.2.1]hepta-2,5-diene **(49)** in methanol and in methylene chloride[140]. As stressed by the authors, the addition of benzeneselenenyl chloride to **49** shows a number of interesting trends. Four products (**151**–**154**), all resulting from homoallylic attack, were isolated from the reaction carried out in methanol (equation 131). Furthermore, it

is noteworthy that the reaction yields adducts arising from both *exo* and *endo* additions, with a predominant *endo* attack (*exo:endo* = 21 : 79). The same reaction carried out on norbornene proceeds exclusively with *exo* stereospecificity.



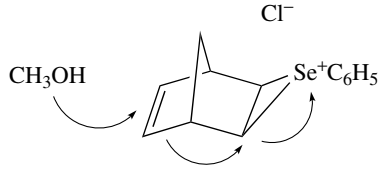
(130)



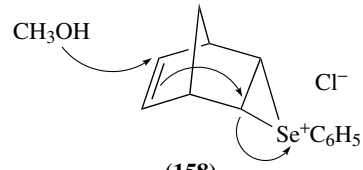
(131)

In chlorinated solvents the reaction of **49** also gives products of *exo* and *endo* attack (*exo:endo* = [**151** + **155**]/[**152** + **156**] = 39 : 61), but in this case compounds of simple 1,2-addition are found to predominate. Once again the solvent-dependent product

formation has been interpreted by assuming that in methylene chloride the collapse of intimate ion pairs to products occurs before the π participation of the homoallylic double bond becomes important. The exclusive formation of nortricyclenes in methanol should be a consequence of the preferential solvent attack upon the homoallylic double bond of the first formed ion pairs **157** and **158**.



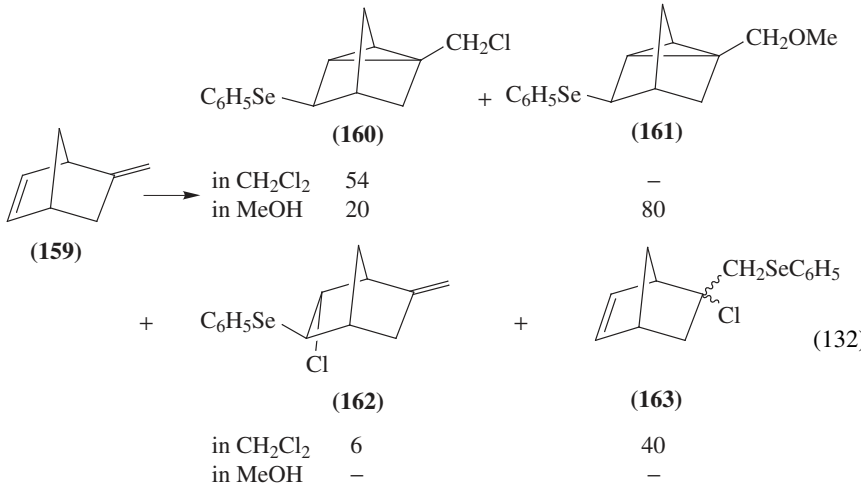
(157)



(158)

A mechanism of this type could explain the high ratio of methoxy/chloro adducts (**151** : **152** : **153** : **154** : **155** : **156** = 8 : 0 : 0 : 0 : 31 : 61) (in CH_2Cl_2) and 2 : 3 : 19 : 76 : 0 : 0 (in MeOH) since the solvent molecules do not have to enter the sterically hindered surrounding of the selenium in order to react.

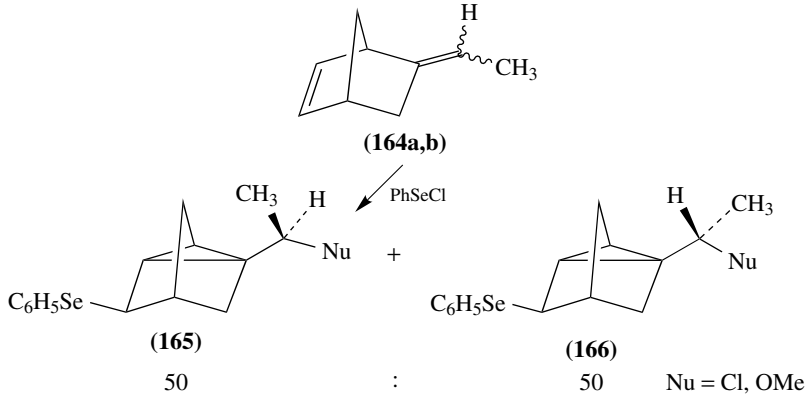
A solvent-dependent chemoselectivity, pointing to a dependence of the relative reactivities of the 1,2- and 1,1-disubstituted double bonds on solvent polarity and nucleophilicity, has been observed in the reaction of benzeneselenenyl chloride with 2-methylenebicyclo[2.2.1]hept-5-ene **(159)** which gives products **160**–**163**[140]. In methylene chloride the reaction occurs with a moderate chemoselectivity, attack on the *endocyclic* bond being preferred over that on the *exocyclic* one in a 60 : 40 ratio. In methanol, the addition is completely chemoselective and the attack occurs exclusively on the *endocyclic* double bond (equation 132). It may be further noted that **162** and **163** isomerize and solvolyze at high temperatures, leading to the homoallylic products **160** and **161**.



(132)

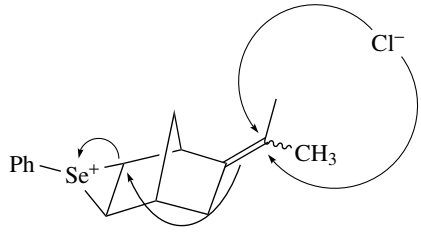
The transformation of **163** into **160** and **161** has been interpreted in terms of a reversible addition sequence, in which **159** and benzeneselenenyl chloride are regenerated and then react to give the more stable adducts **160** and **161**.

Finally, in the case of the geometrical isomers **164a,b**, only products from an *exo* addition to the *endocyclic* double bond followed by homoallylic rearrangement are observed[140], both in methanol and in methylene chloride. The electrophilic attack is *exo* specific, while the subsequent nucleophilic trapping by methanol or chloride proceeds non-stereospecifically giving equal amounts of **165** and **166** (equation 133).

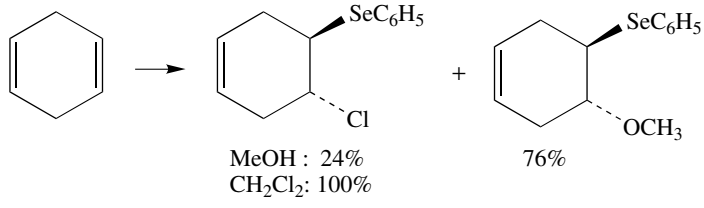


(133)

The absence of further products, particularly those resulting from β-attack on the seleno moiety and those arising from Wagner–Meerwein rearrangements, points to a mechanism involving a non-configurationally selective attack by Cl^- or methanol upon the seleniranium intermediate, as demonstrated below for Cl^-.



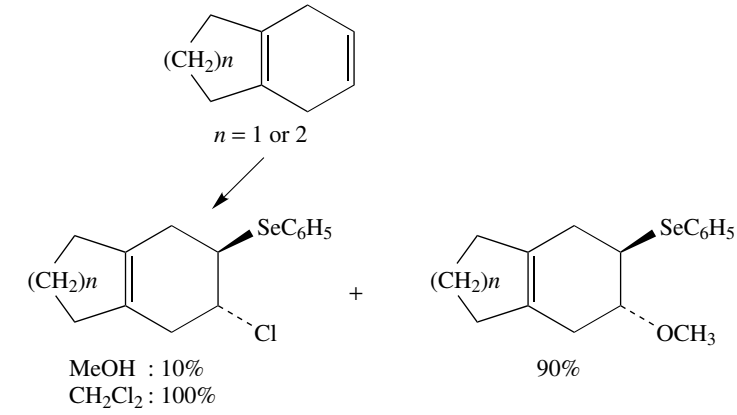
It is noteworthy that, at variance with norbornadiene derivatives, the addition of benzeneselenenyl chloride to 1,4-cyclohexadienes gives only products of *anti* 1,2-addition without any π participation (equations 134 and 135)[140].



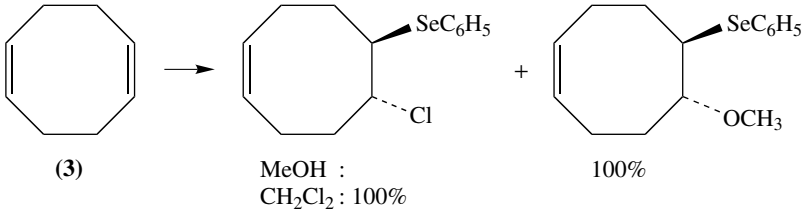
(134)

The same stereochemical behavior has also been observed in the addition of benzeneselenenyl chloride to 1,5-cyclooctadiene **(3)** (equation 136). However, **3** reacts with

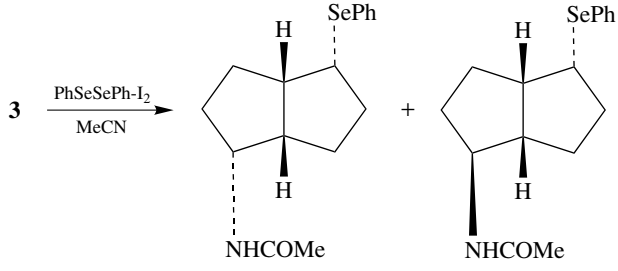
'benzene selenenyl iodide', prepared *in situ* by reaction of phenyl diselenide with iodine, in MeCN at room temperature to give the bicyclo[3.3.0]octane derivatives **167** and **168** (equation 137). The nucleophile, the solvent and/or the counterions therefore affect the possibility of obtaining products arising from π participation[21].



(135)

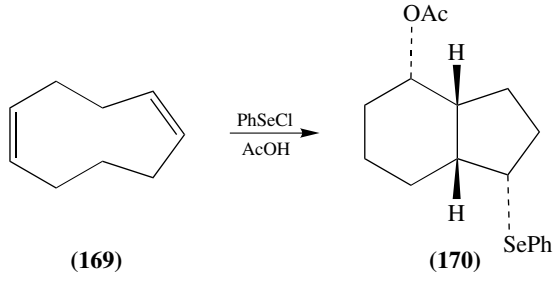


(136)



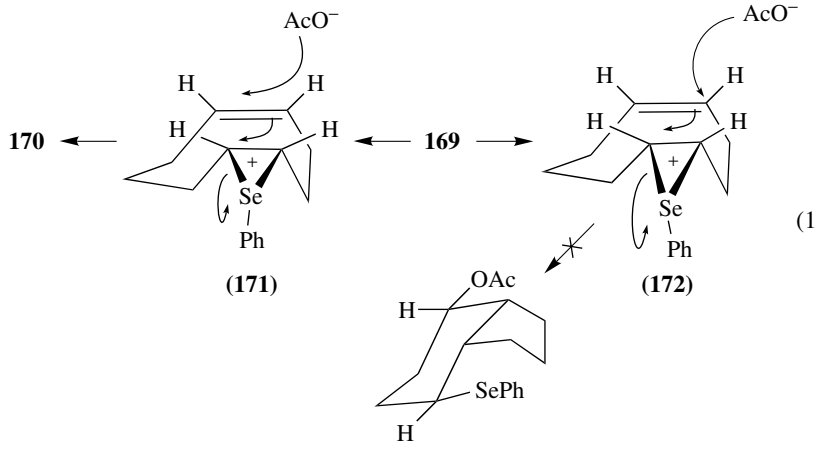
(137)

The larger (*Z*,*Z*)-1,5-cyclononadiene **(169)** reacts[141] stereoselectively with PhSeCl in AcOH to give the substituted hydrindan **170** (equation 138). In consideration of the *anti* addition mode of selenenyl reagents to double bonds, the transannular reactions of **169** have been rationalized on the basis of the two reaction intermediates, **171** or **172**, which are liable to place the PhSe- and AcO- groups in a *cis*-1,4-relationship and *trans* to the bridgehead hydrogen (equation 139). The preferential formation of **170** has thus been attributed to the fact that the pathway via **172** should involve a boat transition state.



(138)

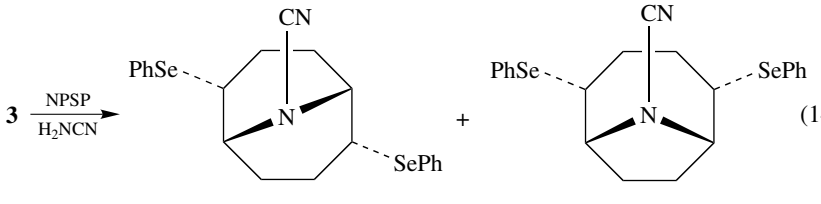
(169) **(170)**



(139)

(171) **(172)**

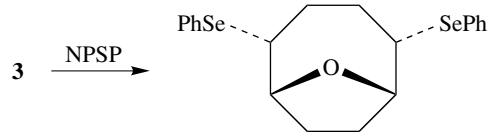
Finally, it must be mentioned that phenylselenation of some diolefins may provide a suitable method for the construction of heterocycles containing two phenylseleno groups. For instance, **3** reacts[142] with *N*-(phenylseleno)phthalimide (NPSP) in the presence of cyanamide (H_2NCN) to give the regioisomeric 9-azabicyclo[3.3.1]- and 9-azabicyclo [4.2.1]-nonanes, **173** and **174**, as the result of a combined process of inter- and intramolecular nucleophilic addition of cyanamide (equation 140).



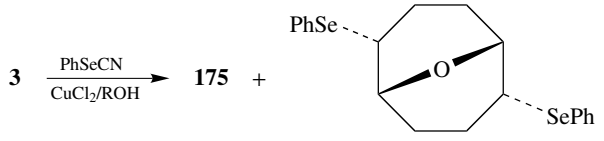
(140)

(173) **(174)**

Analogously, when the reaction of *N*-(phenylseleno)phthalimide or *N*-(phenylseleno) succinimide with **3** is carried out in methylene chloride in the presence of 2–3 equivalents of water, compound **175** can be obtained in high yield (equation 141)[16]. A mixture of isomeric cyclic ethers **175** and **176** was obtained also by treatment of **3** with phenylselenocyanide, in the presence of copper(II) chloride (equation 142)[143].

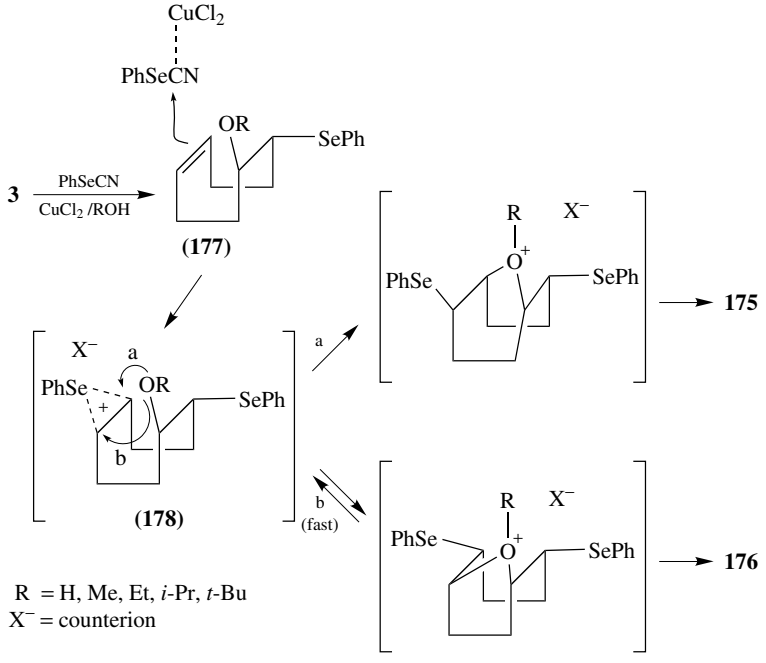


(175) (141)



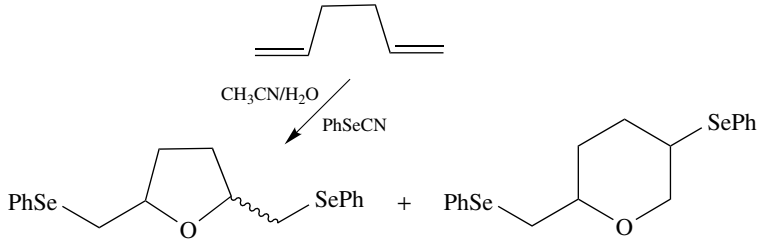
(176) (142)

The isomer ratio has been found to depend on the solvent, and a suitable choice of solvent results in the selective formation of one of the two isomers. This behavior has been explained by considering[143] that the first step of this reaction should be the oxyselenation of one double bond to produce **177**. In the subsequent transannular reaction of an alkoxy or hydroxy group with the seleniranium ion formed at the other double bond of **178**, the formation of an oxonium ion having a [4.2.1] framework is kinetically favored (path b). When R is hydrogen, it is removed prior to the isomerization in the chosen solvent (aqueous THF) to give **176** as the sole product. When R is an alkyl group reluctant to undergo elimination (Me > Et > *i*-Pr > *t*-Bu), an isomerization to a thermodynamically more stable intermediate having a [3.3.1] framework occurs to give **175** as the major product (path a, equation 143).



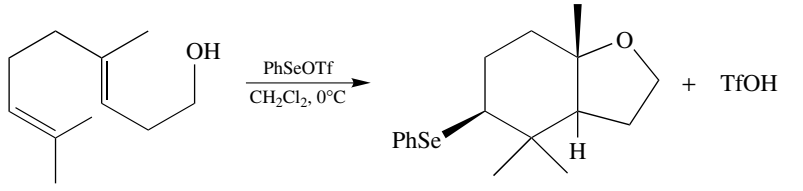
(143)

Interestingly, attempts to apply this cyclization reaction to linear diolefins using an alcoholic solvent give unsatisfactory results. Cyclic ethers have instead been obtained in aqueous acetonitrile. Under these conditions 1,5-hexadiene gives a 91 : 9 mixture of 2,5-bis[(phenylseleno)methyl]tetrahydrofuran and 2-[(phenylseleno)methyl]-5-(phenylseleno) tetrahydropyran in 86% yield (equation 144).

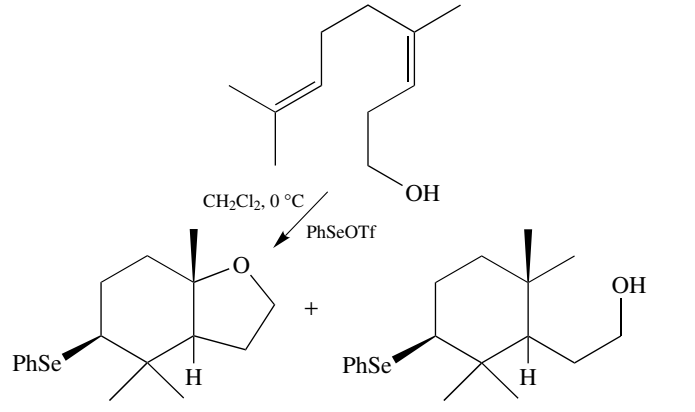


(144)

Similarly, electrophilic cyclizations of dienols and trienols, such as homogeraniol and homonerol, were carried out without addition of strong acid, using benzeneselenenyl triflate[18,144] as the organoselenium reagent (equations 145 and 146).



(145)



(146)

VI. ELECTROPHILIC MERCURY

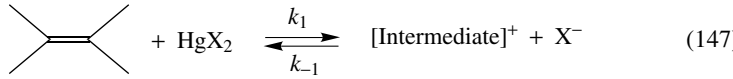
A. General Aspects[2a,145]

Addition of electrophilic mercury(II) salts to carbon–carbon double bonds in nucleophilic solvents (i.e. oxymercuration, solvomercuration etc.) is a well documented methodology in organic synthesis[146]. In these reactions a mercuric salt, usually the chloride or

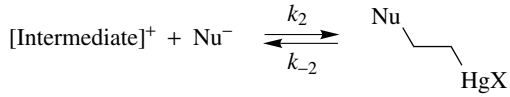
acetate but sometimes the trifluoroacetate or nitrate, is added in a suitable solvent. The products are 1 : 1 adducts, whose composition depends upon the solvent and any added nucleophile.

Mercuration usually occurs without rearrangement of the carbon skeleton and gives products arising from an almost complete Markonikov addition, with only a few exceptions. The product stereochemistry depends widely upon the structure of the alkene; generally *anti* addition is obtained although mercuration of strained alkenes can occur by *syn* addition.

The solvomercuration reaction is thought to be a two-step process. In the first step (equation 147), electrophilic attachment of mercury ion to the alkene produces a positively charged intermediate. In the second step (equation 148), a nucleophile (generally a solvent molecule) reacts with the intermediate leading to the organomercury compound.



(147)



(148)

Generally, mercuration reactions are overall second order, first order in the alkene and first order in the mercuric salt (equation 149)

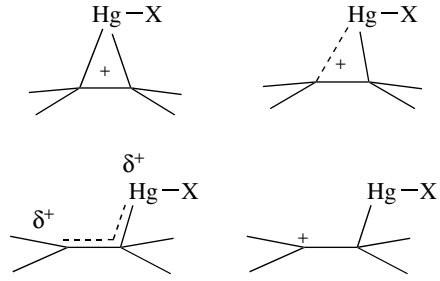
$$\text{rate} = (k_1 k_2 / k_{-1})\ [\text{alkene}]\ [\text{Hg salt}] \tag{149}$$

Substituent effects on the solvomercuration reaction differ markedly from those on many other electrophilic additions and these have been explained by assuming that the *formation* of the intermediate is often rate limiting in electrophilic additions whereas the *reaction* of the ionic intermediate with nucleophiles is rate limiting in solvomercuration[147]. In other words, the solvomercuration involves a fast pre-equilibrium formation of an intermediate, followed by rate-limiting attack of the nucleophile on this species.

Steric control has been invoked to explain the kinetic substituent effects as well as the *syn* stereoselectivity observed in these additions, for example to *trans*-cyclooctene and *trans*-cyclononene. In these cyclic compounds, one side of the π-bond is more shielded by the rest of the molecule and hence *anti* attack by a nucleophile is difficult.

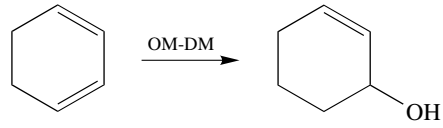
A symmetrically bridged 'mercurinium' ion, which might be described as a resonance hybrid, has been proposed as the intermediate by analogy with other electrophilic additions[148,149]. However, evidence has been presented both for and against the involvement of this intermediate in the mechanism of mercuration. Furthermore, CNDO/2 calculations have revealed[150] that there is only a shallow energy minimum on the potential energy surface associated to a shift of the mercury atom along the C−C axis, as shown below, so that asymmetrical ions might be lower in energy for asymmetrically substituted alkenes.

On the basis of theoretical and experimental results a symmetrical mercurinium ion, with most of the positive charge on mercury, has therefore been proposed in reactions of symmetrically substituted alkenes[151], while asymmetrical mercurinium ions or weakly bridged mercury-substituted carbocations have been proposed when there is a substituent, such as an aryl group, on the double bond[152]. Finally, with substituents highly capable of stabilizing carbocations, fully open intermediates have been proposed[151].



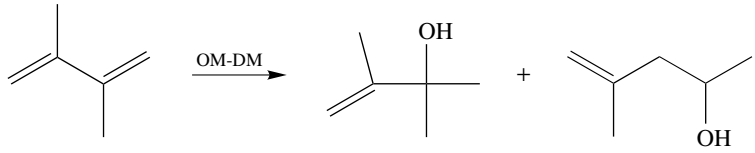
B. Conjugated Double Bonds

The possibility of converting alkenes into alcohols through a pair of reactions known as oxymercuration–demercuration (OM-DM) affords a convenient synthetic procedure for the hydration of carbon–carbon double bonds. However, little is known concerning the oxymercuration of dienes. The first studies related to the addition of mercury salts to conjugated double bonds, carried out using the standard OM-DM procedure [mercuration with an equimolar amount of $Hg(OAc)_2$ in THF–water followed by reduction of the oxymercurial with $NaBH_4$], provided information only about the regioselectivity of the reaction and about the applicability of the method[153]. Selecting as models of symmetrically conjugated dienes 2,3-dimethyl-1,3-butadiene and 1,3-cyclohexadiene, and as models of asymmetrically conjugated dienes 2-methyl-1,3-butadiene and *trans*-1,3-pentadiene, H. C. Brown and his coworkers showed[153] that Markovnikov hydration products are generally formed in these reactions, in yields often approaching 50%. In particular, it has been shown that 1,3-cyclohexadiene was readily converted into the allylic derivative, 2-cyclohexen-1-ol (equation 150), in contrast to a previous report[154] in which the formation of the isomeric homoallylic alcohol, 3-cyclohexen-1-ol, was observed.



(150)

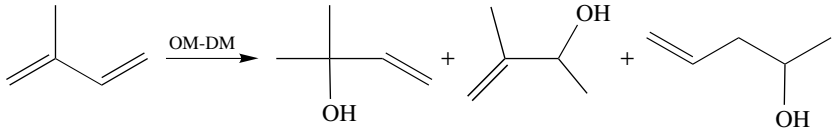
2,3-Dimethyl-1,3-butadiene underwent reaction to give the expected product 2,3-dimethyl-3-buten-2-ol besides a product containing a rearranged carbon structure, whose formation has been attributed to a radical process occurring during the demercuration step (equation 151).



(151)

A very low yield characterized instead the reaction of isoprene. From this olefin, only 16% of the expected 2-methyl-3-buten-2-ol has been isolated besides a small amount of the isomeric 3-methyl-3-buten-2-ol and of a rearranged alcohol, 4-penten-2-ol (equation 152). Finally, *trans*-1,3-pentadiene was converted to 3-penten-2-ol in 56% yield (equation 153), the electrophilic attack occurring at the position predicted on the basis of the relative

reactivities of 1-pentene and *trans*-2-pentene toward mercury electrophiles.



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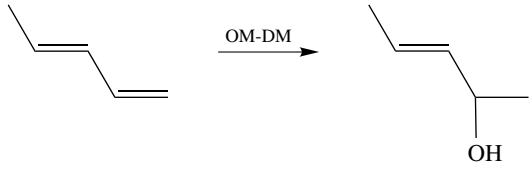


(153)

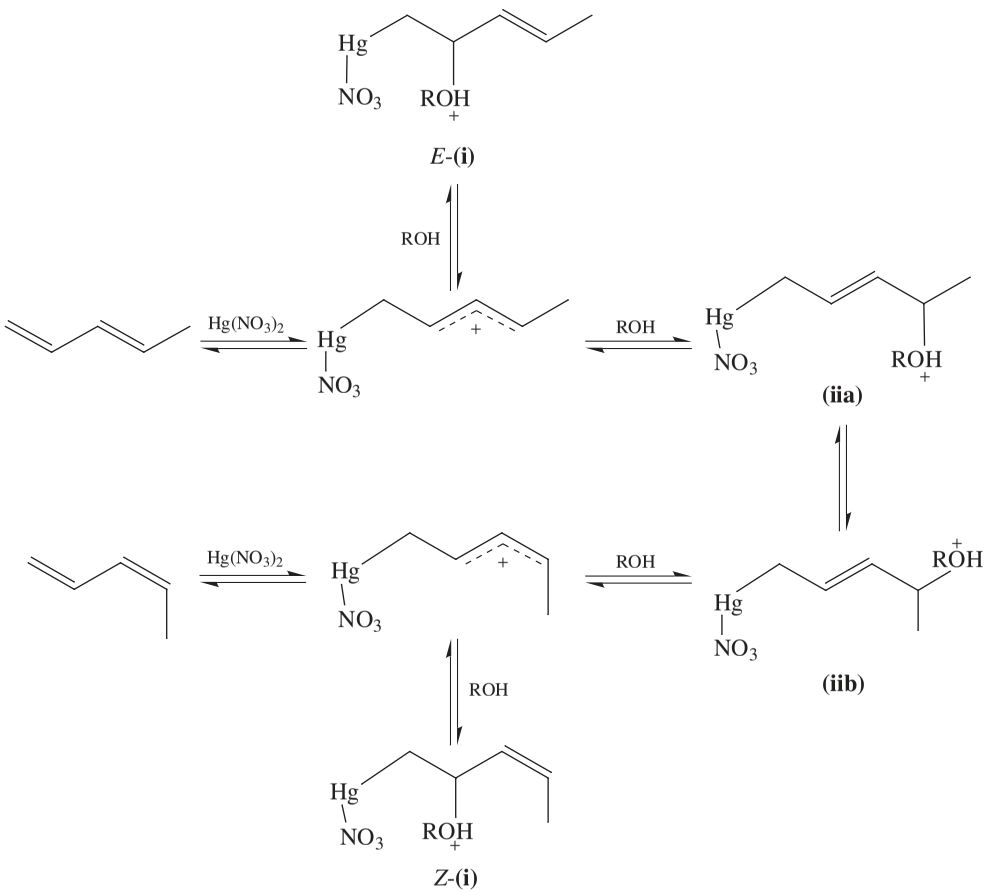
Subsequent isolation of solvomercuration products has supplied information about the stereoselectivity of the mercury addition and at the same time has shown that these reactions can give 1,2- and/or 1,4-addition products. In particular, the identification by ^{1}H NMR spectroscopy of a 1,4-adduct from 1,3-pentadiene and mercury(II)nitrate in methanol has provided[155] the first direct evidence that oxymercuration of conjugated dienes can proceed by 1,4-addition. Furthermore, the observed *Z*,*E*-isomerization of the diene has shown that the 1,4-oxymercuration is a reversible process.

On the basis of equation 154, the 1,2-adduct should be formed faster than the 1,4-adduct, the latter being obtained under conditions of thermodynamic control. The 1,2- and 1,4-adducts arise by deprotonation of **i** and **ii**, respectively. Rotation around the C(3)−C(4) bond of the 1,4-adduct **(iia ⇌ iib)** should provide a pathway for the ready isomerization of the diene. The involvement of an intermediate 1,4-adduct has been also reported[156] to rationalize the formation of 1,4-cycloamination products in the 'one-pot' reaction of linear and cyclic 1,3-dienes with primary aromatic amines and mercury(II) oxide-tetrafluoroboric acid (equations 155 and 156).

Considering that β-aminomercury(II) tetrafluoroborates are polar enough to undergo nucleophilic attack by the lone electron pair of an amine, ether or alcohol in the case of the 1,3-cyclooctadiene, **179**, it has been assumed that the first formed 1,4-adduct can give the reaction product by displacement of mercury by amine with direct participation of the nucleophile in an assisted breakage of the *anti* C−Hg bond (path a) or by spontaneous reduction of mercury in the intermediate allylic organomercurial (path b) (equation 157).

An alternative hypothesis, that the reaction product arises from a first formed 1,2-adduct, from which the same ionic intermediate may be generated (equation 158), has been ruled out by considering the directive effect of the conjugated double bonds on oxymercuration, which favors the attack of mercury at the terminal positions of conjugate π-systems.

Furthermore, more recent work about the monoalkoxymercuration of a series of conjugated dienes with different mercury salts has shown[157] that the alkoxymercuration of these compounds proceeds in two steps, the first being the formation of 1,2-adducts in which, with the exception of the mercuration of α-terpinene, the alkoxy group occupies the allylic position. The 1,2-alkoxymercurials are in equilibria with the corresponding 1,4-regioisomers, which are easily solvolyzed owing to the allylic character of the C−Hg bond. Moreover, the 1,2-adducts are stable when derived from mercury(II)acetate. With more ionic salts, such as tetrafluoroborate or nitrate, the 1,2-adducts are rapidly transformed into the 1,4-adducts, only that of *trans*-piperylene being characterizable at room temperature. Finally, the 1,4-adducts undergo fast decomposition to the corresponding


Hg
NO3
ROH
+
E-(i)
ROH
Hg(NO3)2
Hg
NO3
+
ROH
Hg
NO3
ROH
+
(iia)
Hg(NO3)2
Hg
NO3
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NO3
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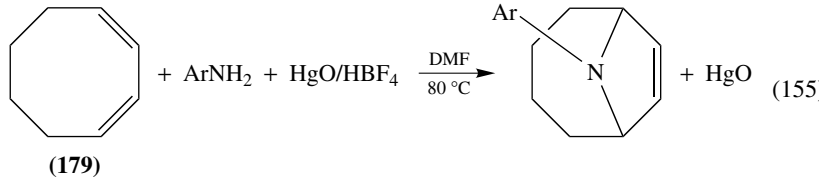
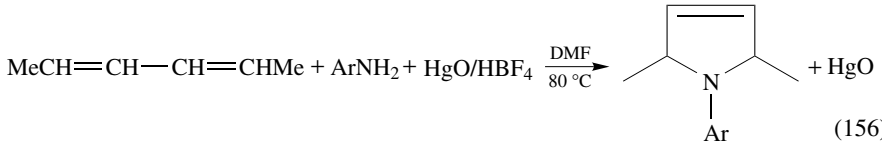
ROH
Hg
NO3
ROH
+
Z-(i)

(154)



(179) (155)



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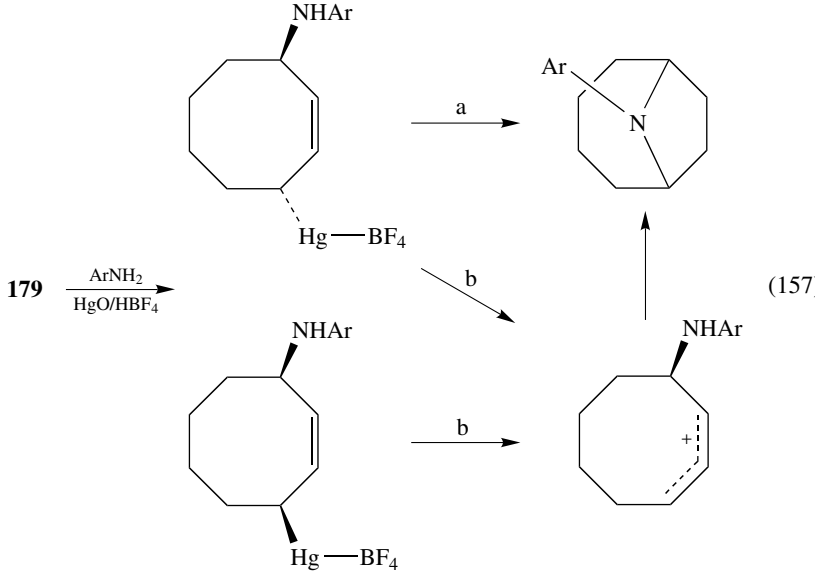
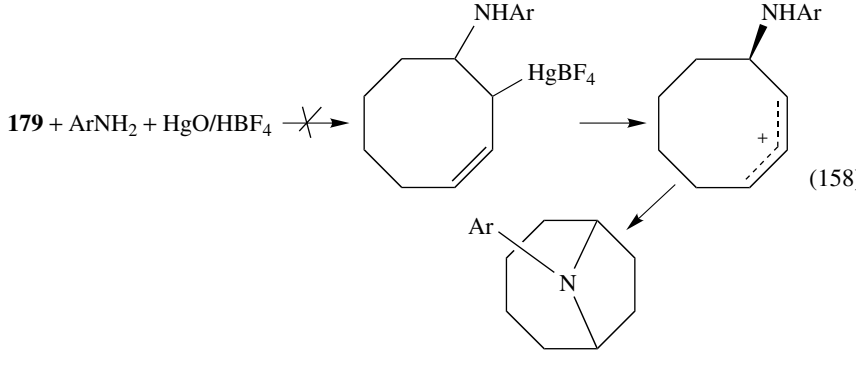


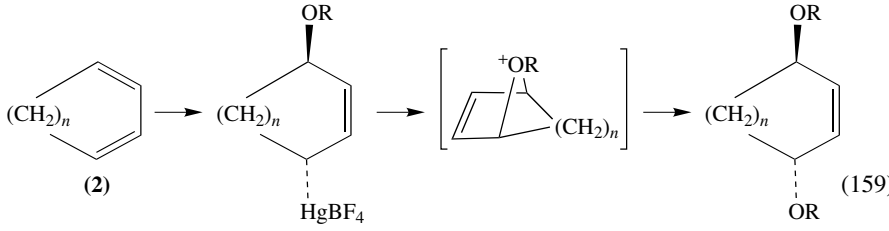
(157)

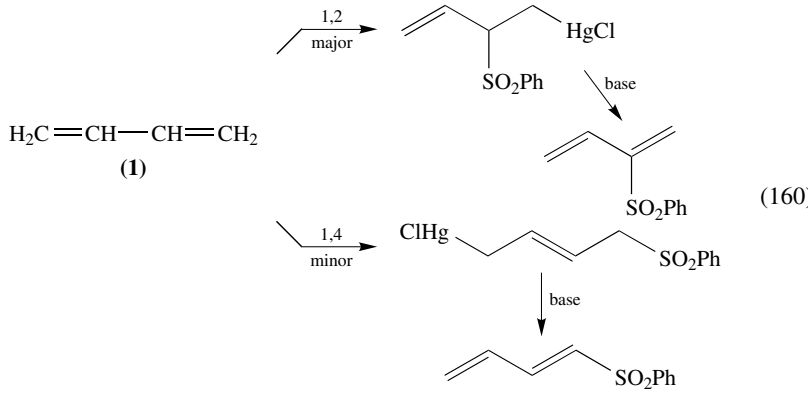


(158)

1,4-diethers. Their formation has been suggested to proceed by solvolytic cleavage of the allylic C−Hg bond in the 1,4-adducts, probably via formation of the corresponding allyl cation. The higher reactivity of the 1,4-adducts arising from cyclic dienes, and in particular that of the *trans* adduct arising from 1,3-cyclooctadiene, has been attributed to the participation of the oxygen lone pair in the displacement of mercury (equation 159). When the ring size decreases, the possibility of an anchimerically assisted displacement of mercury by oxygen is less important for geometrical reasons, the oxymercurial becomes more stable and the steroselectivity in the diether formation decreases. With respect to the stereochemistry of the diethers, most reactions occur with a reasonably high degree of stereoselectivity, always affording the *trans*-isomer as the major product.

Finally, the phenylsulfenylmercuration (using preformed mercury benzenesulfinate complex) of 1,3-dienes has also been reported[158] to give 1,2- and 1,4-mercury adducts (equation 160). In most cases the reaction proceeds regioselectively to give 2-(phenylsulfonyl)-1,3-dienes.





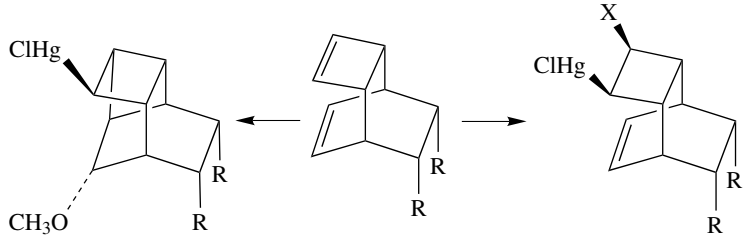
(160)

However, the reaction of 1,3-cycloheptadiene is less regioselective. Isoprene and *E*,*E*-2,4-hexadiene afford 1,2-/1,4-adducts in ratios of 87 : 13 and 83 : 17, respectively. The high selectivity for 1,2-addition (>95%) to 1,3-pentadiene is opposite to the corresponding oxymercuration of the same diene, which has been reported[159] to give mainly 1,4-adducts. The different regiochemistry has therefore been explained by assuming that sulfomercuration occurs under kinetic control whereas oxymercuration occurs under thermodynamic control.

C. Non-conjugated Double Bonds

The stereochemistry and the mechanism of the electrophilic additions to tricyclo[4.2.2.0^{2,5}]deca-3,7-diene derivatives have been studied frequently, although some unambiguous

structural assignments of the products were made. In particular, methoxymercuration of diester **60** has been investigated by Cookson[160] and the tetracyclic structure **180** has been assigned to the solid reaction product. Subsequently, the same reaction was reinvestigated by Mehta and Pandey[93]. A tricyclic structure **181** has been attributed to the reaction product on the basis of the NMR data (equation 161).

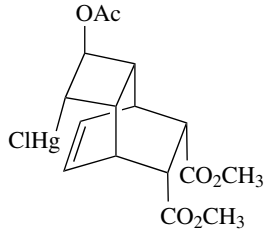


(161)

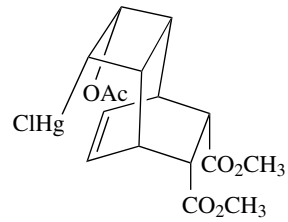
(180) R = $COOCH_3$ **(60)** R = $COOCH_3$ **(181)** R = $COOCH_3$; X = OCH_3
(62) R = CH_3 **(182)** R = $COOCH_3$; X = OH
(63) R = CH_2OCH_2 **(183)** R = $COOCH_3$; X = N_3
(184) R = CH_3; X = OCH_3
(185) R = CH_2OCH_2; X = OCH_3

A similar structure has furthermore been attributed[93] to the hydroxy- and azidomercuration products **182** and **183**. Methoxymercuration of the dimethyl compound **62** and of the ether **63** proceeded rapidly and smoothly to furnish again the *syn* methoxy mercurials **184** and **185** (equation 161). The rate of methoxy- and hydroxymercuration of these dienes increased markedly on going from **60** to **63** and **62**, in agreement with a strong transannular reactivity depression of the cyclobutene ring as a result of the substituent change. Therefore, considering that oxymercuration of simple olefins generally occurs with *anti* stereospecificity the exclusive formation of *syn* products in oxymercuration of **60**, **62** and **63**, and the consistent absence of compounds arising from either carbenium ion rearrangement or transannular participation have been rationalized[93] in terms of the 'twist strain' theory.

More recently the formation of an *endo trans*-adduct **186** has been reported[161] for the reaction of **60** with $Hg(OAc)_2$ in acetic acid, while in tetrahydrofuran an *endo cis*-isomer **187** has also been obtained[162].

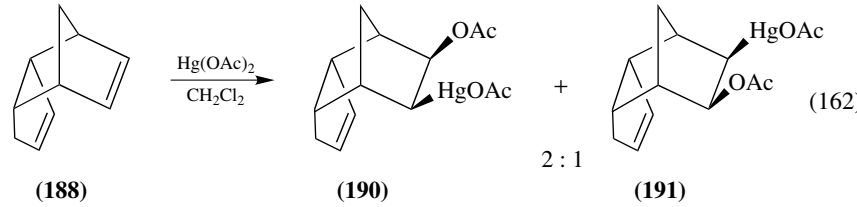


(186)

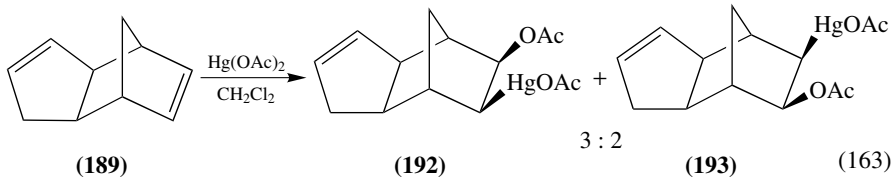


(187)

Nevertheless, the selective formation of *exo-syn* adducts has been observed in the mercuration of norbornadiene[163] and its derivatives **188** and **189**[164].



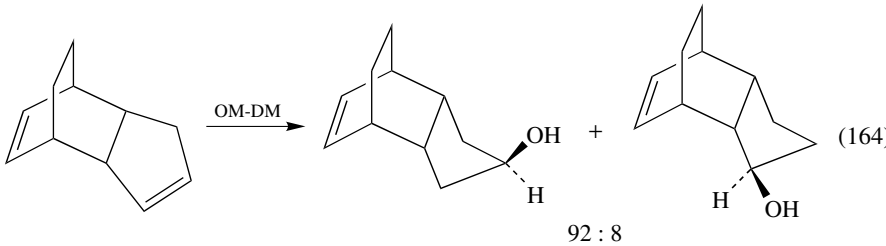
(188) (190) (191) (162)



(189) (192) (193) (163)

Oxymercuration in dichloromethane at room temperature afforded the adducts **190** and **191** from **188** (equation 162), and **192** and **193** from **189** (equation 163), the electrophilic mercury attack preferentially occurring at the C(3) carbon atom. A similar selectivity was previously observed also in OM-DM of **188**[165].

OM-DM reaction of *endo*-tricyclo[5.2.2.0^{2,6}]undeca-3,8-diene **(194)** was found[166] to proceed with high regio- and stereoselectivity, giving mainly 4-*exo*-hydroxy-*endo*-tricyclo [5.2.2.0^{2,6}]undec-8-ene **(195)** together with **196** (equation 164). Saturation of the 8,9-ethylenic bond in **194** resulted in a large reduction in reactivity as well as in stereoselectivity.



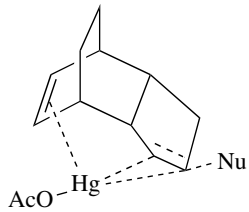
(194) (195) (196) (164)

These results have been interpreted in terms of *trans* addition of mercuric ion and nucleophile where the attack of the mercuric ion takes place from the more hindered side of the diene molecule. A transition state **197**, involving an *endo* attack of mercuric ion with some stabilization by coordination to the 8,9-ethylenic bond to the mercury atom, has been proposed to support the suggested mechanism. Analogously, and in sharp contrast to the results obtained[167] in the mercuration of norbornadiene which reacts with mercury salts via the usual scheme of *exo-syn* addition, the principal pathway in the mercuration of bicyclo[2.2.2]octa-2,5-diene is the formation of *endo-syn* products (equation 165).

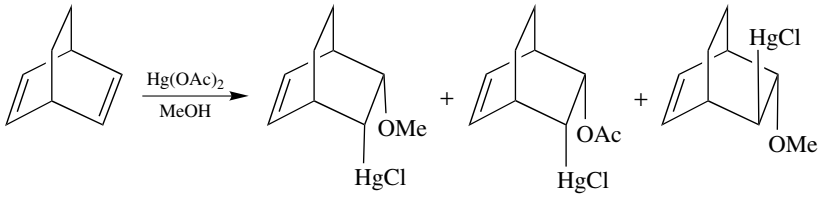
Therefore, although it is generally accepted that electrophilic mercuration of di- and polycyclic systems containing a double bond takes place in accordance with the *exo-syn* addition rule, at least a part of the reported results shows that the strain of the unsaturated system is insufficient to be the only determining factor for *syn* addition of mercury salts.

Finally, although mercuration–demercuration of dienes is a suitable method for synthesis of unsaturated alcohols and amines, 1,5-dienes cannot be used for this purpose

since these compounds undergo intramolecular cyclization to give five-membered cyclic systems, regardless of the diene/mercuric salt ratio employed.

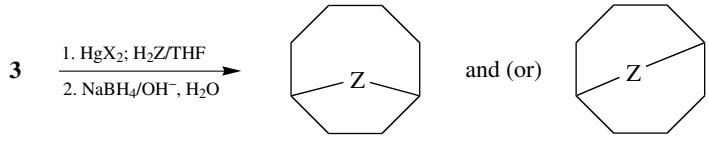


(197)



(165)

The mercuration–demercuration reaction of *cis,cis*-1,5-cyclooctadiene **(3)** has been widely studied in order to get some insight into the synthesis of 9-oxa and 9-azabicyclononane derivatives. However, the results of the reaction have often been the subject of some controversy since the ratio of the two isomeric bicyclo[3.3.1]- [**199** and **201**] and [4.2.1]- [**198** and **200**] nonanes, after reduction (equation 166), strongly depended on the reaction conditions of the mercuration step[168,169].

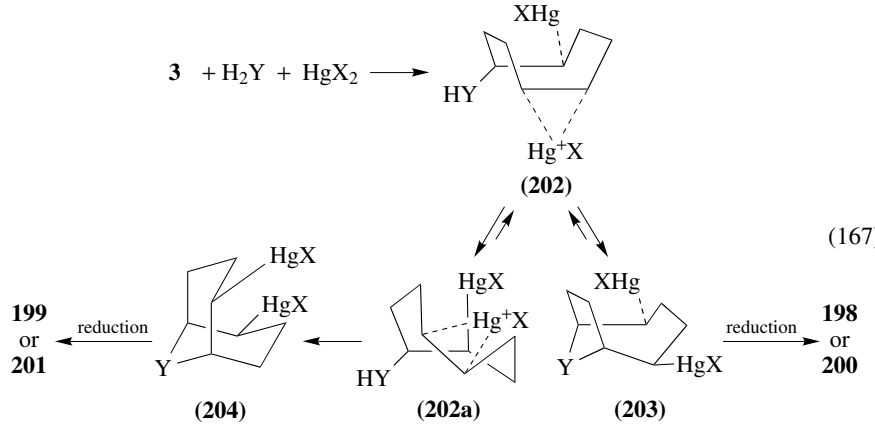


(166)

Z = O **(198)** **(199)**
Z = NAr **(200)** **(201)**

The ratio of the two products is primarily affected by the nature of the mercury(II) salt and also by the reaction conditions. Since the formation of these compounds could result from either a kinetically or a thermodynamically controlled mercuration process, a study of the mercuration of **3** in the presence of aromatic amines using various mercury(II) salts has been more recently carried out in order to determine the conditions under which aminomercuration is reversible, and the results have been compared to those of the oxymercuration[170].

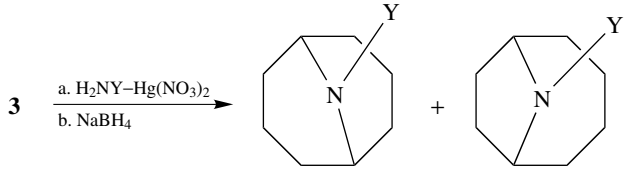
On the basis of these results, cyclization should proceed in two steps, the second one being the intramolecular amino (or oxy) mercuration of the second double bond. For geometric reasons, the reaction which leads to mercurial **203** from **202** is expected to be kinetically favored since it does not require any conformational change on going to the transition state, and hence this isomer should be obtained under kinetic control[170]. The mercurial **204**, arising from the intermediate **202a**, in equilibrium with **202**, should give instead the more stable [3.3.1]isomer **201** (or **199**), which should therefore predominate under thermodynamic control, i.e. in reversible aminomercuration of **3** (equation 167).



(167)

It has therefore been established[170] from the product distributions that, while the oxymercuration is reversible, unless a base (e.g. sodium acetate) is added to the reaction medium, and gives almost exclusively the more stable compound **199**, the aminomercuration takes place to give the kinetically controlled adduct **200**, or under thermodynamic control the aminomercurial **201**. Reactions are kinetically controlled when the mercurating species is a mercury(II) salt deriving from a weak acid such as mercury(II) acetate. Conversely, they are thermodynamically controlled with the covalent mercury(II) chloride. In the latter case, the presence of a strong acid in the medium allows the thermodynamically controlled product to be obtained.

Analogously, mixtures of *N*-alkoxycarbonyl- and *N*-tosyl-9-azabicyclo[3.3.1]- and [4.2.1]nonanes were obtained by reaction of **3** with carbamates or *p*-toluenesufonamide in the presence of mercury(II) nitrate followed by *in situ* demercuration with sodium borohydride (equation 168)[171,172].

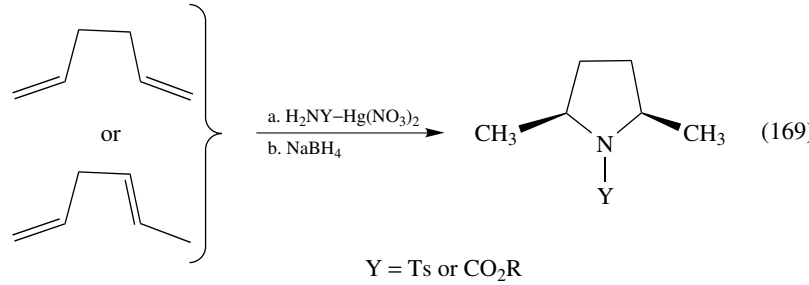


(168)

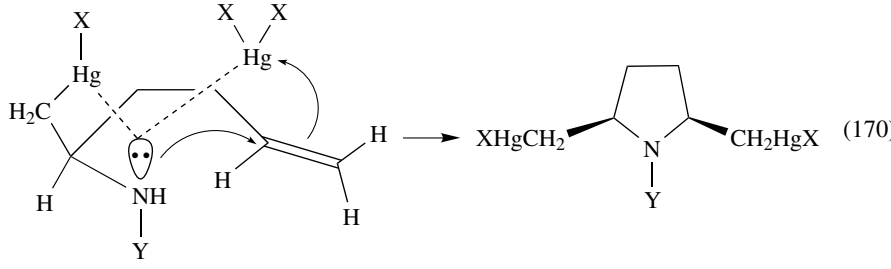
In contrast, the amido and the sulfamidomercuration–demercuration of acyclic 1,4- and 1,5-dienes yield saturated nitrogen-containing heterocycles (equation 169)[172].

It is noteworthy that a complete stereoselectivity toward the *cis*-isomer, which is opposite to that found in aminomercuration of the same dienes[173] characterizes these reactions. The following mechanism has therefore been proposed to rationalize the stereochemical behavior. After the addition to one of the double bonds, the electron pair of the nitrogen should interact with the mercury atom. In a second step, another mercury(II) ion from an additional molecule of mercury(II) nitrate is similarly complexed by the electrons of the nitrogen atom, requiring an approach from that same side and resulting in a *cis*

configuration of both mercurial groups (equation 170).



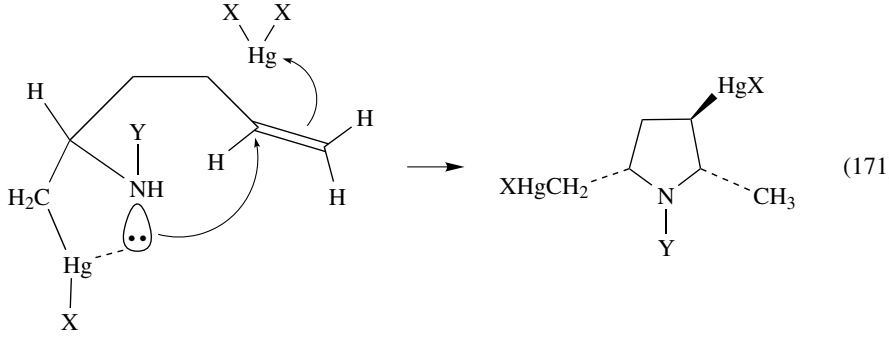
(169)



(170)

The preliminary electronic interaction seems to be required since, if the first mercury atom is absent, a *trans* addition takes place. Furthermore, a possible important role of the basicity of the nitrogen has been underlined taking into account that aminomercuration of 1,4- and 1,5-hexadienes with aromatic amines leads mainly to the *trans* isomer.

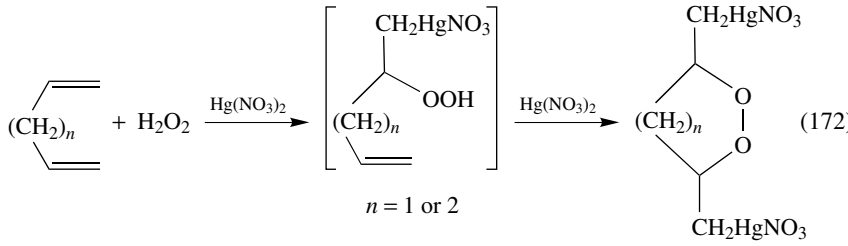
Considering the monoaminomercuration–demercuration of 1,4-hexadiene with *N*-methylaniline leads to *N*-methyl-*N*-(1-methylpent-3-enyl)aniline, the stereoselective synthesis of *N*-alkoxycarbonyl or *N*-tosyl *cis*-2,5-dimethylpyrrolidine from the same diene has been explained[172] on the basis of an initial amidomercuration reaction on the terminal bond followed by the second addition of mercury(II) salt to the internal double bond, on the less sterically hindered site (equation 171).



(171)

Finally, cyclic secondary alkyl peroxides have been prepared in high yield via the reaction of dienes with hydrogen peroxide and mercury(II) nitrate followed by hydrogen

or bromodemercuration[174]. Hydroperoxymercuration of suitable dienes (1,4-penta- and 1,5-hexadiene) affords unsaturated hydroperoxides capable of cyclization by a subsequent intramolecular peroxymercuration (equation 172).



(172)

With mercury(II) nitrate, the five-membered ring peroxide was obtained as an approximately equimolar mixture of isomers, while the 1,2-dioxacyclohexane contained about three times as much *trans*- as *cis*-isomer. Peroxymercuration of alkyl-substituted 1,4-penta- and 1,5-hexadienes, followed by demercuration, afforded mixtures of isomeric cyclic alkyl peroxides in yields strongly dependent on the number and position of the substituents[175].

VII. CONCLUSIONS

More than twenty years ago, G. H. Schmid and D. G. Garratt in their review[2a] on electrophilic additions to carbon–carbon double bonds concluded: 'experimental verification is lacking for all the proposed mechanisms'. Today, this conclusion applies fairly well to the electrophilic reactivity of dienes and polyenes. Most of the present interpretations are mainly suggested by partial results on the 1,2-/1,4-addition competition. Despite the huge number of available results, the association of kinetic and product data which has been very successful in detailed mechanistic investigations of other reactions, e.g. solvolysis or electrophilic additions to monoenes, has never been attempted for diene reactions. Moreover, most of the present mechanisms used for rationalizing the outcome of diene and polyene reactions with electrophiles have been postulated by analogy to those suggested for the monoene reactions a long time ago, and are not necessarily reasonable. On the one hand, the electrophilic behavior of dienes and polyenes involving interactions between two or several π bonds or between a π bond and a developing positive charge can differ markedly from that of alkenes. The related problem of the structure of the ionic intermediates, bridged versus allylic cations, has been discussed at length qualitatively based on the product data but, e.g., it has never been tackled directly by spectroscopic techniques. On the other hand, many features of electrophilic additions to monoenes, in particular bromination and sulfenylation, have been reinvestigated in much detail in recent years[2d,3,7] but the mechanisms for the analogous reactions of dienes did not take any advantage of these advances. For example, the characterization of bromine–alkene charge transfer complexes and their involvement in the reaction pathway[7a,c] have not been extended to polyenes. The nucleophilic solvent assistance (preassociation mechanism) to ionization of these CTCs into ion pairs, which has been shown to be related to the stereochemistry of the monoene reactions[7d,176], has not been considered in the interpretations of the 1,2-/1,4-addition competition. The well-established independence of bromine bridging of the solvent[7d,177] is systematically ignored in the rationalizations of the products of polyene reactions. The reversibility of the ionization step and its relation to the rate of the product-forming step[7d,178], either a nucleophilic trapping controlled by the intermediate lifetime

or a rearrangement in the case of strained olefins[3c,179], was revealed to be essential to the understanding of the chemo-, regio- and stereoselectivity of the monoene reaction. All these questions would have to be tackled in order to reach consistent interpretations of the nature of the products obtained by electrophilic additions to dienes and polyenes under a large variety of reaction conditions. It must be emphasized that the most recent activity in the field was focused on the access to polyfunctionalized diene derivatives of interest in organic synthesis rather than on reaction mechanisms. Therefore, the challenge concerning electrophilic reactions of dienes and polyenes is in developing their potential in synthetic methodology, despite or because of their high versatility as regards their selectivity.

A large number of multistep syntheses of natural compounds, such as terpenes or steroids, involves at some stage an electrophilic addition to or a cyclization of polyunsaturated substrates[17]. Lab-scale preparations of some chemical intermediates of interest as building blocks in heterocyclic chemistry have been reported under the headings 'Electrophilic sulfur, selenium and mercury'. Moreover, the diene and polyene reactions with 'electrophilic oxygen' involving oxo- or peroxometal complexes as oxygen carriers, which are reviewed in a specific chapter of Vol. 1 of this book[180], are very promising in the context of organic synthesis. The electrophilic additions to allenes and cumulenes, a very important reaction for synthesis, described elsewhere in this series, are not included in this report since these unsaturated compounds cannot be viewed as conjugated π-systems and exhibit a very different behavior[181].

Many large-scale applications of electrophilic additions to polyenes, particularly in polymer industry, have also been mentioned in this report. Most of these industrial procedures involve catalytic activation of the electrophilic dienes and polyenes by complexation with transition metals. These extensions have opened the way to a new field of organometallic chemistry on the reactivity of metal–diene complexes[182], which can be viewed as resulting from the diene electrophilicity and as activation of conjugated systems toward nucleophilic attack. In this context, methodologies for obtaining regio- and stereocontrolled 1,4-additions have been proposed. The wide synthetic utility of this field in selective organic transformations is illustrated in the previous volume of this book in the chapter[183] 'Palladium-catalyzed oxidation of dienes'.

VIII. ACKNOWLEDGMENTS

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CHAPTER **8**

Nucleophilic additions to dienes, enynes and polyenes

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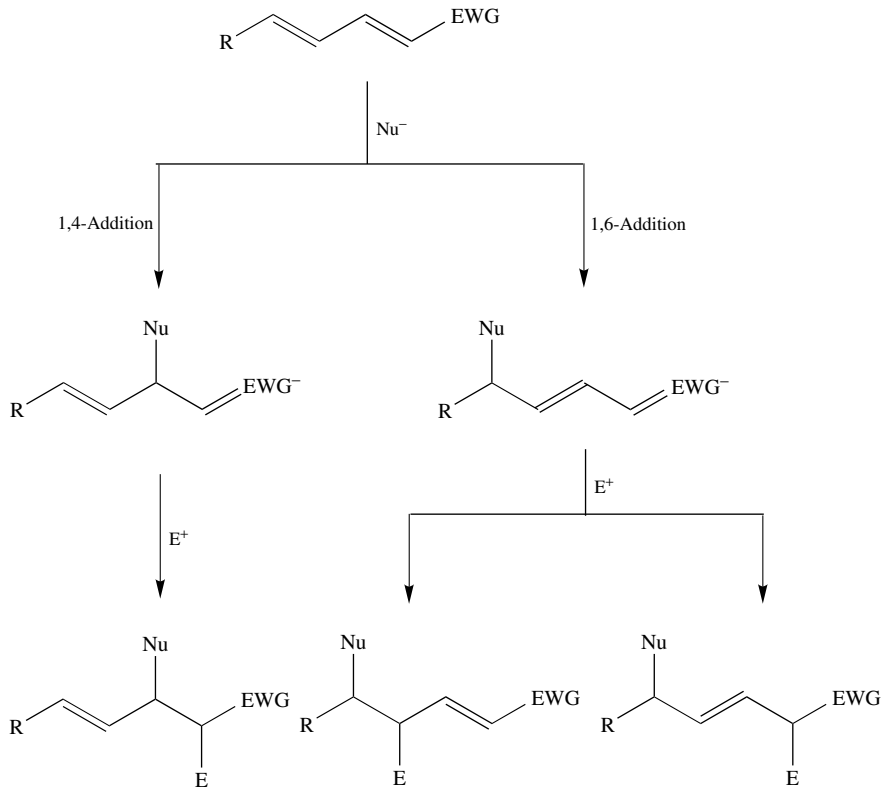
I. INTRODUCTION

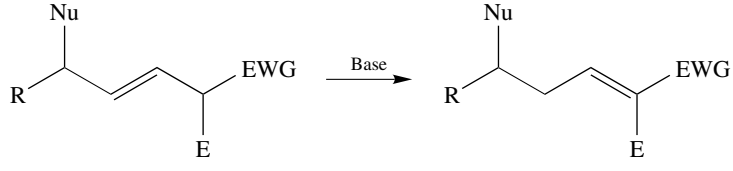
Due to their electron-rich π-systems, unsaturated hydrocarbons normally do not undergo nucleophilic but rather electrophilic additions. In order to activate a double bond for a nucleophilic attack, its electron density has to be decreased; this can be achieved by coordination to a metal, e.g. palladium(II)[1], or more conveniently by introduction of an electron-withdrawing group which acts as an intramolecular π-acceptor. Nucleophilic additions to these ambident acceptor dienes and polyenes substituted with electron-withdrawing groups (EWGs), can provide several isomeric products; hence, it is of particular importance to control the *regioselectivity* and *stereoselectivity* of these transformations (Scheme 1). Besides direct nucleophilic attack on the acceptor group, an activated diene may undergo a 1,4- or 1,6-addition; in the latter case, capture of the ambident enolate with a soft electrophile (E^+) can also take place at two different positions. Thus, the nucleophilic addition can produce three regioisomeric alkenes which may be formed as E/Z isomers. Depending on the nature of nucleophile and electrophile, the adducts also contain one or two centers of chirality.

The product distribution may depend on the reaction conditions if the nucleophilic attack is reversible (kinetic vs. thermodynamic control). An additional complication arises from



SCHEME 1

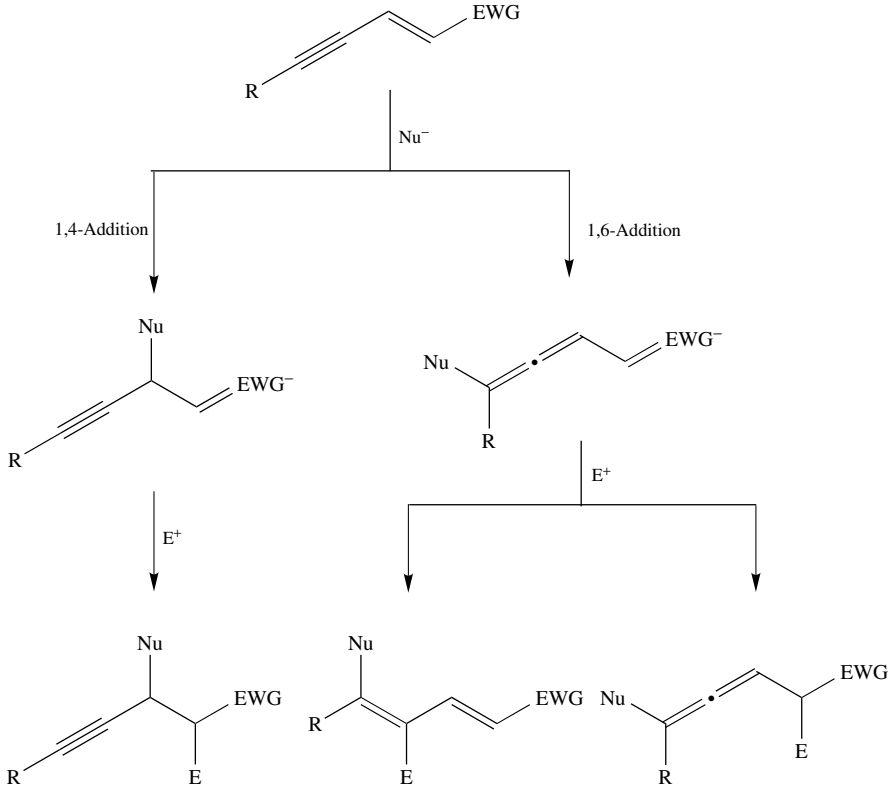
the fact that β,γ-unsaturated carbonyl compounds (and other acceptor-substituted alkenes of this type) are readily isomerized to the thermodynamically more stable conjugated isomers under basic conditions (equation 1, where EWG is a conjugating group, e.g., a carbonyl group).



(1)

Similar schemes can be developed easily for analogous reactions of acceptor-substituted polyenes. For example, a triene with an acceptor group in 1-position can form six regioisomeric products of Michael addition and electrophilic capture, and each of these exists as E/Z stereoisomers, diastereomers and/or enantiomers. Thus, reactions of this type are only useful if both the regio- and stereoselectivity can be controlled; fortunately, only one isomeric Michael adduct is formed in many cases. This is true in particular for polyunsaturated Michael acceptors which bear at least one triple bond besides one or more double bonds. An additional feature of the latter substrate type is that nucleophilic additions can

give rise to the formation of axial chirality (Scheme 2). For example, the addition of a nucleophile to an acceptor-substituted enyne may take place in a 1,4- or 1,6-fashion, and the ambident allenyl enolate formed in the latter case can trap a soft electrophile to furnish either an allene or a conjugated diene. Again, several stereoisomeric products can be obtained in each case.



SCHEME 2

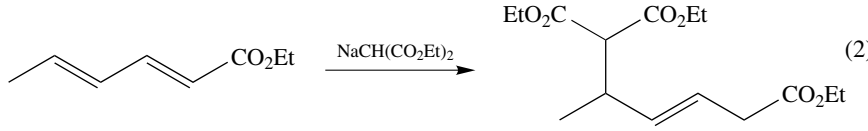
In this chapter, nucleophilic 1,*n*-additions ($n = 4, 6, 8, \ldots$) to acceptor-substituted dienes, enynes and polyenes are presented[2]. Addition reactions which obviously proceed via non-nucleophilic pathways (e.g. catalytic reductions, electrophilic or radical additions[3]), as well as 1,2-additions to the acceptor group, are not covered.

II. DIENES

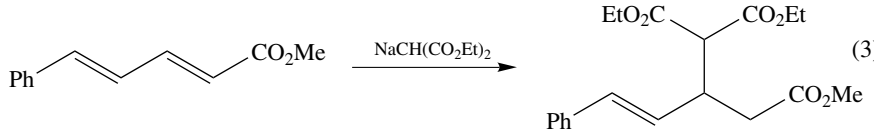
A. Carbon Nucleophiles

Early investigations of additions of soft carbon nucleophiles to simple Michael acceptors like ethyl sorbate date back to the beginning of the 20th century. Already in 1906, Vorländer and coworkers[4–6] described additions of malonate anion; whereas ethyl sorbate provided the 1,6-addition product[6] (equation 2), the 1,4-adduct was obtained from methyl 5-phenyl-2,4-pentadienoate[4] (equation 3). Thus, it seems that the regioselectivity

of the Michael addition is sensitive to the steric properties of the substrate. Similarly, phenyl-substituted 2,4-dienones reacted with sodium malonate under 1,4-addition[4,5]. The products were analyzed by oxidative degradation.

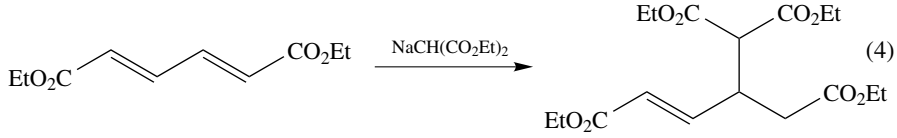


(2)



(3)

This work was repeated by several groups[7–11]; in the reaction of sodium dimethylmalonate with methyl sorbate, Farmer and Metha[9] observed small amounts of the 1,4-adduct besides the 1,6-addition product. Difficulties in conducting the transformations and analyzing the products are evident from reports on malonate additions to ethyl muconate[12–14]: depending on the reaction conditions, the expected 1,4-adduct (equation 4) or isomerization products formed by double bond displacement were isolated. Nucleophilic 1,4- and 1,6-addition reactions to 2,4-pentadienenitrile were also reported[15–17].



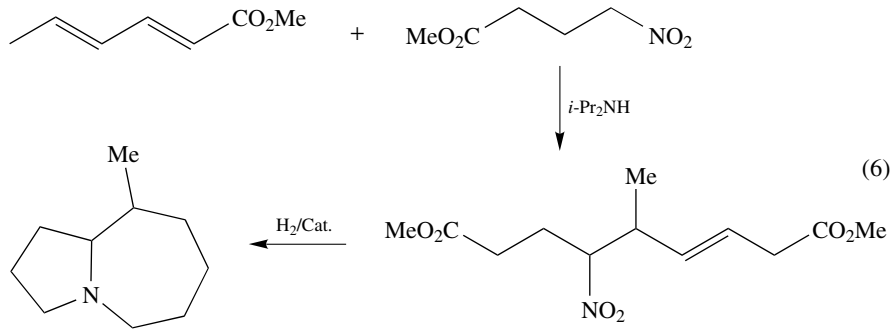
(4)

Michael additions to acceptor-substituted dienes are often followed by (spontaneous or induced) cyclizations. This was already noted by Vorländer and Groebel[4] who obtained a substituted 1,3-cyclohexanedione by treatment of 6-phenyl-3,5-hexadien-2-one with diethyl malonate (equation 5). Obviously, the 1,4-addition product which is formed initially then undergoes cyclization, ester hydrolysis and decarboxylation. Similarly, reaction of methyl sorbate with methyl 4-nitrobutyrate gave the 1,6-adduct which was reductively cyclized to 6-methyl-1-azabicyclo[5.3.0]decane[18] (equation 6).

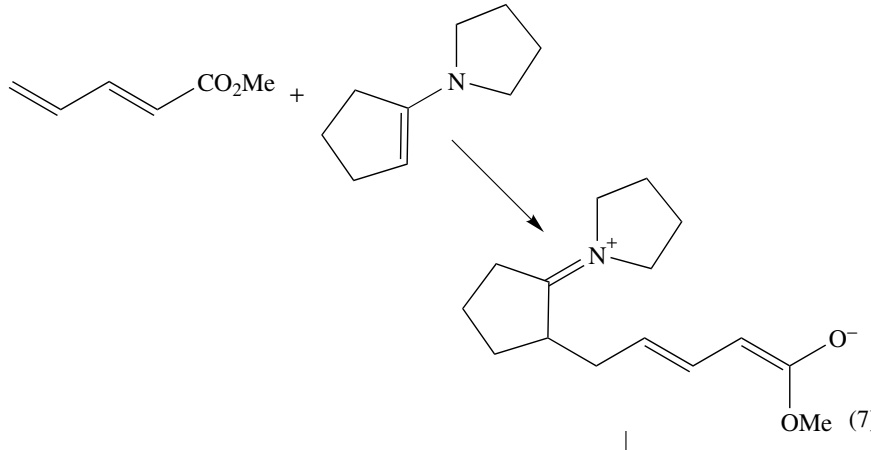
(5)

In 1965, Danishefsky and Cunningham[19] and Berchtold and coworkers[20] simultaneously reported 1,6-addition reactions of enanimes to conjugated dienoates; the zwitterionic intermediates cyclize spontaneously and eliminate an amine to furnish 1,3-cyclohexadienes

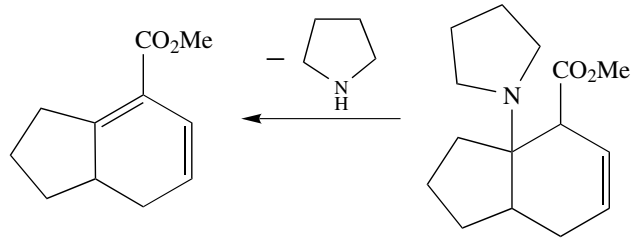
which can be oxidized easily to benzenes (equation 7). A similar approach was used by Heuschmann[21] who employed 1,3-dimethyl-2-methylenimidazolidine as nucleophile. Analogously, quinolines and isoquinolines were obtained when piperidone enamines were used for the 1,6-addition[22] (equation 8).



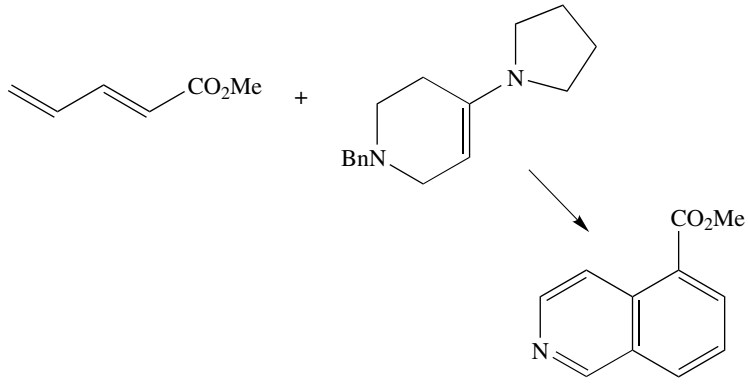
(6)



(7)

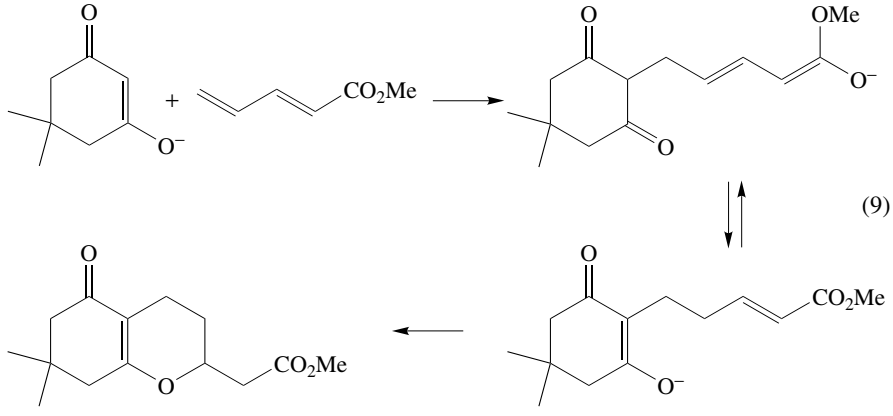


91%



(8)

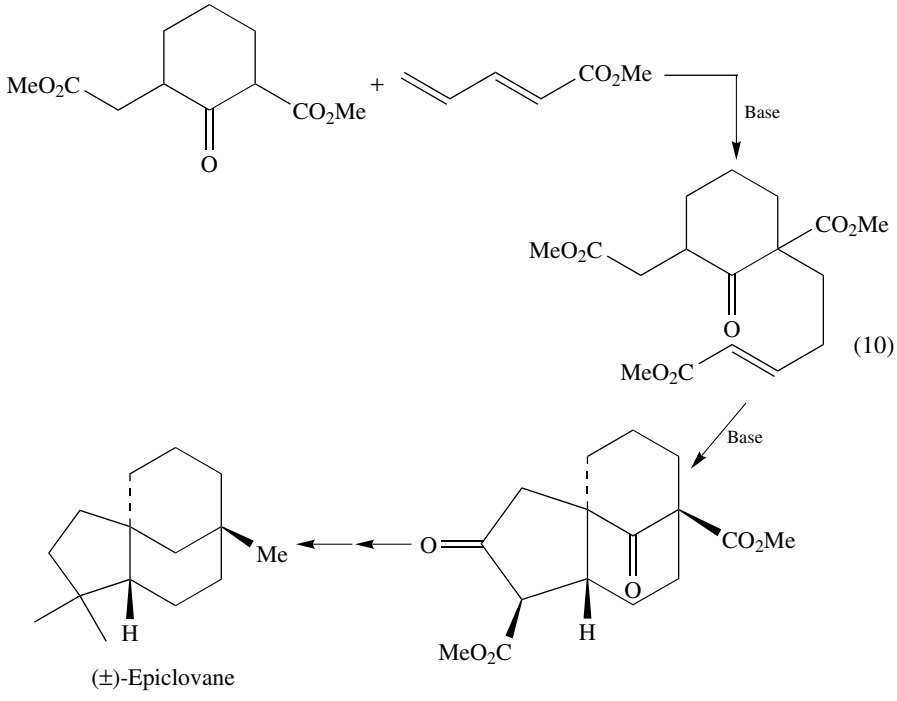
In a very similar manner, tandem 1,6- and 1,4-additions of β-dicarbonyl compounds to methyl 2,4-pentadienoate were utilized by Danishefsky and coworkers[23–25] for the formation of several bi- and tricyclic ring systems. For example, reaction of the enolate of dimedone with this ester gave the expected 1,6-addition product; protonation/deprotonation set the stage for a subsequent intramolecular 1,4-addition (equation 9)[23]. Likewise, a ketodiester was used to transform the pentadienoate in a one-pot procedure by consecutive 1,6- and 1,4-additions into a richly functionalized tricyclic product which was then converted into the natural product (±)-epiclovane[25] (equation 10). According to this principle, Irie and coworkers[26] obtained several decalin-2,7-diones by treatment of 2-methylen-2-cyclohexenones with dimethyl 3-oxoglutarate.



(9)

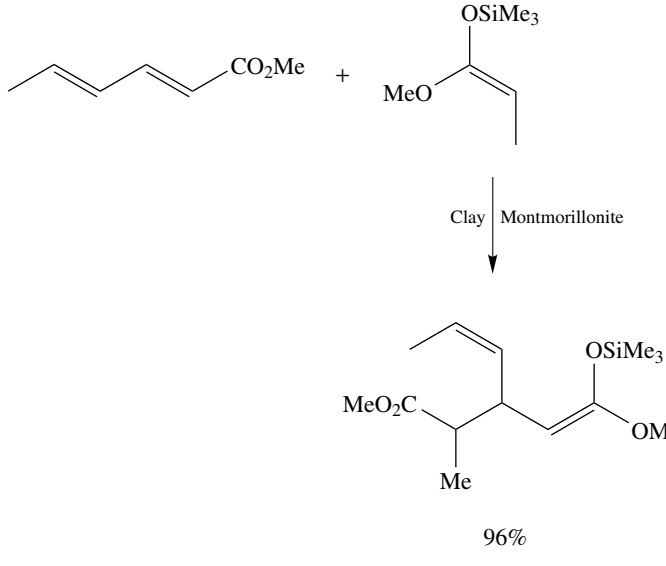
In contrast to these transformations, Michael additions of simple enolates to acceptor-substituted dienes often yield mixtures of 1,4- and 1,6-addition products[27–30]. For example, a 70 : 30 mixture of 1,4- and 1,6-adducts was isolated from the reaction of the lithium enolate of methyl propionate with methyl sorbate[30]. This problem can be solved by using the corresponding silyl ketene acetal in the presence of clay montmorillonite as acidic promoter: under these conditions, almost exclusive formation of the 1,4-addition product (*syn/anti* mixture) was observed (equation 11)[30]. Highly regioselective 1,4-additions

to activated dienes were also reported with allyltrimethylsilane/*n*-Bu_4NF[31] and tin(II) dienolates[32] as nucleophiles.



(10)

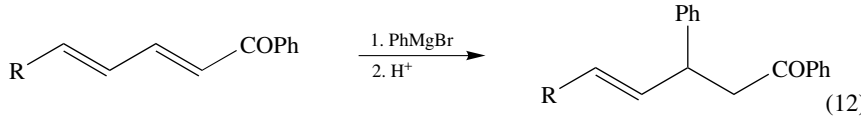
(±)-Epiclovane



(11)

96%

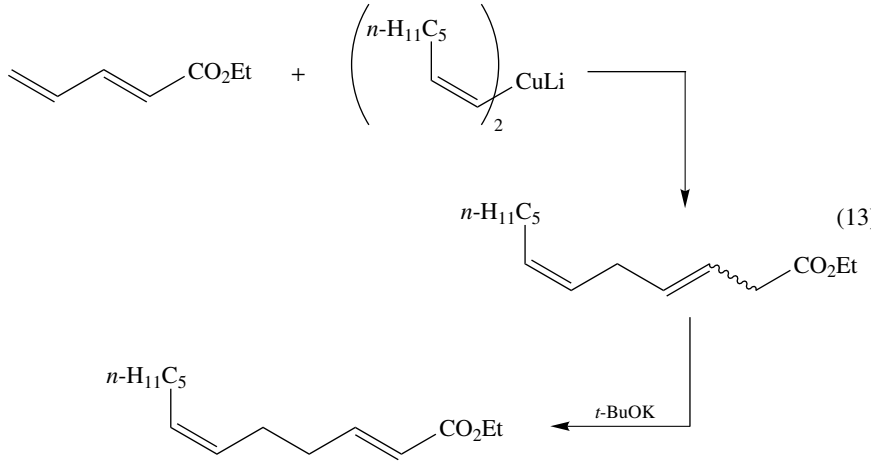
Simple organometallic reagents have to be used as nucleophiles in order to transfer unfunctionalized groups to a Michael acceptor. Already in 1926, Kohler and Butler[7] demonstrated that regioselective Michael additions of Grignard reagents to acceptor-substituted dienes are feasible. Treatment of 1-phenyl- and 1,5-diphenyl-2,4-pentadienone with phenylmagnesium bromide gave rise to the formation of the 1,4-addition products (equation 12). Likewise, organolithium compounds were found to add with high 1,4-regioselectivity to dienoic thioamides[33] and acylylides[34]. In contrast to this, 1-naphthyl-[35] and 2-styryloxazolines[36] react with Grignard and organolithium reagents under 1,6-addition. Analogously, 1,6-addition products were obtained from simple aromatic carbonyl compounds, such as benzaldehyde and benzophenone, and organolithium reagents when the carbonyl group was shielded by complexation with the sterically demanding Lewis acid aluminum tris(2,6-diphenylphenoxide)[37].



(12)

R = H, Ph

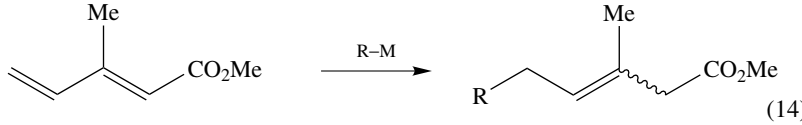
Subsequent studies by many different groups have shown that organocopper compounds are the reagents of choice for these transformations[38]. The major advantage of these nucleophiles is that the regioselectivity of the Michael addition can be controlled by 'tuning' of the reagent (see below); this feature distinguishes organocopper reagents from all other nucleophiles which can be used in additions to polyunsaturated substrates. The first example was reported by Näf and coworkers[39] who used lithium di-(*Z*)-1-heptenylcuprate in a Michael addition to ethyl 2,4-pentadienoate. The reaction proceeded with high regioselectivity to furnish a 1 : 1 mixture of ethyl (3*E*,6*Z*)- and (3*Z*,6*Z*)-3,6-dodecadienoate which was converted into the Bartlett pear constituent ethyl (2*E*,6*Z*)-2,6-dodecadienoate by basic isomerization (equation 13).



(13)

Subsequently, Corey and coworkers[40–42] described nucleophilic addition reactions of organocopper reagents and organocuprates to several acceptor-substituted dienes. The

choice of the reagent did not affect the regioselectivity, since exclusive 1,6-addition took place in all cases examined. However, organocopper reagents RCu reacted also stereoselectively to give the addition products with (*E*)-configuration whereas Gilman cuprates R_2CuLi yielded 1 : 1 mixtures of the *E*/*Z* isomers (equation 14)[41]. Similarly, propargylcopper reagents can be added regio- and stereoselectively to 2,4-dienoates[43].

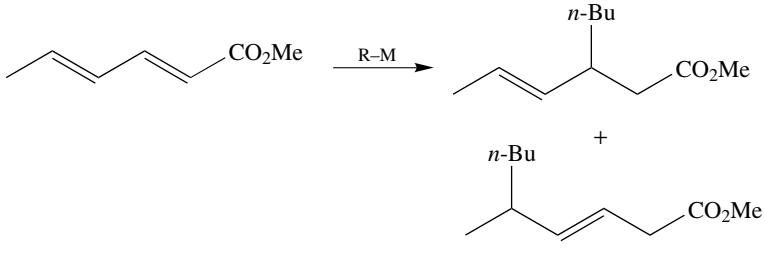


(14)

R-M = *n*-BuCu or $H_2C{=}CHCu$: *E* : *Z* = >95 : <5

n-Bu_2CuLi or $(H_2C{=}CH)_2CuLi$: *E* : *Z* ≈ 50 : 50

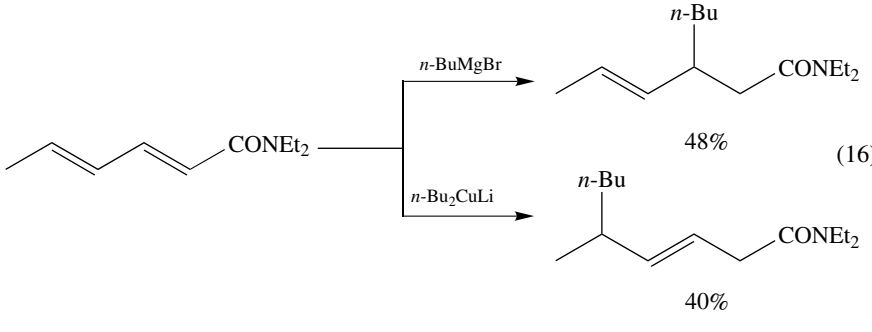
Whereas these and other reports[44–48] did not indicate the possibility of 1,4-cuprate additions to activated dienes, Yamamoto and coworkers[49,50] showed in their seminal contributions that this is indeed feasible: while the reaction of methyl sorbate with the Gilman cuprate *n*-Bu_2CuLi provided exclusively the 1,6-addition product, the reagent formed from butylcopper and the Lewis acid boron trifluoride led to the 1,4-adduct as the major product (equation 15). The synthetically very useful organocopper compounds RCu • BF_3[50] have been named Yamamoto reagents. In certain cases, the regioselectivity of these transformations can also be controlled by using different nucleophiles[31,51], for example with *N*,*N*-diethylsorbic amide as substrate (equation 16): whereas Gilman cuprates again reacted under 1,6-addition, the 1,4-adducts were obtained with Grignard reagents[51].



(15)

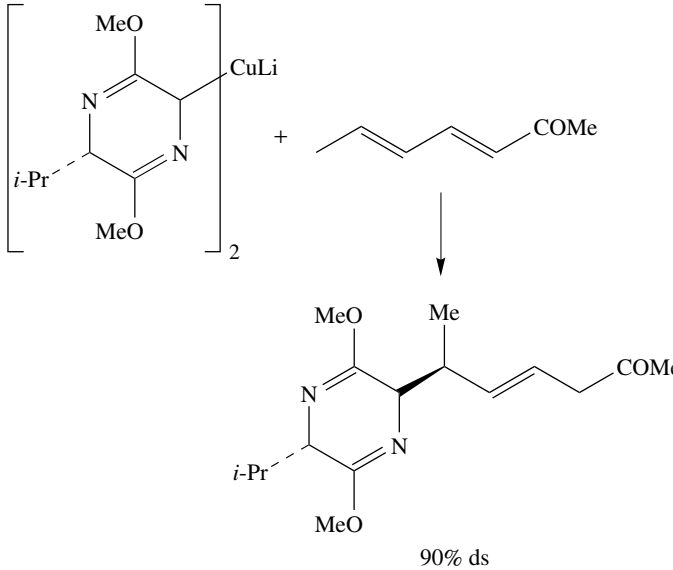
R-M = *n*-BuCu • BF_3: 93 : 7

n-Bu_2CuLi: <1 : >99



(16)

Nucleophilic 1,4- and 1,6-additions of cuprates and other organometallic reagents to acceptor-substituted dienes have been utilized extensively in target-oriented stereoselective synthesis[52–61]. Schöllkopf and coworkers[55] reported the diastereoselective 1,6-addition of a bislactim ether-derived cuprate to 3,5-heptadien-2-one (90% ds; equation 17). The corresponding reactions of dienoates were conducted with the lithiated bislactim ether and proceeded with diastereoselectivities of >99% ds (equation 18)[56]; the adducts could be converted easily into diastereo- and enantiomerically pure amino acid derivatives.

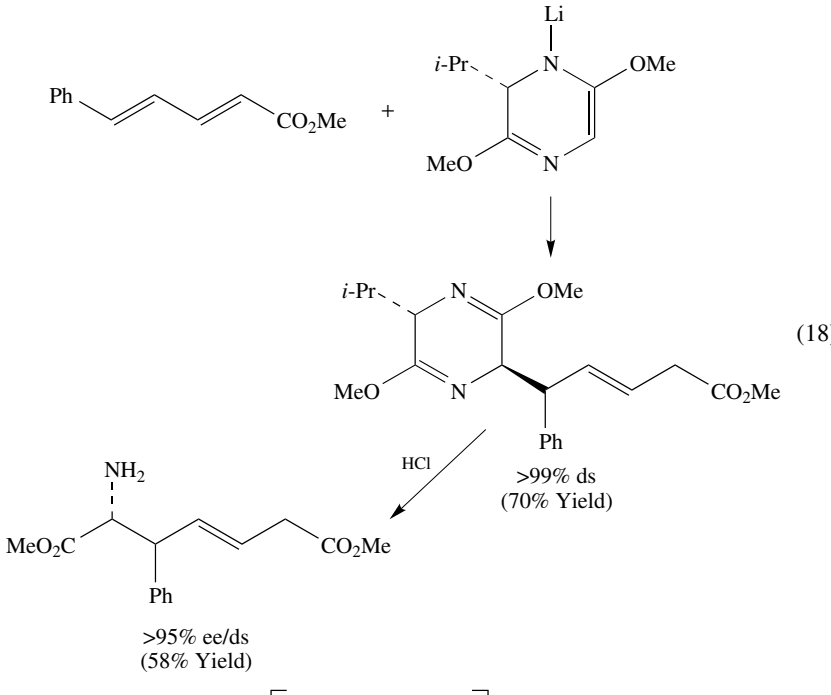


(17)

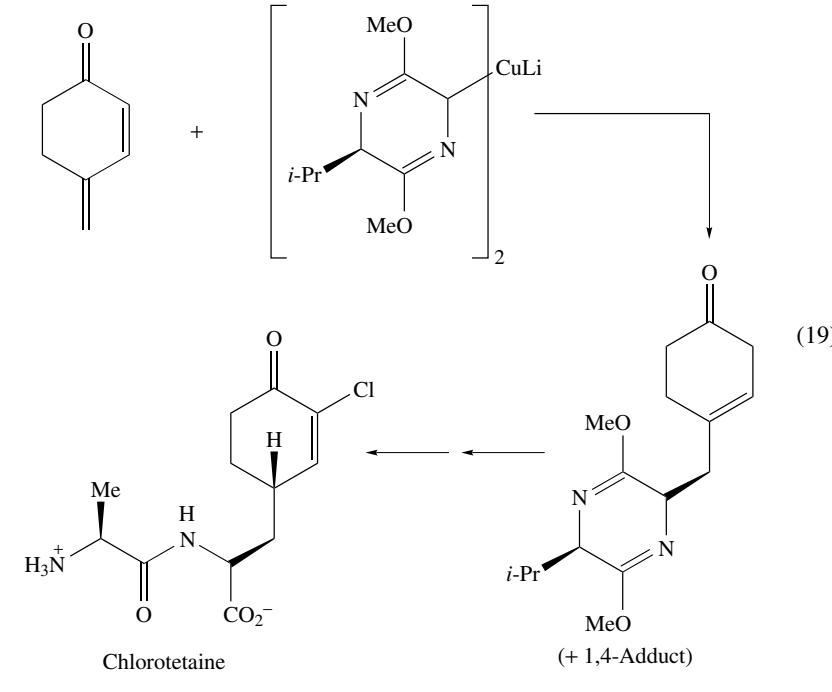
90% ds

The Schöllkopf bislactim ether cuprate was also used in the first total synthesis of the antimycotic dipeptide chlorotetaine (equation 19)[58]. In this case, however, the nucleophilic addition to 4-methylene-2-cyclohexenone did not proceed regioselectively since a 63 : 37 mixture of the 1,6- and 1,4-adduct was obtained. The 1,6-addition product was converted via several steps into diastereo- and enantioselectively pure chlorotetaine.

Most applications of stereoselective Michael additions of organometallic reagents to activated dienes are directed towards the synthesis of steroid hormones. Particularly interesting are estradiol derivatives bearing an alkyl chain in the 7α-position since these steroids were found to bind with high affinity and specificity to estrogen receptors; i.e. they are effective antiestrogenic agents[62] and may therefore be useful for the treatment of mammary tumors (breast cancer)[63]. The obvious way to introduce a group in the 7-position of a steroid backbone is a nucleophilic 1,6-addition to an acceptor-substituted doubly unsaturated $\Delta^{4,6}$-derivative, and many organometallic reagents (in particular organocopper compounds) do indeed react with the desired regioselectivity[63–88]. Here, the major challenge is the control of the diastereoselectivity of the Michael addition since the 7β-isomers are less effective enzyme inhibitors[63]. Addition reactions to tetrahydro-3*H*-naphthalen-2-ones, which can be considered as model substrates for $\Delta^{4,6}$-steroids, were examined by several groups[64–70]. Already in 1958, Yanagita and coworkers[64] observed a *trans*-selective 1,6-addition reaction of diethyl malonate to the 1,4a-dimethyl-substituted naphthalenone. In a series of papers, Marshall and coworkers[65–68] reported copper-catalyzed Michael additions to various bicyclic dienones; for example, treatment of

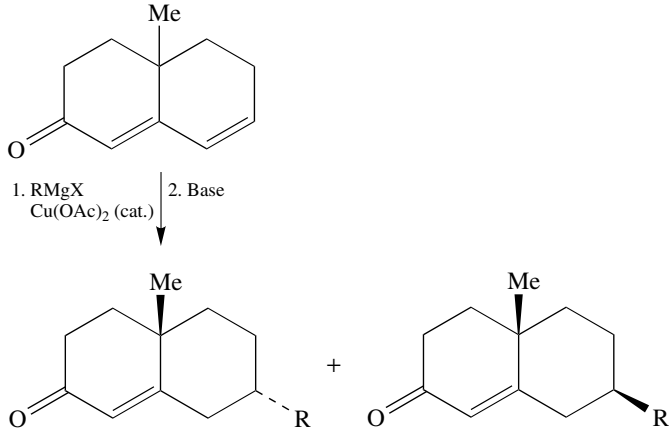

Ph
CO2Me
+
Li
i-Pr
N
OMe
MeO
N
i-Pr
N
OMe
MeO
N
CO2Me
Ph
HCl
>99% ds
(70% Yield)
NH2
MeO2C
CO2Me
Ph
>95% ee/ds
(58% Yield)

(18)


O
+
MeO
CuLi
N
N
i-Pr
MeO
2
O
MeO
N
N
i-Pr
MeO
(+ 1,4-Adduct)
O
Cl
H
Me
H
N
H3N+
O
CO2−
Chlorotetaine

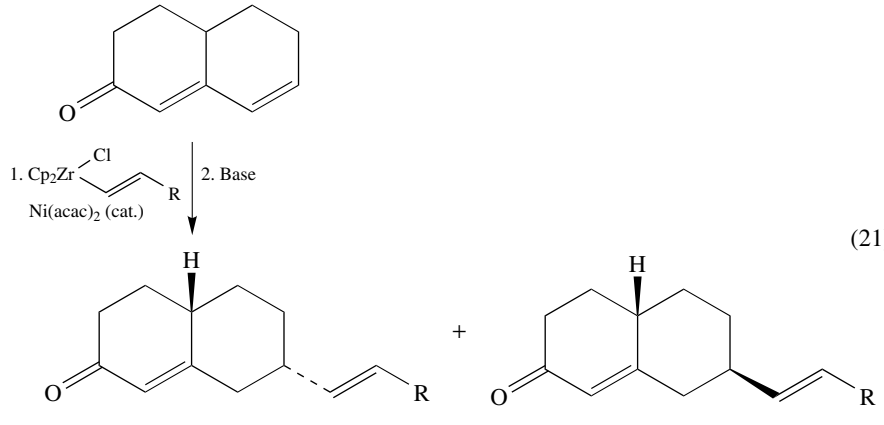
(19)

4a-methyl-4,4a,5,6-tetrahydro-3*H*-naphthalen-2-one with Grignard reagents in the presence of $Cu(OAc)_2$ furnished mixtures of 1,2- and 1,6-addition products. The 1,6-adducts consisted mainly of the *trans* isomer, and the diastereoselectivity increased with increasing steric bulk of the Grignard reagent (equation 20)[65]. In contrast to this, diastereoselectivities close to 1 : 1 were reported in the Cu(II)-catalyzed 1,6-addition of *n*-hexylmagnesium bromide[65] and the Ni(II)-catalyzed 1,6-addition of alkenylzirconium reagents to the unsubstituted naphthalenone (equation 21)[69]. The regioselectivity of cuprate additions to bicyclic dienones depends very strongly on the substitution pattern of the Michael acceptor[66].



(20)

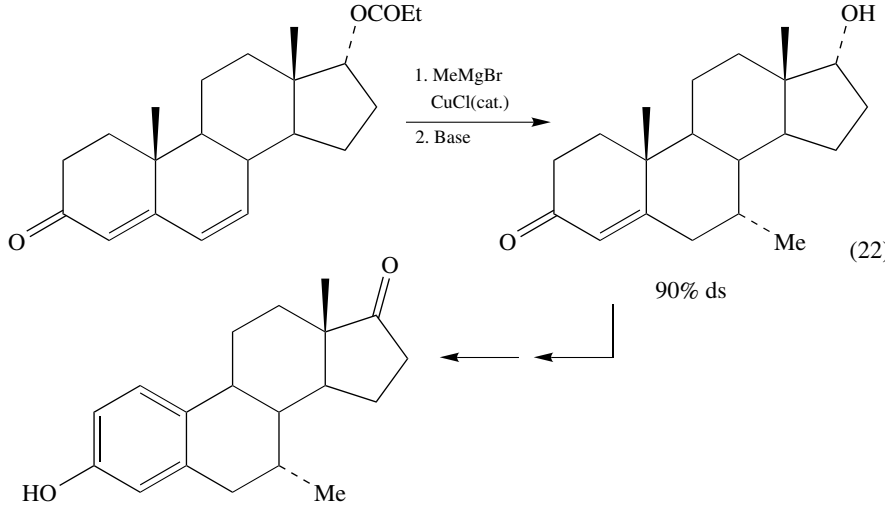
RMgX =		
MeMgI:	93	: 7
EtMgBr:	98	: 2
i-PrMgBr:	>99	: <1
t-BuMgCl:	>99	: <1

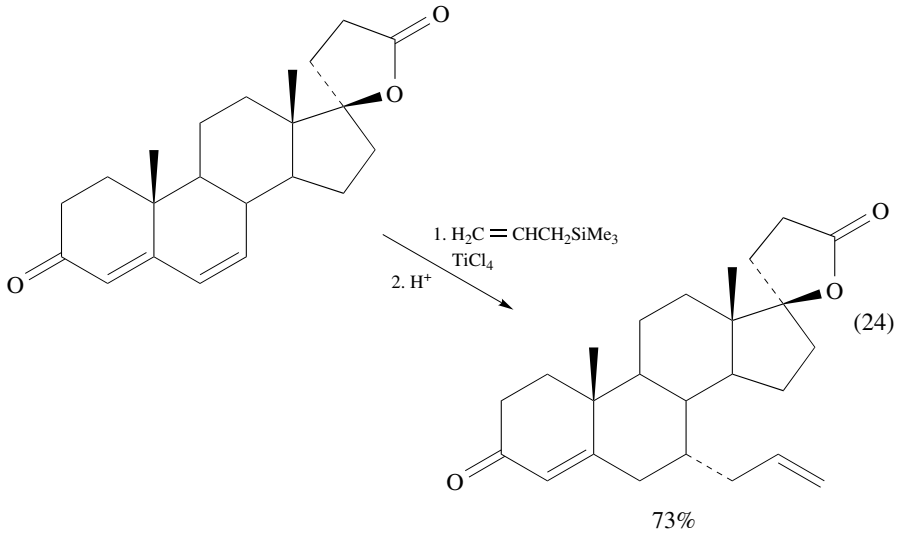


(21)

R =		
n-Bu:	59	: 41
t-Bu:	46	: 54

Early investigations of nucleophilic additions of organometallic reagents to $\Delta^{4,6}$-steroids were actually carried out before the discovery of the antiestrogenic behavior of the 7α -substituted steroids[71−78]. The interest in these transformations was prompted by the desire to prepare new, unnatural corticosteroids with possible interesting pharmacological activities. Campbell and Babcock[71] found in 1959 that the diastereoselectivity of the copper-promoted 1,6-addition of MeMgBr to $\Delta^{4,6}$-steroids depends strongly on the substitution pattern of the substrate: whereas 17β-hydroxy-17α-methyl-4,6-androstadien-3-one provided mainly the 7α-adduct, a mixture of both epimers was obtained from the substrate with an additional 11β-hydroxy group. The preference for the addition of methylmagnesium halides from the α-side was also observed by other groups[72−76]; for example, Wieland and Auner[75] reported an α -selectivity of 90% in the copper-catalyzed 1,6-addition of MeMgBr to 17β-propionyloxy-4,6-androstadien-3-one. The product was converted over several steps into 7α-methylestrone (equation 22). Interestingly, cross-conjugated $\Delta^{1,4,6}$-steroids also undergo 1,6-addition under these conditions[73−75]; here, attack of the nucleophile at C-1 seems to be disfavored because of repulsive steric interactions with the adjacent angular methyl group. Other possibilities to introduce a carbon nucleophile regio- and stereoselectively in the 7α-position of $\Delta^{4,6}$-steroids is the hydrocyanation with Et_2AlCN (equation 23)[77−80] and the Sakurai reaction with allyltrimethylsilane/$TiCl_4$ (equation 24)[81,82].





(24)

73%

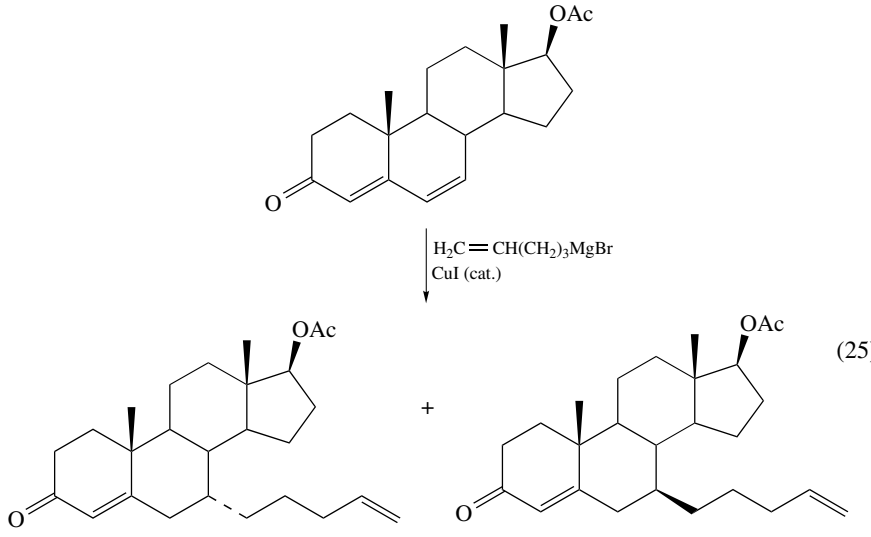
In contrast to these transformations, the introduction of longer alkyl chains by copper-promoted 1,6-addition reactions to $\Delta^{4,6}$-steroids normally proceeds with unsatisfactory $\alpha : \beta$ ratios[63,83–88]. In some cases, however, the diastereoselectivity could be improved by 'fine tuning' of the reaction conditions; for example, the ratio of α- and β-epimeric products in the copper-catalyzed 1,6-addition of 4-pentenylmagnesium bromide to 17β-acetoxy-4,6-androstadien-3-one rose from 58 : 42 to 82 : 18 upon variation of the number of equivalents of the nucleophile and the solvent composition (equation 25)[88].

B. H-, N-, O-, P-, Se- and S-Nucleophiles

Besides carbon nucleophiles, many other nucleophilic reagents can be added regioselectively to acceptor-substituted dienes. The simplest nucleophile is a hydride ion, its synthetic equivalent being a complex metal hydride or another reducing agent. In 1982, Camps ans coworkers[89] examined the reaction of sorbic acid with sodium dithionite; in this case, 1,6-reduction took place mainly to furnish 3-hexenoic acid as a mixture of E/Z isomers (equation 26). Likewise, reduction of methyl sorbate and other 2,4-dienoates under these conditions proceeded with high regioselectivities and good chemical yields to furnish the 1,6-reduction products (again as E/Z-mixtures). The reaction probably involves a nucleophilic attack of the sulfoxylate anion, followed by protonation of the resulting carbanionic species[89–91].

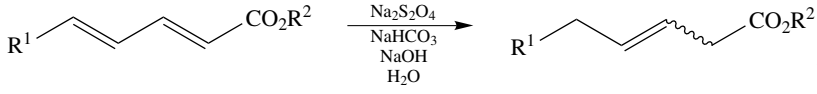
Complex hydrides have been used rather frequently for the conjugate reduction of activated dienes[92–95]. Just and coworkers[92] found that the reduction of α,β-unsaturated ketene *S*,*S*-acetals with lithium triethylborohydride provided mixtures of 1,4- and 1,6-reduction products which were transformed into enals by treatment with mercuric salts (equation 27). Likewise, tetrahydro-3*H*-naphthalen-2-ones can be reduced with L-Selectride® to the 1,6-reduction products[93–95]; this reaction has been utilized in the stereoselective synthesis of several terpenes, e.g. of (*R*)-(−)-ligularenolide (equation 28)[95]. Other methods for the conjugate reduction of acceptor-substituted dienes involve the use of methylcopper/diisobutylaluminum hydride[96] and of the Hantzsch ester

(3,5-diethoxycarbonyl-2,6-dimethyl-1,4-dihydropyridine) in the presence of silica gel[97] as nucleophiles.



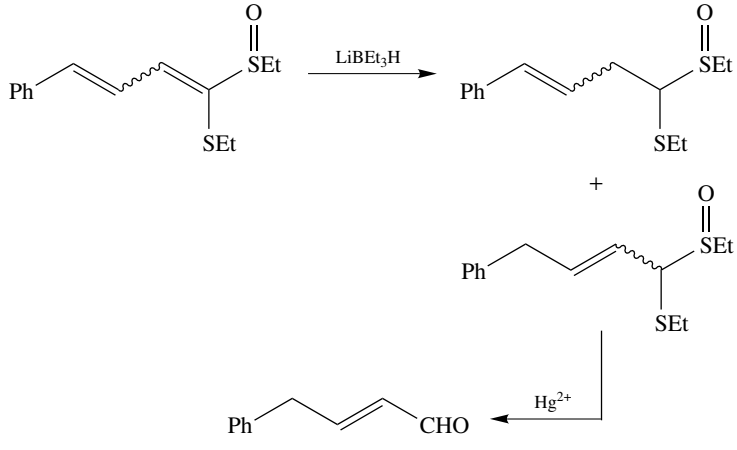
(25)

Eq. Grignard	Ratio THF / diethyl ether	α : β
12	1 : 9	58 : 42
12	1 : 4	60 : 40
12	1 : 1	78 : 22
4	1 : 1	82 : 18

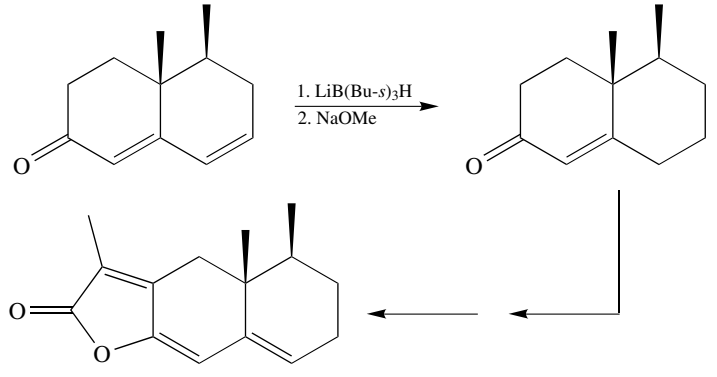


(26)

R^1 = Me, *n*-C_5H_{11}, *n*-C_7H_{15}; R^2 = H, Me, Et



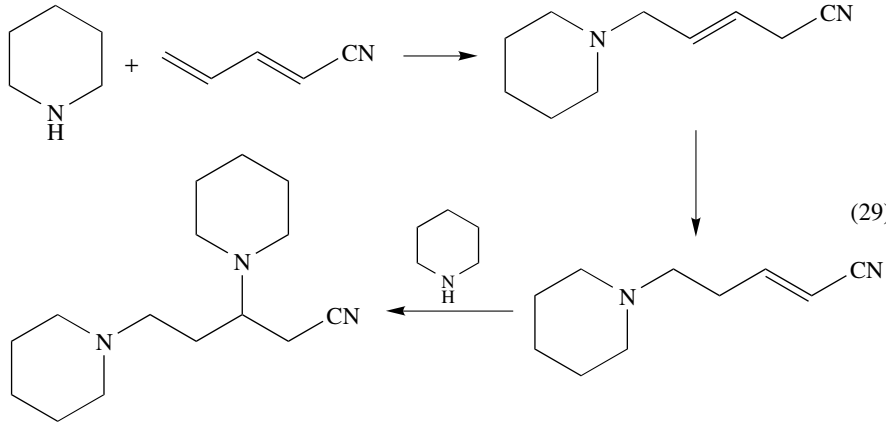
(27)



(28)

(*R*)-(−)-Ligularenolide

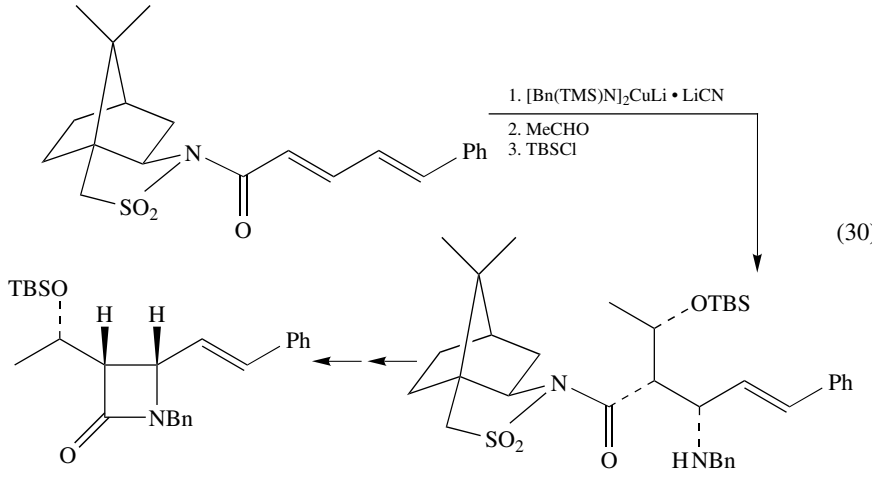
Nucleophilic additions of amines to acceptor-substituted dienes were examined as early as 1950. Frankel and coworkers[98] found that the reaction of 2,4-pentadienenitrile with various secondary amines proceeded regioselectively to furnish the 1,6-addition products (equation 29). In some cases, these could converted into the 2,4-diamino-substituted pentanenitriles by isomerization and 1,4-addition of a second molecule of amine. Analogous results were reported by other groups[17,99,100] and extended to hydrazine as nucleophile[101] and to vinylcyclobutenones[48] and dienoates[102−104] as Michael acceptors.



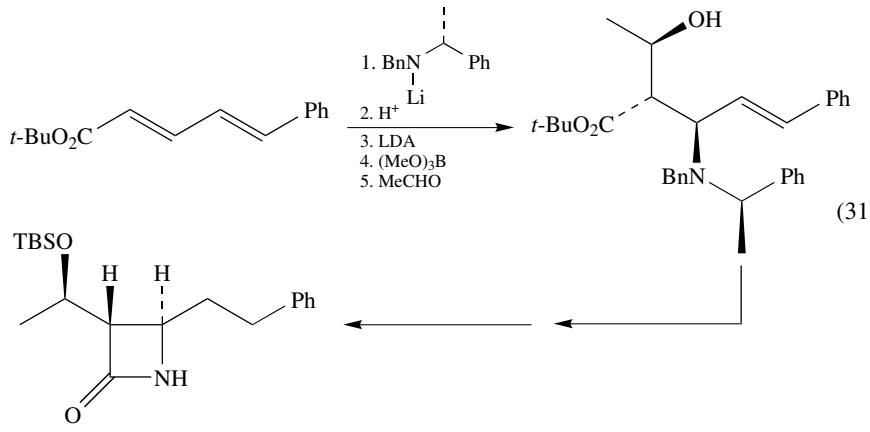
(29)

Recently, metalated amines were utilized in stereoselective addition reactions to activated dienes. In a series of papers, Yamamoto and coworkers[105−107] described new stereoselective syntheses of β-lactams utilizing 1,4-addition reactions of lithium amides and amidocuprates to 2,4-dienoic acid derivatives. For example, regio- and diastereoselective addition of the amidocuprate $[Bn(TMS)N]_2CuLi \bullet LiCN$ to a diene bearing a bornanesultam auxiliary, followed by trapping of the enolate with acetaldehyde and protection, provided the product with three contiguous stereogenic centers which could then be cyclized to the enantio- and diastereomerically pure β-lactam (equation 30)[105,107].

Alternatively, a chiral lithium amide was added regio- and diastereoselectively to an achiral 2,4-dienoate, and the 1,4-addition product formed could again be converted into the desired, stereochemically pure β-lactam (equation 31)[106].



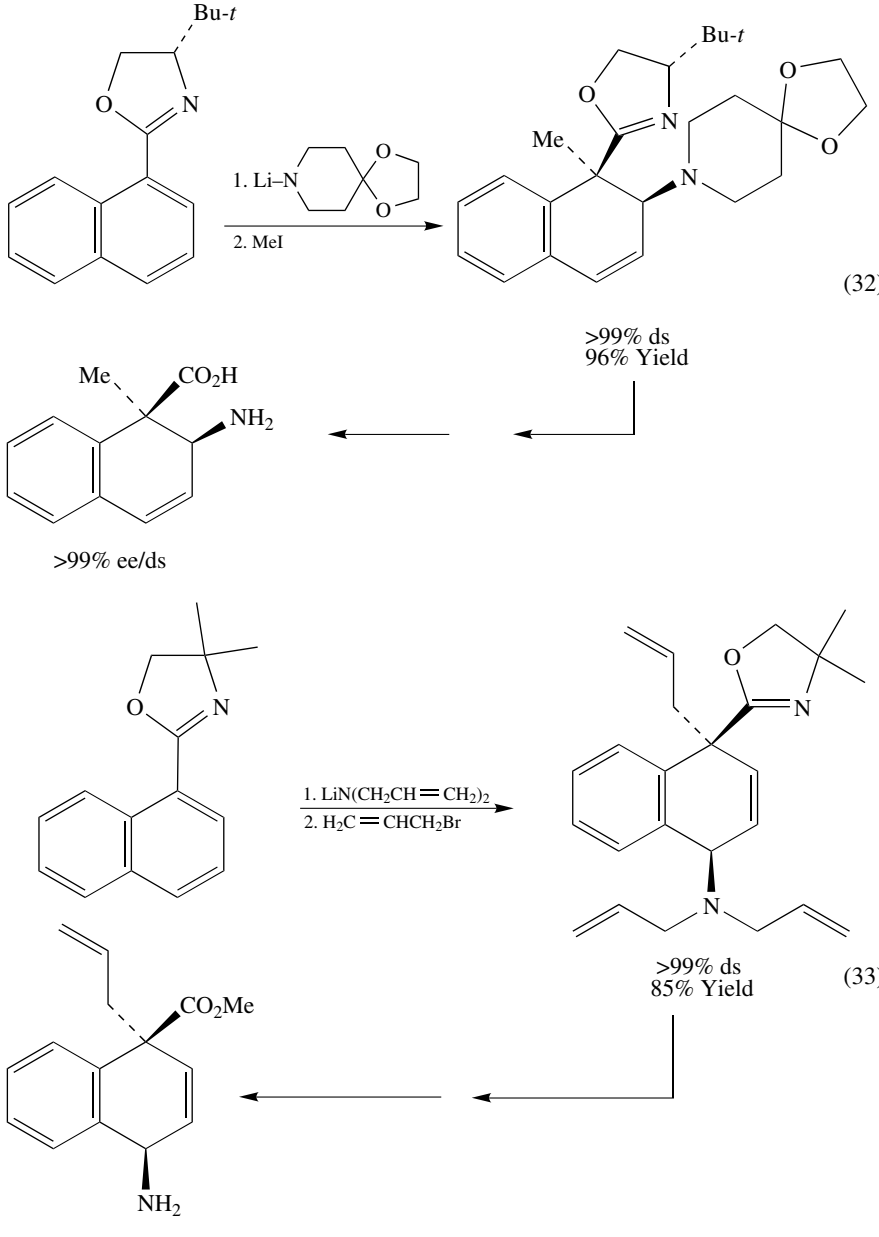
(30)



(31)

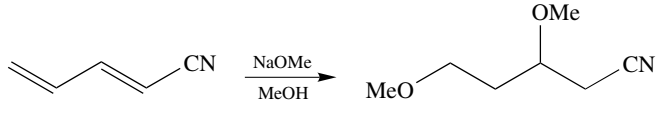
Diastereoselective 1,4- and 1,6-addition reactions of lithium amides to chiral naphthyloxazolines were used by Shimano and Meyers[108–110] for the synthesis of novel amino acids. For example, treatment of (*S*)-2-(1-naphthyl)-4-*t*-butyloxazoline with lithiated 1,4-dioxa-8-azaspiro[4.5]decane and iodomethane provided the diastereomerically pure 1,4-addition product with excellent yield; cleavage of the heterocyclic rings then gave the desired β-amino acid (>99% ee/ds; equation 32)[108,109]. In contrast to this, most acyclic lithium amides reacted with these oxazolines under 1,6-addition; the products were transformed smoothly to δ-amino acid derivatives (equation 33)[110].

The number of reports about addition reactions of oxygen nucleophiles to acceptor-substituted dienes is rather limited. Coffman[111] and Kurtz[17] examined the reaction of 2,4-pentadienenitrile with sodium methoxide and isolated the 2 : 1 adduct 3,5-dimethoxypentanenitrile formed by successive 1,6- and 1,4-additions (equation 34). Analogous treatment



of 4-chloro-3,5-hexadien-2-one resulted in the incorporation of three methoxy groups by 1,4-addition/elimination, 1,6-addition/isomerization and another 1,4-addition reaction (equation 35)[112,113]. Recently, Neuenschwander and coworkers[114] reported nucleophilic

1,6-additions of phenolate and other alcoholates to 2-aminopyrylium salts. An acid-catalyzed intramolecular 1,6-addition served for the stereoselective construction of a key intermediate in a synthetic approach to the natural quassinoid bruceantin (equation 36)[115].



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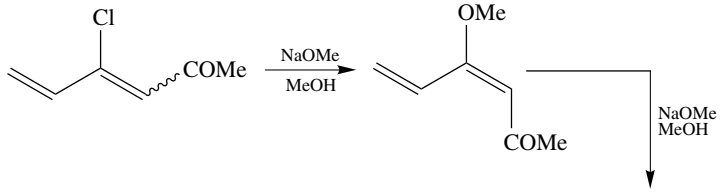

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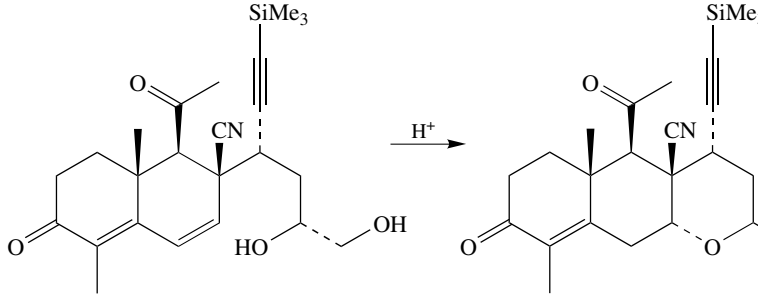
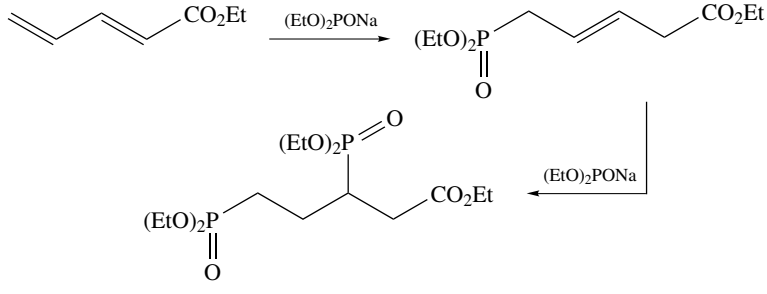
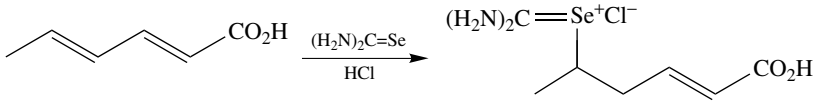


(36)

Like oxygen nucleophiles, phosphorus and selenium nucleophiles have been employed rarely in Michael additions to activated dienes. The reaction of phosphites with acceptor-substituted dienes was studied by several Russian groups[116–118]; again, 1,6-adducts and 2 : 1 addition products were formed (equation 37). The acid-catalyzed reaction of selenourea with sorbic acid was also reported to provide a 1,6-addition product[119] (equation 38).

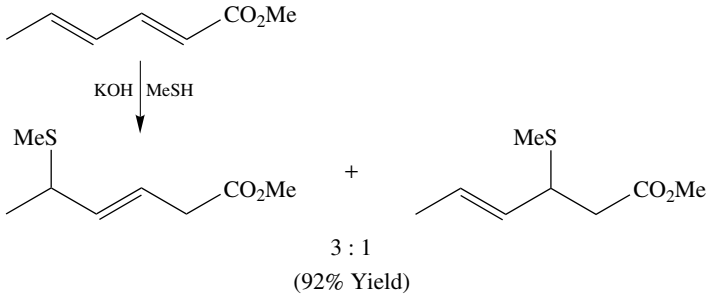


(37)



(38)

By far most of the reports on addition reactions of hetero-nucleophiles to activated dienes deal with sulfur-nucleophiles[17,48,80,120–137], in particular in the synthesis of 7β-sulfur-substituted steroids which, like their carbon-substituted counterparts (Section II.A), are of interest because of their ability to inhibit the biosynthesis of estrogens[80,129–137]. Early investigations[17,120–122] concentrated on simple acyclic Michael acceptors like methyl sorbate and 2,4-pentadienenitrile. Bravo and coworkers[120] observed the formation of a 3 : 1 mixture of the 1,6- and 1,4-adduct in the reaction of methyl sorbate with methanethiol in basic medium (equation 39). In contrast to this, 2,4-pentadienenitrile adds various thiols regioselectively at C-5, i.e. in a 1,6-fashion (equation 40)[17,121,122], and the same is true for reactions of this substrate with hydrogen sulfide (equation 41), sodium bisulfite and ethyl thioglycolate[17].



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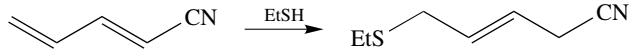

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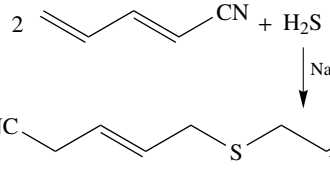
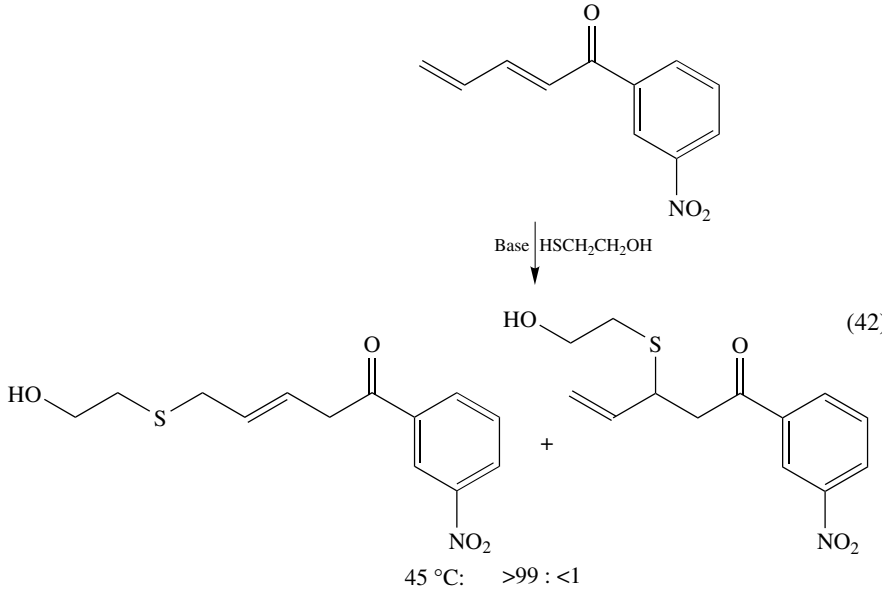


(41)

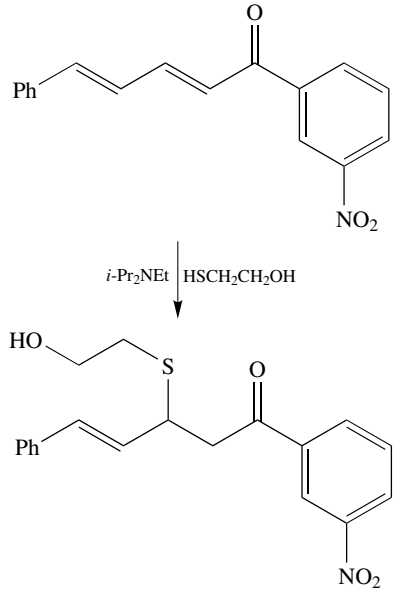
The regioselectivity of Michael additions of thiolates to 2,4-dienones can be altered drastically by variation of the reaction conditions and addition of Lewis acids to the reaction mixture. Lawton and coworkers examined the reaction of 2-mercaptoethanol with 1-(3-nitrophenyl)-2,4-pentadien-1-one and observed a high regioselectivity in favor of the 1,6-addition product at 45 °C (equation 42)[123,124]. Lowering of the reaction temperature caused an increase in the amount of 1,4-adduct, and at −40 °C, a product ratio of 40 : 60 was found. These events suggest that kinetic control favors the 1,4-addition product whereas the 1,6-adduct is thermodynamically more stable. If, however, the reaction was carried out with a complex of the dienone and titanium tetrachloride, only the 1,4-adduct was isolated after hydrolytic workup[123]. Obviously, this product is trapped as a metal chelate which prevents formation of the 1,6-adduct by retro-Michael/Michael addition. In the absence of the chelating Lewis acid, the 1,4-addition product can indeed be converted

into the 1,6-adduct by treatment with diisopropylethylamine. Introduction of a sterically demanding substituent, e.g. a phenyl group, at C-5 of the dienone, prevents the formation of the 1,6-addition product even in the absence of a Lewis acid (equation 43)[123].



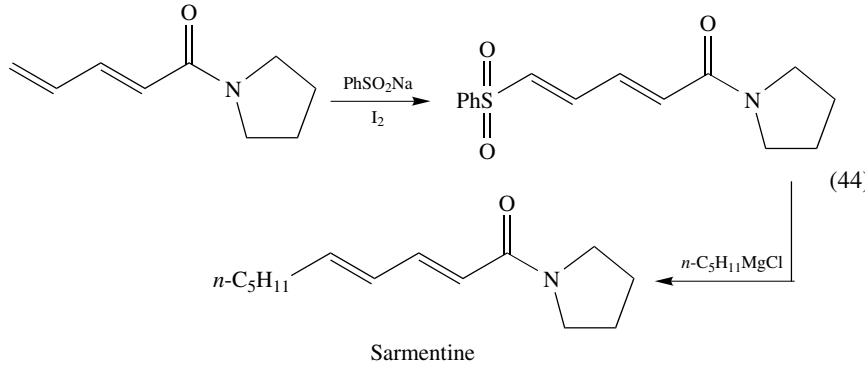
(42)

45 °C: >99 : <1
–40 °C: 40 : 60
$TiCl_4$, –40 °C: <1 : >99



(43)

Regioselective 1,6-addition reactions of sulfur nucleophiles to activated dienes were utilized by several groups for the synthesis of biologically relevant target molecules[125–128]. Nájera and coworkers[125] prepared several 5-tosyl-2,4-pentadienamides by 1,6-addition of sodium 4-toluenesulfinate to 2,4-pentadienamides, iodination and spontaneous dehydroiodination (equation 44). These transformations took place with complete control of the configuration of the olefinic double bonds. The products underwent 1,6-addition/elimination reactions with carbon and sulfur nucleophiles; with benzylthiolate, a double 1,6-addition could be realized. Treatment of the pyrrolidinyl derivative with pentylmagnesium chloride led directly to the natural product sarmentine, again with retention of the configuration of the double bonds. The 1,6-addition products of L-cysteine and various derivatives of this amino acid to trifluoroethyl 2-propyl-2,4-pentadienoate were prepared and identified as possible metabolites of the anticonvulsant agent valproic acid (2-propylpentanoic acid; equation 45)[126].



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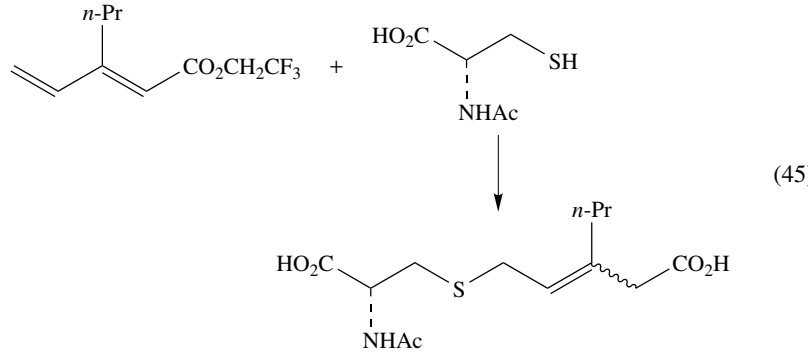
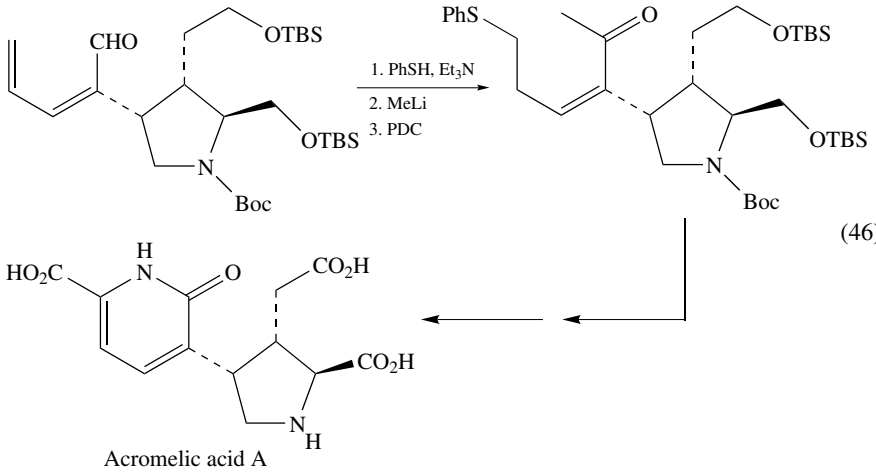


(45)

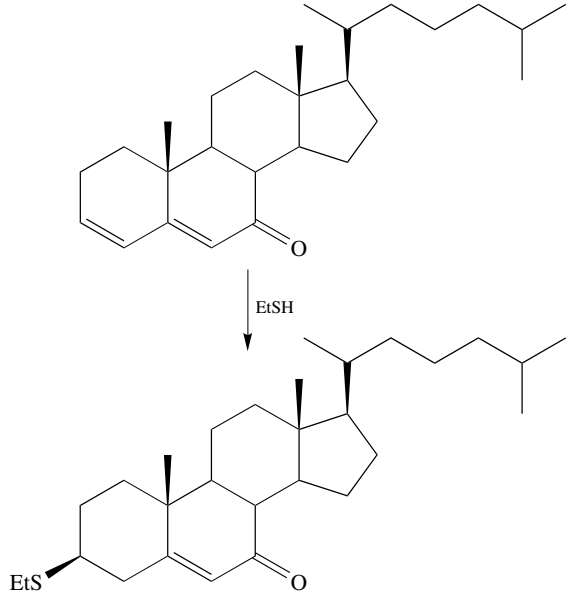
Structurally rather complicated target molecules can be synthesized with the aid of thiolate 1,6-addition reactions to acceptor-substituted dienes as well. For example, a richly functionalized proline derivative with a 2,4-pentadienal side chain was converted into the corresponding 6-phenylthio-3-hexen-2-one derivative by 1,6-addition of phenylthiolate, treatment of the adduct with methyl lithium and oxidation (equation 46)[127]. The product was transformed into acromelic acid A, the toxic principle of *clitocybe acromelalga ichimura*. Similarly, the 1,6-addition reaction of cesium triphenylmethylthiolate to methyl 2,4-pentadienoate served for the construction of the disulfide bridge of the macrobicyclic antitumor depsipeptide FR-901,228[128].



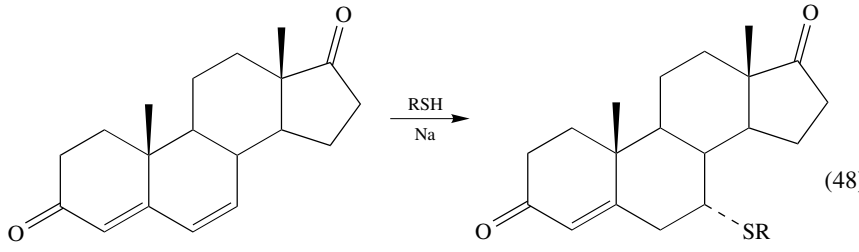
(46)

Acromelic acid A

The first 1,6-addition reactions of thiolates to steroid dienones were examined well before the discovery of the antiestrogenic properties of 7α-substituted steroids. Ralls and coworkers[129] and Djerassi and coworkers[130] studied thiol additions to $\Delta^{3,5}$-steroids; for example, the reaction of 3,5-cholestadien-7-one with ethanethiol was reported to proceed with high 1,6-regioselectivity and β-stereoselectivity (equation 47)[129]. In a series of papers, Brueggemeier and coworkers[131–137] described the synthesis and biochemical evaluation of numerous 7α-sulfur-substituted steroids which were prepared by Michael addition to steroid dienones. Thus, 4,6-androsta-3,17-dienone was treated with various

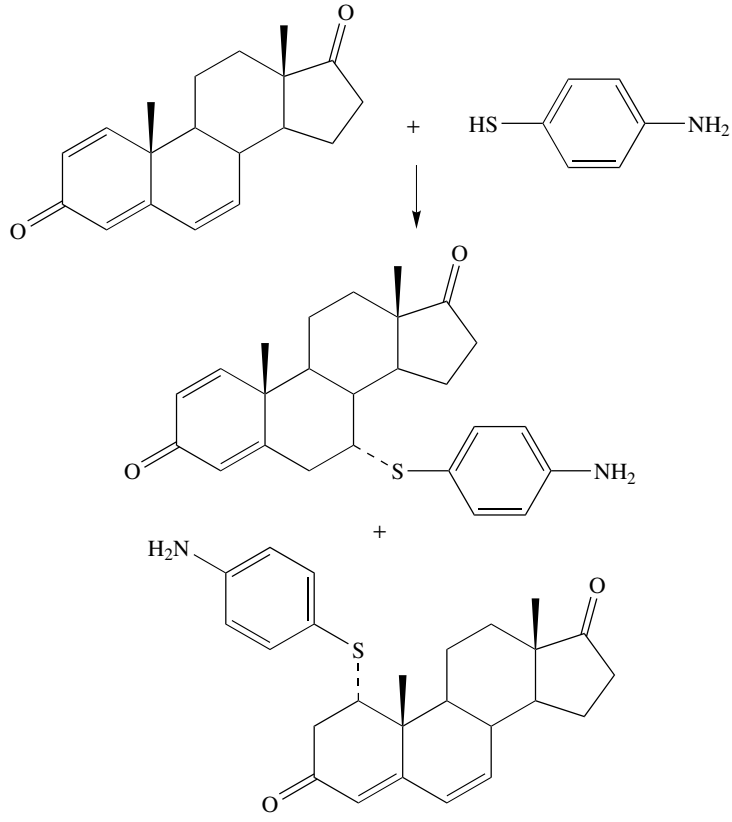


(47)



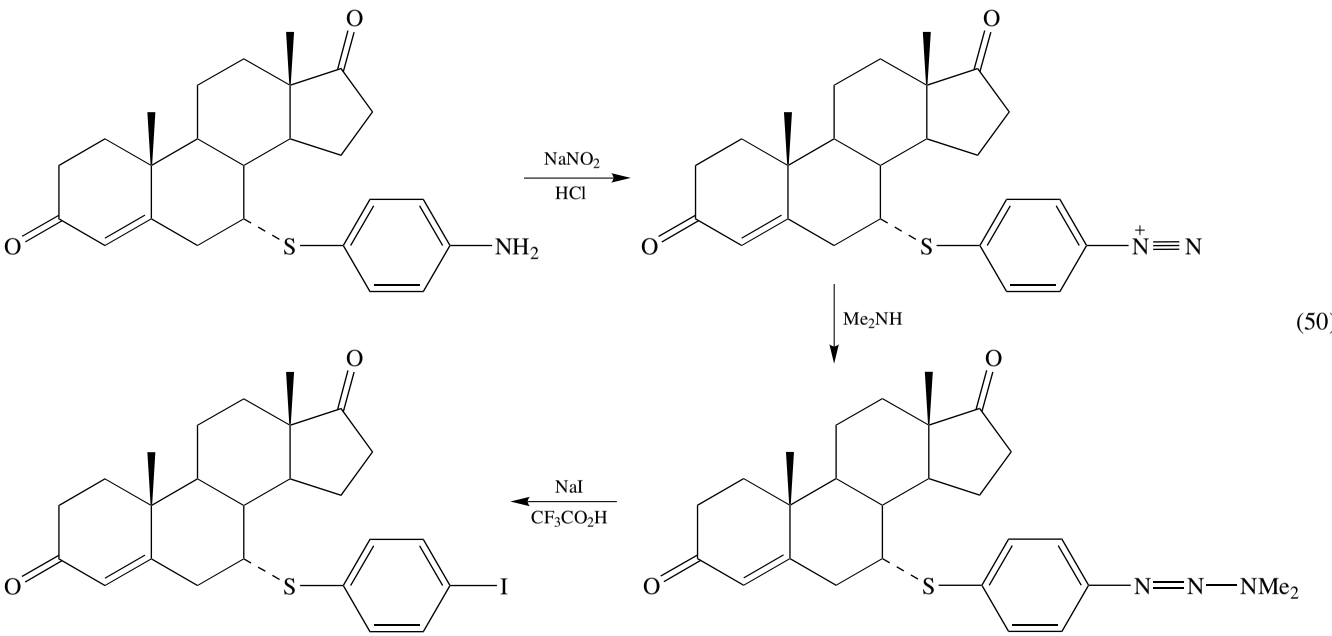
(48)

R = *n*-Bu: 58%
Ph: 84%
Bn: 98%
4-$H_2NC_6H_4$: 91%



(49)

aliphatic and aromatic thiols to furnish the 7α-substituted adducts with moderate to excellent yield (equation 48)[131−136]. The analogous reaction of $\Delta^{1,4,6}$-steroids gave mixtures of 1,6-adducts and 1,4-addition products resulting from attack of the thiolate at C-1 (equation 49)[134,137]. Subsequent functionalization provided steroids which were not directly accessible by 1,6-addition (equation 50)[132,133,136].

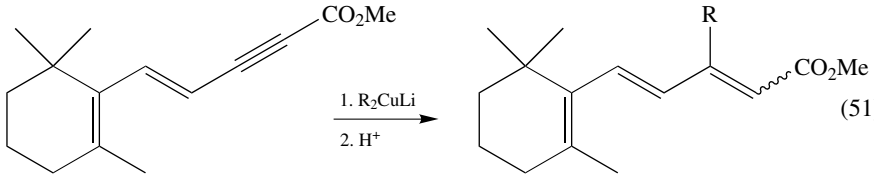


(50)

III. ENYNES

A. Carbon Nucleophiles

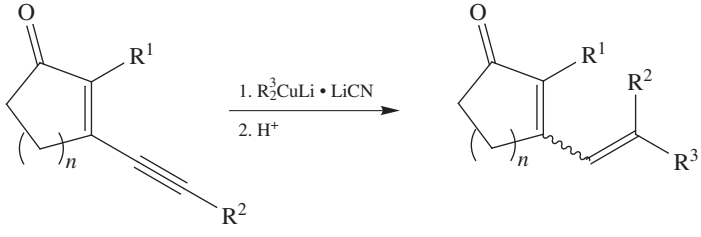
As in the case of addition reactions of carbon nucleophiles to activated dienes (Section II.A), organocopper compounds are the reagents of choice for regio- and stereoselective Michael additions to acceptor-substituted enynes. Substrates bearing an acceptor-substituted triple bond besides one or more conjugated double bonds react with organocuprates under 1,4-addition exclusively (equation 51)[138–140]; 1,6-addition reactions which would provide allenes after electrophilic capture were not observed (cf. Section IV).



(51)

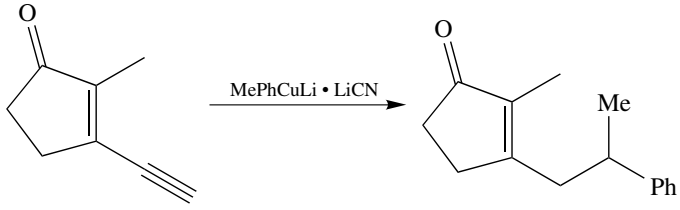
R = Et, *t*-Bu, Me_3Si

In contrast to these transformations, nucleophilic additions to enynes with an acceptor substituent at the double bond are highly rewarding from both the preparative and mechanistic point of view[38,141]. According to Scheme 2 (Section I), the outcome depends strongly on the regioselectivity of the nucleophilic attack and of the electrophilic trapping of the enolate formed. Recent investigations have demonstrated that the regio- and stereoselectivity of both steps can be controlled by the choice of the reactants, in particular by 'fine-tuning' of the organocopper reagent and the electrophile. The first example was reported by Hulce[142,143] who found that 3-alkynyl-2-cycloalkenones react with cuprates at the triple bond in a 1,6-addition and the allenyl enolate is protonated at C-4 with the formation of conjugated dienones as mixtures of *E*/*Z*-isomers (equation 52). As observed in other cuprate addition reactions[138,139], the *Z*-stereoselectivity rises with increasing size of the group R^3. Interestingly, substrates of this type can also undergo tandem 1,6-5,6-additions, indicating that the allenyl enolate formed by 1,6-cuprate addition is sufficiently electrophilic to react with another organometallic reagent in a carbometalation of the allenic double bond distal to the electron-releasing enolate moiety[144]. In this way, it is also possible to introduce two different groups at the terminus of the Michael acceptor, either by using two organometallic reagents successively or by employing a mixed cuprate (equation 53).



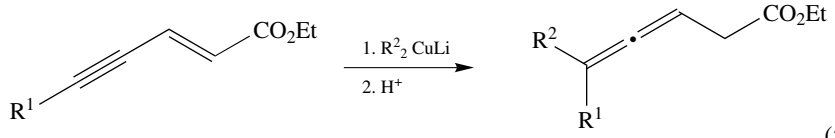
(52)

n = 1,2; R^1 = H, Me; R^2 = H, Ph, HMe_3Si; R^3 = Me, Et; *i*-Pr, *n*-Bu, *t*-Bu, Ph, CH═CH_2



(53)

More interesting in preparative terms would be the possibility of shifting the regioselectivity of the electrophilic quenching reaction towards formation of allenes, since the number of synthetic methods for the preparation of functionalized allenes has been rather limited[145]. Furthermore, a stereoselective reaction of this type would open up a route to these axially chiral compounds in enantiomerically enriched or pure form. Indeed, the Gilman cuprate $Me_2CuLi \bullet LiI$ and cyanocuprates $R_2CuLi \bullet LiCN$ ($R \neq Me$) in diethyl ether react regioselectively with variously substituted 2-en-4-ynoates in a 1,6-fashion (equation 54). Protonation with dilute sulfuric acid gives the β-allenic esters with alkyl, alkenyl, aryl and silyl substituents in good yield[146].



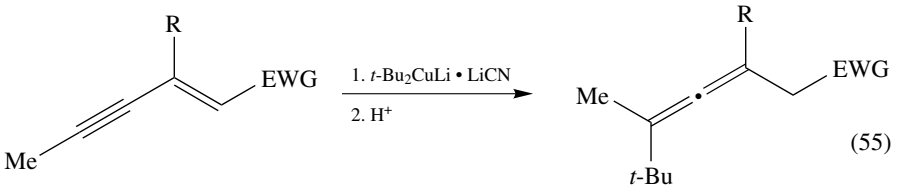
(54)

R^1 = Ph, R^2 = Me:	79%
R^1 = Ph, R^2 = *t*-Bu:	81%
R^1 = *n*-Bu, R^2 = Ph:	62%
R^1 = Me_3Si, R^2 = Me:	57%

The regioselectivity of the addition of organocuprates to acceptor-substituted enynes is hardly influenced by the nature of the acceptor substituent. Enynes containing ester, thioester, lactone and dioxanone as well as keto, sulfonyl, sulfinyl, cyano and oxazolidino groups react in a 1,6-manner to give the corresponding functionalized allenes (equation 55)[146–148]. Only 1-nitro-l-en-3-ynes are attacked at the C=C double bond with the formation of 1,4-adducts (equation 56)[148]. The differences in reactivity can be described qualitatively by the following reactivity scale: EWG = NO_2 > COR, CO_2R, COSR > CN, SO_3R, oxazolidino > SO_2R > SOR ≫ $CONR_2$. Remarkably, the regioselectivity of the cuprate addition to acceptor-substituted enynes is also insensitive to the steric properties of the substrate; enynes with *t*-butyl substituents at the triple bond undergo 1,6-addition, even when the cuprate itself is sterically demanding (equation 57)[147]. The reaction is therefore highly suitable for the preparation of sterically encumbered allenes.

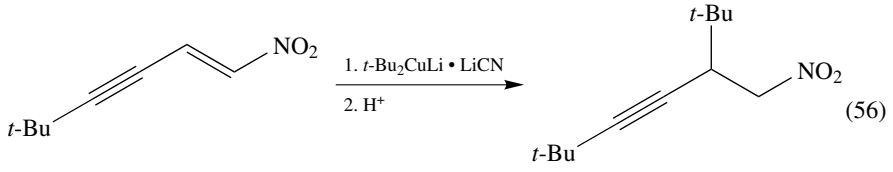
In order to achieve acceptable yields with the less reactive Michael acceptors, it is often necessary to use more reactive organocopper reagents or Lewis acid catalysis. Thus, the reaction of (1-penten-3-yn-1-yl) phenyl sulfone with five equivalents of Me_2CuLi alone gave no trace of addition product, whereas the analogous reaction with Me_3CuLi_2 provided the desired allene in 16% yield (equation 58)[148]. With two equivalents of Me_2CuLi in the presence of one equivalent of Me_3SiI the yield increased to 45%, while with added Me_3SiOTf the allene was isolated in 29% yield. Only amides fail to form 1,6-adducts

under these conditions.

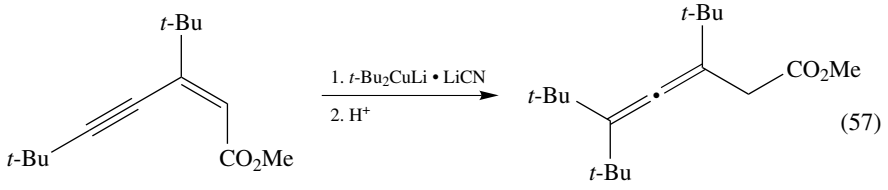


(55)

EWG = CN, R = Me:	79%
EWG = SO_2Ph, R = H:	91%
EWG = SO_3Et, R = H:	49%



(56)



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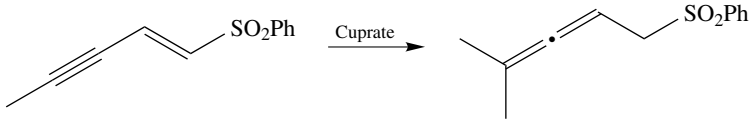
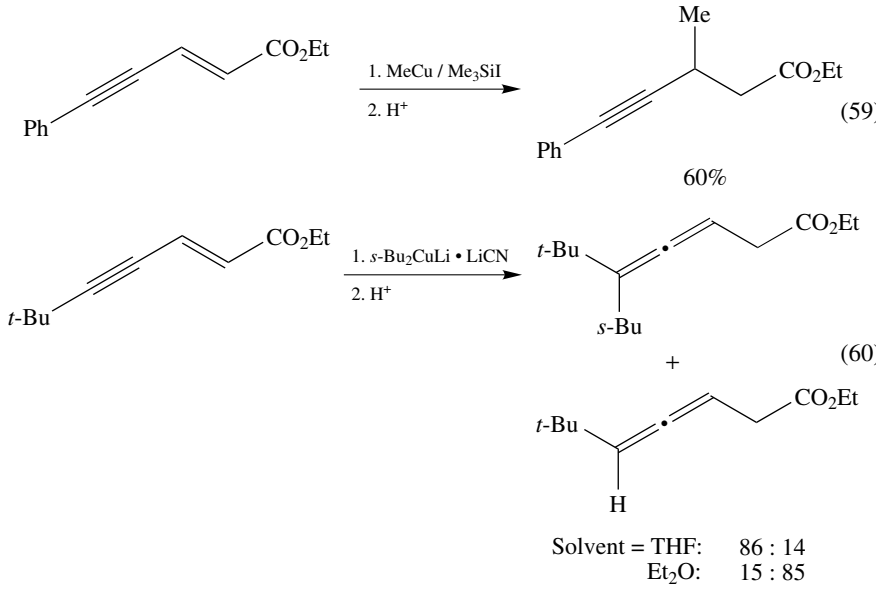


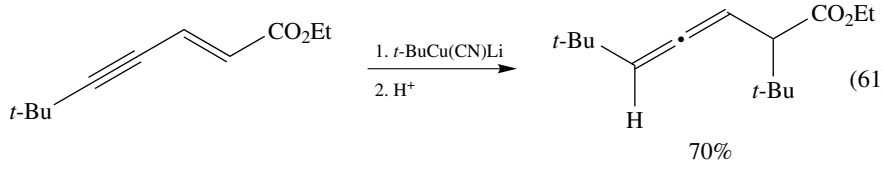
(58)

Me_2CuLi:	0%
Me_3CuLi_2:	16%
Me_2CuLi / Me_3SiI:	45%
Me_2CuLi / Me_3SiOTf:	29%

In contrast to the substrate, the organocuprate has a pronounced influence on the regioselectivity of the addition to acceptor-substituted enynes. While the Gilman cuprate Me_2CuLi • LiI and cyanocuprates R_2CuLi • LiCN ($R \neq Me$) add regioselectively in a 1,6-manner, the Yamamoto reagent RCu • BF_3[50] and the reagent combination RCu/Me_3SiI[149] lead to 1,4-adducts (equation 59)[38,146]. The behavior of the cyanocuprate *s*-Bu_2CuLi • LiCN towards 2-en-4-ynoates is particularly unusual since the reaction is very solvent-sensitive. In THF the 1,6-adduct is obtained as the major product, whereas in diethyl ether the 1,6-reduction product is the main component of the product mixture (equation 60)[150]. Other cyanocuprates of the stoichiometry R_2CuLi • LiCN react with acceptor-substituted enynes in THF very slowly under 1,6-addition or not at all[38]. A 1,6-reduction was also observed in the reaction of benzyl 3-methyl-2-penten-4-ynoate with Me_2CuLi/*n*-Bu_3P[141]. The reduction products may be formed by electron transfer from the cuprate or by hydrolysis of a stable copper(III) intermediate.

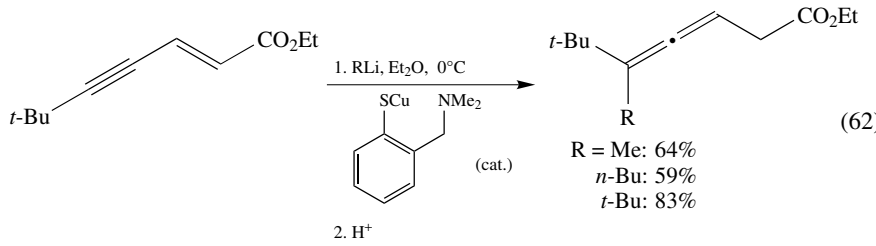


So-called 'lower order cyanocuprates' RCu(CN)Li do not generally react with acceptor-substituted enynes. An exception is the cuprate *t*-BuCu(CN)Li which undergoes anti-Michael additions with 2-en-4-ynoates and nitriles (equation 61)[151]. The mechanistic aspects of this very unusual reaction are unknown; radical intermediates and electron transfer steps have not been found.



In analogy to copper-catalyzed 1,6-addition reactions of Grignard reagents to activated dienes (Section II.A), the 1,6-addition to acceptor-substituted enynes can also be conducted under catalytic conditions. However, only very carefully controlled reaction conditions lead to the 1,6-adduct as the major product, i.e. use of copper (2-dimethylaminomethyl)thiophenolate as catalyst and simultaneous addition of the substrate and an organolithium reagent to a suspension of the catalyst in diethyl ether at 0 °C (equation 62)[152]. Under these conditions variously substituted β-allenylcarboxylates are obtained with yields comparable to those of the stoichiometric cases. Other copper(I) salts and the use of Grignard reagents as the nucleophile led to very low yields of 1,6-addition products. A second catalytic version takes advantage of the fact that the products of the (stoichiometric) 1,6-cuprate addition, the lithium allenyl enolate and the organocopper compound are formed as independent species. The cuprate can be regenerated by addition of one equivalent of RLi such that it reacts with a further equivalent of the Michael acceptor. This procedure can, in principle, be repeated infinitely. The reaction is best conducted in a continuous mode by adding the substrate and the organolithium reagent

simultaneously to a solution of the cuprate (equation 63)[38].



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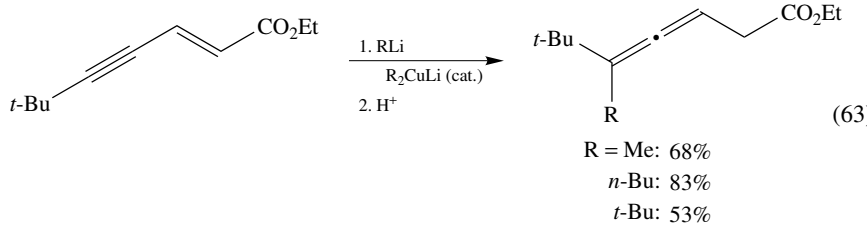
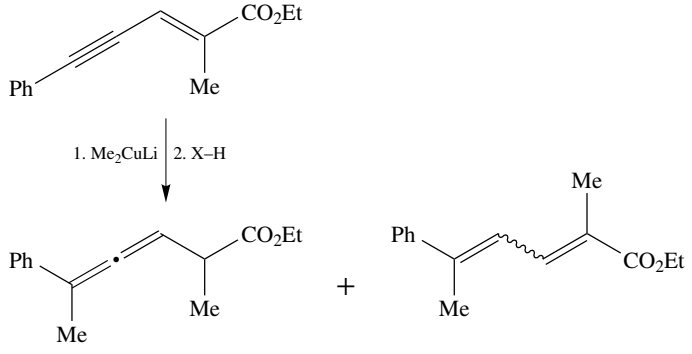


(63)

As mentioned repeatedly, a precondition for the successful preparation of allenes by 1,6-addition is that the allenyl enolate reacts regioselectively with an electrophile at C-2 (or at the enolate oxygen atom to give an allenylketene acetal; see Scheme 2). The regioselectivity of the simplest trapping reaction, the protonation of the allenyl enolate, depends on the steric and electronic properties of the substrate and the proton source. Whereas the allenyl enolates obtained from 3-alkynyl-2-cycloalkenones always provide conjugated dienones by protonation at C-4 (possibly via allenyl enols; see equation 52)[141–143], ester enolates are usually protonated at C-2 (equation 54), in particular when sterically demanding groups at C-5 block the attack of a proton at C-4 (equation 57)[38,146–148]. However, with a substituent at C-2 of the enolate, mixtures of allenes and conjugated dienes are formed, since now protonation at C-2 is sterically hindered. In the case of ester enolates this problem can be solved by using weak organic acids as proton source (equation 64).

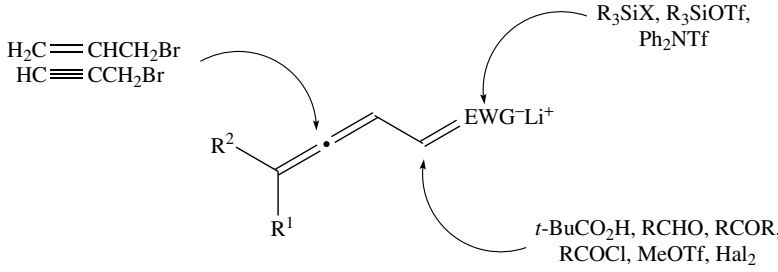


(64)

X-H = 2N H_2SO_4, 25 °C: 50 : 50
AcOH, 25 °C: 64 : 36
t-BuCO_2H, 25 °C: 82 : 18
t-BuCO_2H, –80 °C: > 99 : < 1

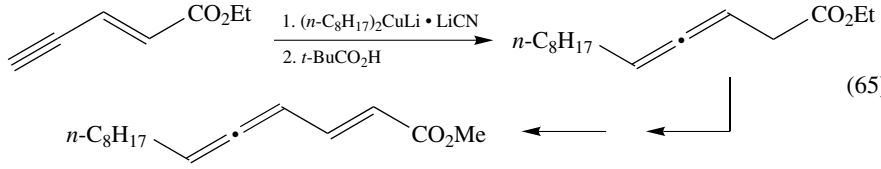
The optimal proton donor to conquer this problem of regioselectivity is pivalic acid (2,2-dimethylpropionic acid). At room temperature, an allene : diene ratio of 82 : 18 was observed, and at −80 °C only the desired allene was formed[146].

In contrast to protonation, the regioselectivity of the reaction of other electrophiles with allenyl enolates derived from 2-en-4-ynoates is independent of the steric and electronic properties of the reaction partners (Scheme 3)[38,148,152–154]. Hard electrophiles such as silyl halides and triflates react at the enolate oxygen atom to form allenylketene acetals, while soft electrophiles such as carbonyl compounds attack at C-2. Only allylic and propargylic halides react regioselectively at C-4 of the allenyl enolate to give substituted conjugated dienes; these reactions may also proceed via allenes which then undergo a Cope rearrangement. Again, cyclic allenyl enolates formed by cuprate addition to 3-alkynyl-2-cycloalkenones show a deviating behavior: treatment with iodomethane provided product mixtures derived from attack of the electrophile at C-2 and C-4, and the reaction with aldehydes and silyl halides took place at C-4 exclusively[141,155,156].



SCHEME 3

The synthesis of allenes by 1,6-addition of organocopper reagents to acceptor-substituted enynes has found a wide range of preparative applications. In addition to sterically encumbered allenes (equation 57)[147] and simple terpenes such as pseudoionone[146], allenic natural products can be prepared by this method (equation 65)[38]. Thus, 1,6-addition of lithium di-*n*-octylcuprate to ethyl 2-penten-4-ynoate, followed by regioselective protonation with pivalic acid, yielded the allene ethyl 2,3-tridecadienoate which can be converted easily into the insect pheromone methyl 2,4,5-tetradecatrienoate. Another application of the 1,6-addition in natural product synthesis relies on vinylallenes as diene components in the Diels–Alder reaction. The synthesis of the fungal metabolite (±)-sterpurene started with a 1,6-addition of lithium dimethylcuprate to a suitable enynoate and regioselective trapping with methyl triflate (equation 66)[157]. The vinylallene thus formed underwent an intramolecular [4 + 2]-cycloaddition upon brief heating in toluene, and the tricyclic product was converted into (±)-sterpurene in a few steps and also into several oxygenated metabolites.



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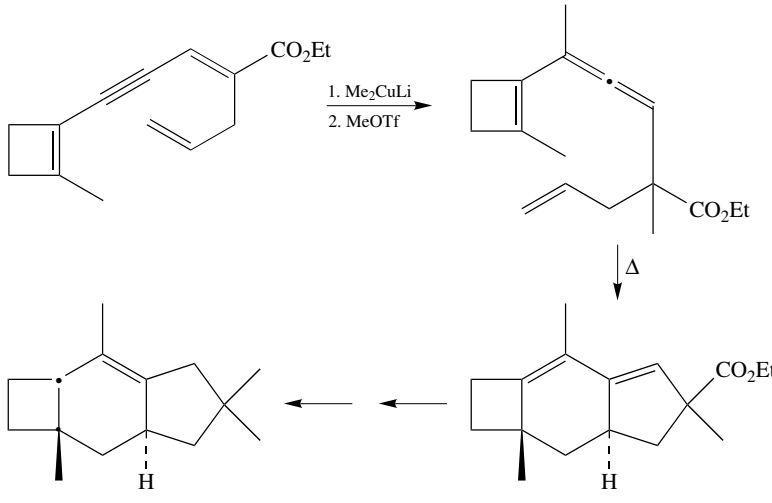
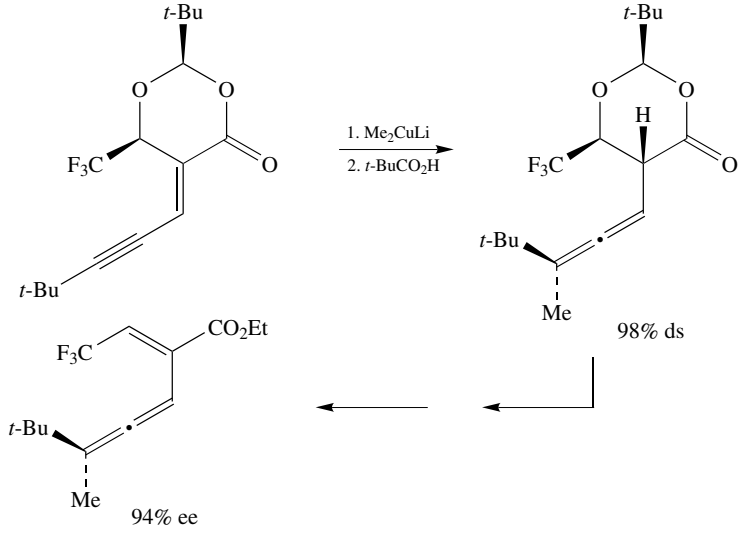


(66)

(±)-Sterpurene

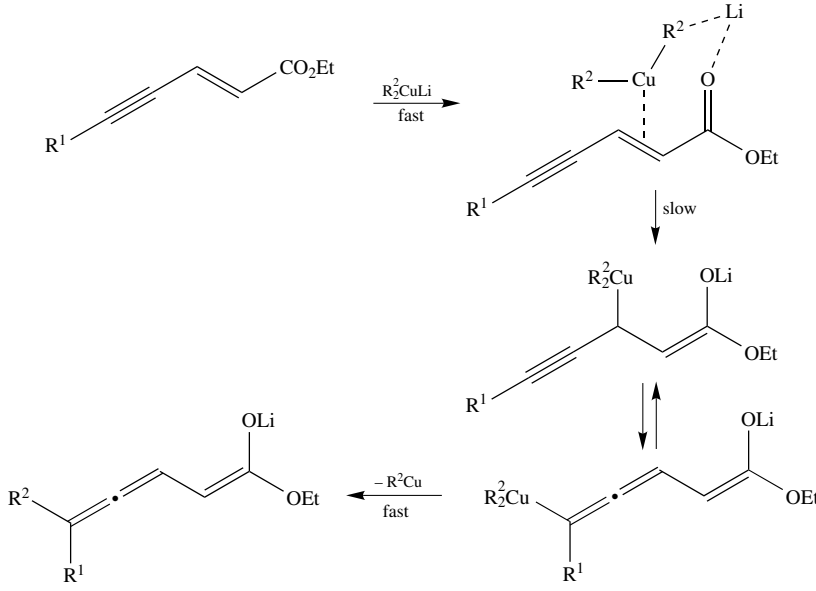
This Diels–Alder reaction is an example of how axially chiral allenes, accessible through 1,6-addition, can be utilized to form new stereogenic centers selectively. This is also possible by intermolecular Diels–Alder reactions of vinylallenes[158], aldol reactions of allenyl enolates[159] and Ireland–Claisen rearrangements of silyl allenylketene acetals[160]. In order to access the required allenes in enantiomerically enriched or pure form, the 1,6-cuprate addition has to be conducted not only regio- but also stereoselectively. This goal can be achieved by employing chiral 5-alkynylidene-1,3-dioxan-4-ones as Michael acceptor; here, the equatorial *t*-butyl group forces the molecule to adopt a very rigid conformation and the trifluoromethyl group protects the top face of the enyne unit, making the preferred point of attack the underside of the molecule (equation 67)[38,161].



(67)

Consequently, reaction with lithium dimethylcuprate and pivalic acid gave the desired allene with a diastereoselectivity of 98% ds, and the stereochemical information generated in this step remained intact even after further conversion into a chiral vinylallene.

In contrast to nucleophilic addition reactions to activated dienes, the mechanism of 1,6-cuprate additions to acceptor-substituted enynes is quite well understood, the main tools being kinetic and NMR spectroscopic investigations[38]. ^{13}C-NMR spectroscopic studies have revealed that these transformations proceed via π-complexes with an interaction between the π-system of the C=C double bond and the nucleophilic copper atom (a soft–soft interaction in terms of the HSAB principle), as well as a second interaction between the hard lithium ion of the cuprate and the hard carbonyl oxygen atom (Scheme 4)[162]. The use of ^{13}C-labeled substrates has confirmed that the cuprate does not interact with the triple bond, and it has also shed light on the structure of the metal-containing part of the π-complexes[163]. Further intermediates on the way from the π-complex to the allenyl enolate could not be detected spectroscopically; however, kinetic measurements have revealed that an intramolecular rearrangement of the π-complex occurs in the rate-determining step[164]. These experimental results can be explained by assuming that a σ-copper(III) species is formed which could be in equilibrium with an allenic copper(III) intermediate. Both intermediates can undergo reductive elimination to produce the 1,4- and 1,6-adduct, respectively. The experimental result of exclusive formation of the 1,6-addition product may indicate that the hypothetical equilibrium lies on the side of the allenic copper(III) species, or that the reductive elimination of the latter occurs much faster than from the first intermediate.

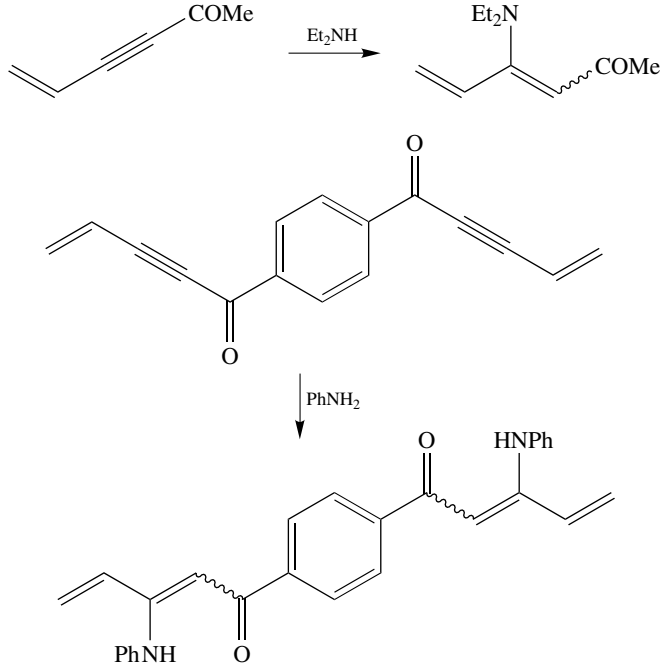


SCHEME 4

B. N-, O-, P-, S- and Si-Nucleophiles

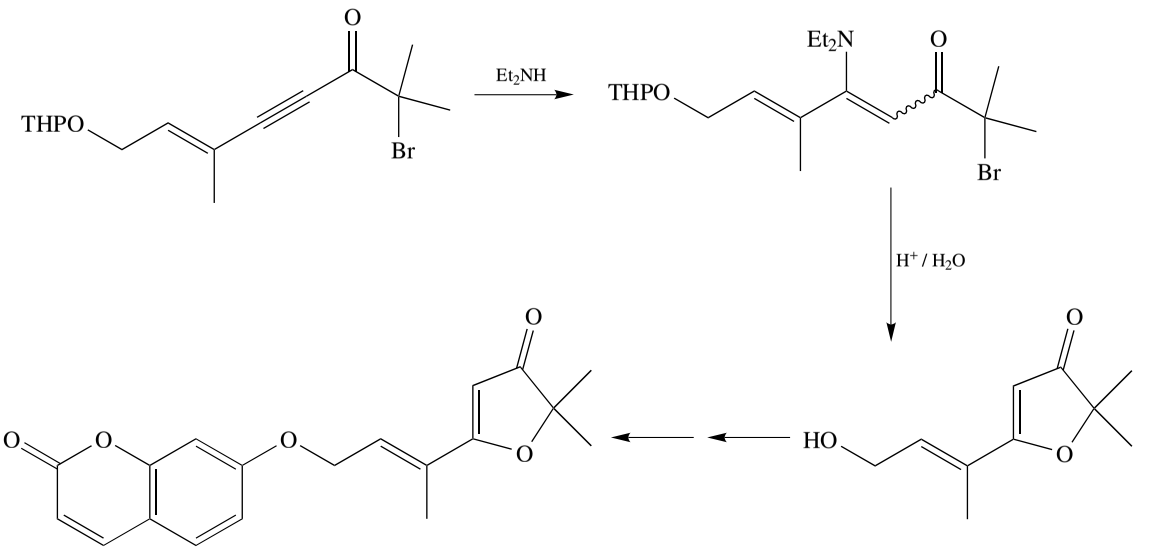
As demonstrated in Section III.A, activated enynes with an acceptor group at the triple bond react with carbon nucleophiles under 1,4-addition exclusively; the same is

true for their reactions with N−, O− and P-nucleophiles[165−174]. In 1946, Bowden and coworkers[165] reported the 1,4-addition of diethylamine to 5-hexen-3-yn-2-one (equation 68). Likewise, a Russian group synthesized several 1,4-adducts by treatment of 1-aryl-4-alken-2-yn-1-ones with aniline[166−168]; in one case, a double addition product was obtained (equation 69)[166]. The resulting aminodienones can be hydrolyzed easily to unsaturated 1,3-diketones[169]. Jackson and Raphael[170,171] employed this sequence in a synthesis of the 3(2*H*)-furanone natural product geiparvarin (equation 70); key steps were the 1,4-addition of diethylamine to a bromo-substituted enynone and the subsequent hydrolysis/cyclization to give the desired heterocycle.



Isolated instances of 1,4-addition reactions of other hetero-nucleophiles to 4-en-2-ynoic acids and derivatives have been reported[172−174]. Thus, treatment of methyl 4-methyl-4-penten-2-ynoate with phenolate provided the 3-phenoxy-substituted conjugated dienoate (equation 71)[172], and the 1,4-addition of water-soluble phosphines to 4-octen-2-ynoic acid afforded dienylphosphonium salts which were transformed into the corresponding phosphine oxides (equation 72)[174].

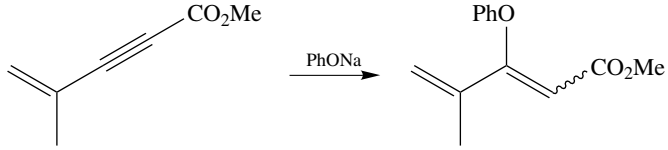
The number of reports on Michael additions of hetero-nucleophiles to enynes bearing an acceptor substituent at the double bond is also rather limited. Bowden and coworkers[165] found that 3-hexen-5-yn-2-one reacts with diethylamine under 1,6-addition to form the 6-amino-substituted dienone (equation 73). Similarly, 1,6-addition products were obtained by Russian groups from reactions of various primary and secondary amines with 2-en-4-ynoates and -nitriles[175−178]. However, enynoates and nitriles bearing *t*-butyl or trimethylsilyl groups at the triple bond were reported to react with methyl- and dimethylamine under 1,4-addition, indicating that the regioselectivity of the nucleophilic attack is



Geiparvarin

(70)

affected by the steric and electronic properties of the Michael acceptor (equation 74)[178,179].



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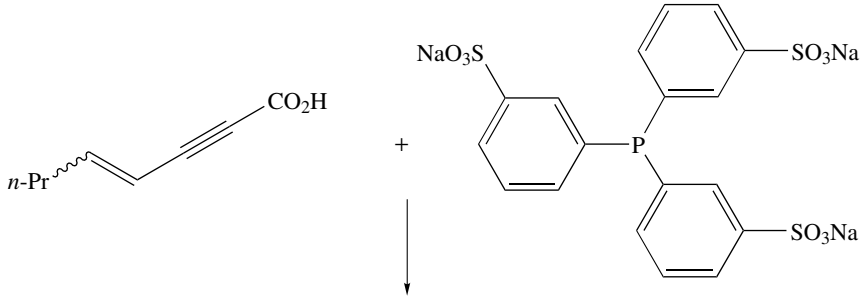

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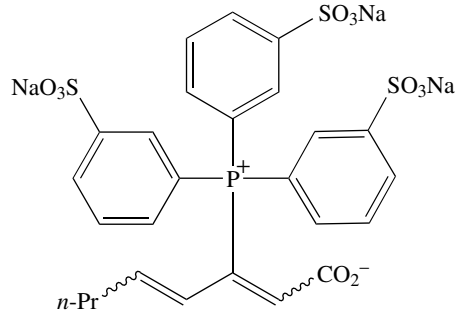

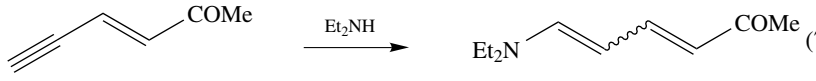

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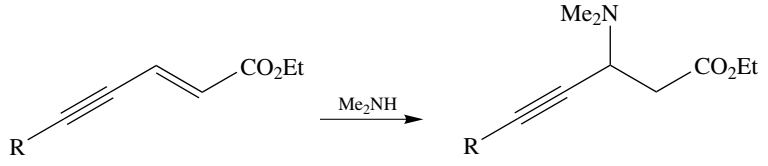
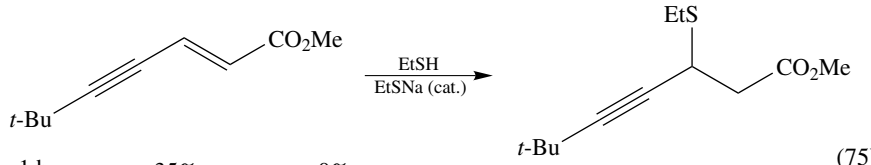


(74)

R = *t*-Bu, Me_3Si

In a thorough investigation of thiolate additions to acceptor-substituted enynes, Shustrova and coworkers[180,181] were able to demonstrate that the ratio of 1,4- and 1,6-addition depends on the reaction conditions, in particular on the duration of the experiment (equation 75): whereas only 1,4-adduct was observed in the reaction of methyl 6,6-dimethyl-2-hepten-4-ynoate and ethyl thiolate after 1 h, the product distribution shifted towards the 1,6-addition product with increasing reaction time, the latter being the sole

product after 48 h. This finding indicates that the Michael addition is reversible and that the (conjugated) 1,6-adduct is the thermodynamically most stable product. A 1,6-adduct was also obtained by treatment of a 3-alkynyl-2-cycloalkenone with lithium thiophenolate[141]. In contrast, treatment of 1-nitro-1-en-3-ynes with ethyl thiolate was reported to afford 1,4-addition products exclusively (equation 76)[182].



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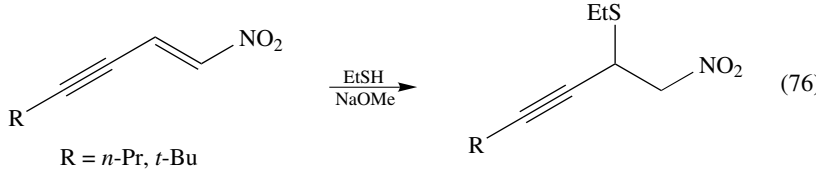
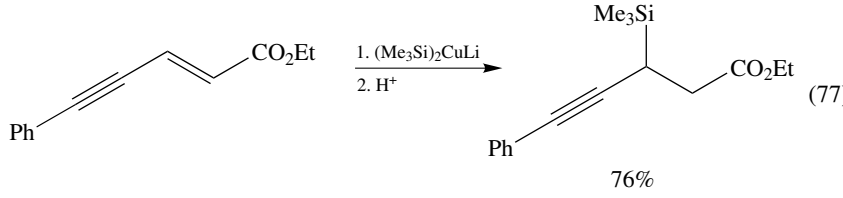


(76)

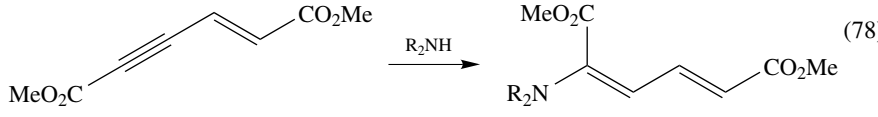
R = *n*-Pr, *t*-Bu

For the addition of silicon nucleophiles to activated enynes, silyl cuprates can be utilized. For example, treatment of ethyl 5-phenyl-2-penten-4-ynoate with $(Me_3Si)_2CuLi$ gave the 1,4-addition product with 76% yield (equation 77)[38].



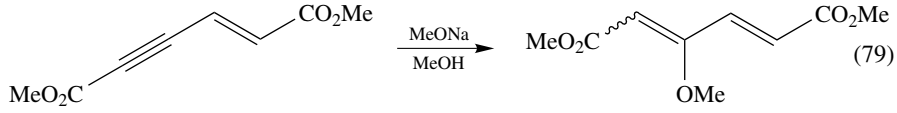
(77)

A particularly interesting Michael acceptor is dimethyl 2-hexen-4-ynedioate since it can react at either position of the double or triple bond to form 1,4- or 1,6-addition products. Winterfeldt and Preuss[183] treated this substrate with several secondary amines and observed exclusive attack at C-5 with formation of the 1,6-addition products (equation 78). In contrast to this, sodium methanolate added at C-4 to give the 1,4-adduct as a mixture of *E*/*Z* isomers (equation 79); with increasing reaction time, the product distribution was shifted towards the thermodynamically more stable *E*,*E*-product[184]. Acheson and



(78)

Wallis[185] examined reactions of dimethyl 2-hexen-4-ynedioate with thioureas and thioamides and observed addition at C-5 via the sulfur atom of these nucleophiles; the adducts often cyclize spontaneously to iminothiazolidinones (equation 80).



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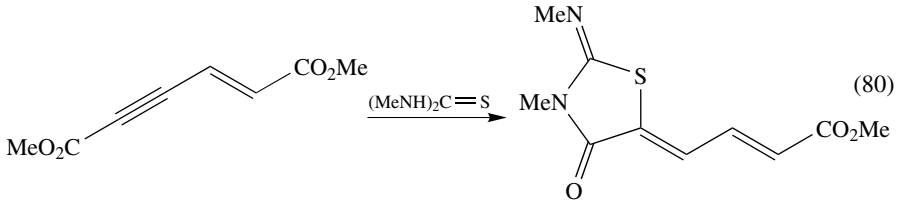
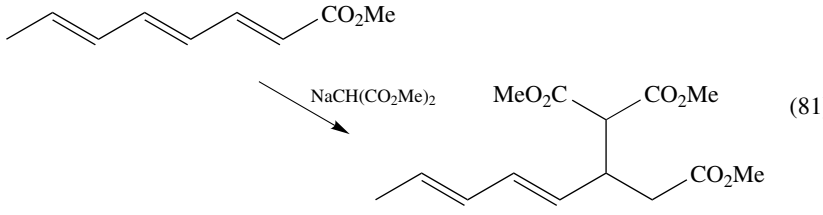


(80)

IV. POLYENES

Only few examples have been reported so far on nucleophilic addition reactions to acceptor-substituted polyenes[123,124,186–188]. In 1933, Farmer and Martin[186] examined the reaction of methyl 2,4,6-octatrienoate with sodium dimethyl malonate and isolated the 1,4-adduct as major product (equation 81). In contrast to this, 3,5,7-nonatrien-2-one and ethyl 2,4,6-octatrienoate react with organocuprates under 1,8-addition to provide the 4,6-dien-2-ones and 3,5-dienoates, respectively (equation 82)[187].



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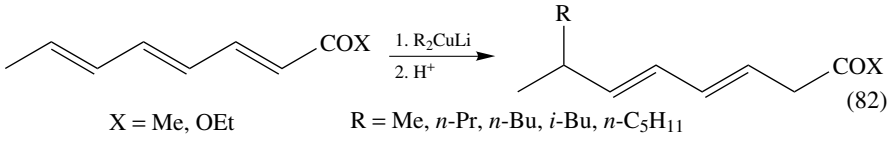
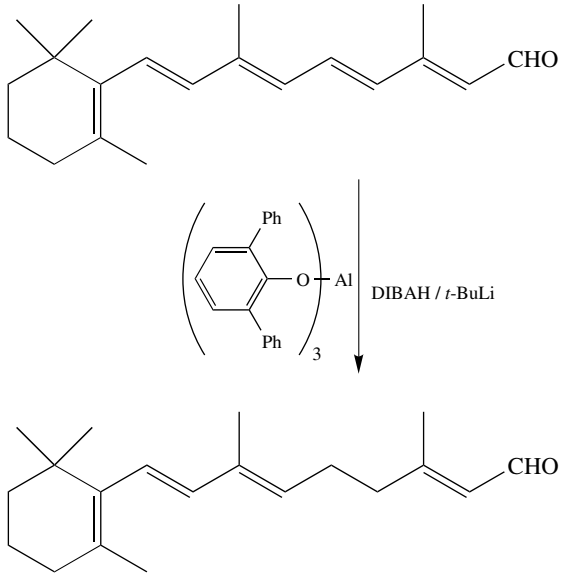


X = Me, OEt R = Me, *n*-Pr, *n*-Bu, *i*-Bu, *n*-C_5H_{11}

(82)

A case of a regioselective 1,6-reduction of retinal by treatment with the bulky Lewis acid aluminum tris(2,6-diphenylphenoxide) and DIBAH/*t*-BuLi as reducing agent was reported recently by Saito and Yamamoto (equation 83)[188]. In analogy to the Michael additions of thiolates to 2,4-dienones (Section II.B; equations 42 and 43), 1-(3-nitrophenyl)-2,4,6-heptatrien-1-one reacted with 2-mercaptoethanol with high 1,8-regioselectivity whereas the 1,4-addition product was formed in the presence of $TiCl_4$ (equation 84)[123]. Again, trapping of the 1,4-adduct as metal chelate seems to be responsible for this reversal

of regioselectivity. Consecutive 1,8-addition of 1,9-nonanethiol to 1-(3-nitrophenyl)-2-(2-hydroxyethylsulfonylmethyl)-2,4,6-heptatrien-1-one, sulfoxide elimination and intramolecular 1,4-addition led to the formation of an 18-membered macrocycle (equation 85)[124].

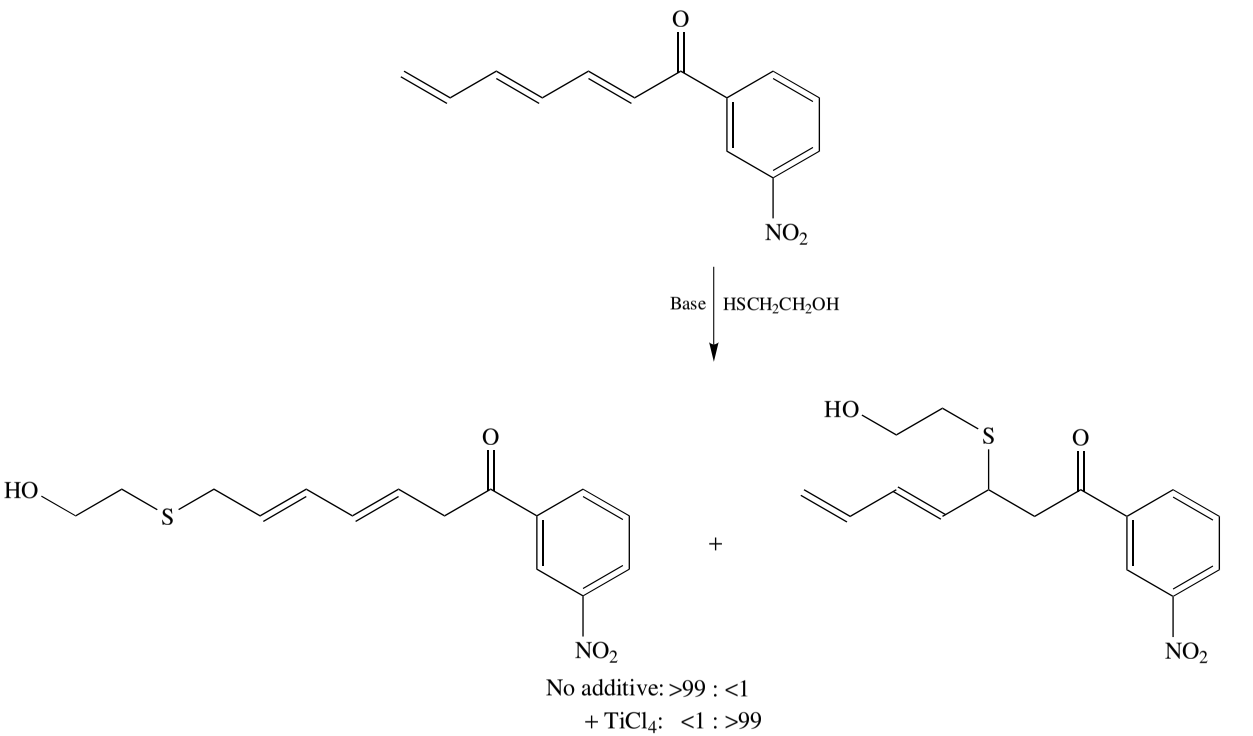


(83)

87%

In Section III it was demonstrated that the inclusion of a triple bond in polyunsaturated Michael acceptors serves to broaden the synthetic utility of these substrates in nucleophilic addition reactions. This is also true for activated dienynes, trienynes etc.; again, the position of the triple bond with respect to the acceptor substituent determines the regioselectivity of the nucleophilic attack. As already mentioned (Section III.A; equation 51), compounds bearing an acceptor-substituted triple bond besides several conjugated double bonds react with organocuprates regioselectively to give the 1,4-addition products. This selectivity has been exploited in the synthesis of several retinoids[138–140]; for example, addition of lithium diethyl- or di-*t*-butylcuprate to methyl 20-nor-13,14-didehydroretinoate afforded the 13-*cis*-substituted retinoates which were transformed into the corresponding retinals by reduction and reoxidation (equation 86)[138,139]. Likewise, treatment of 20-nor-13,14-didehydroretinal with hydrazoic acid furnished 13-nor-13-azidoretinal besides small amounts of the corresponding azirine (equation 87)[139,189]. Other examples for the addition of hetero-nucleophiles to acceptor-substituted dienynes involve the 1,4-addition of diethylamine to dimethyl 2,4-hexadien-6-ynedioate[190] and an intramolecular 1,8-thiolate addition observed in a bicyclic model compound for the enediyne antibiotic neocarzinostatin (equation 88)[191].

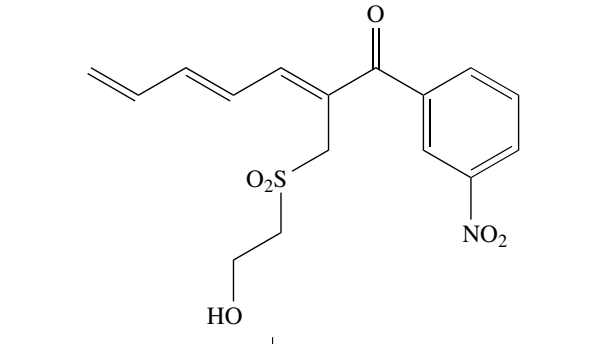
It was already noted that activated enynes bearing an acceptor substituent at the double bond react with organocuprates under 1,6-addition to provide functionalized allenes (see Section III.A)[38]. Interestingly, the preference of these reagents for triple bonds persists even when the distance between the acceptor group and the triple bond is increased by the introduction of further double bonds. For example, lithium dimethylcuprate attacked ethyl 8,8-dimethyl-2,4-nonadien-6-ynoate at the triple bond exclusively, and regioselective



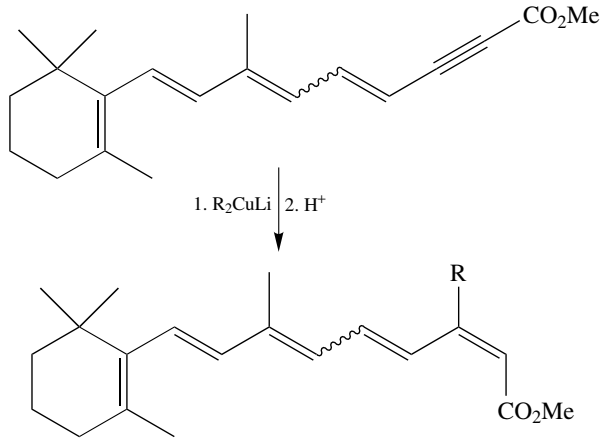
(84)

No additive: >99 : <1

+ $TiCl_4$: <1 : >99



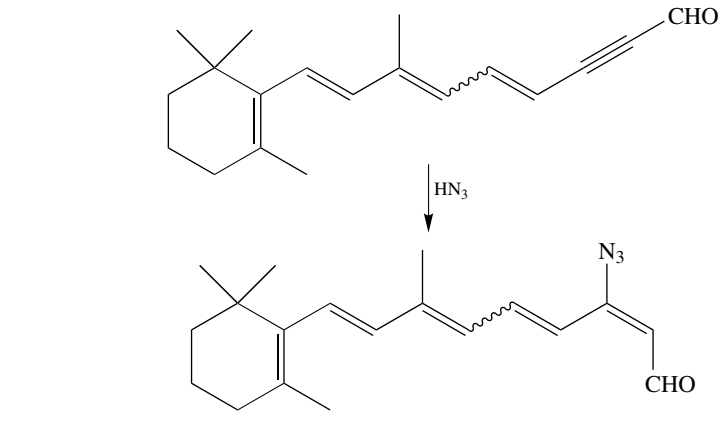
(85)



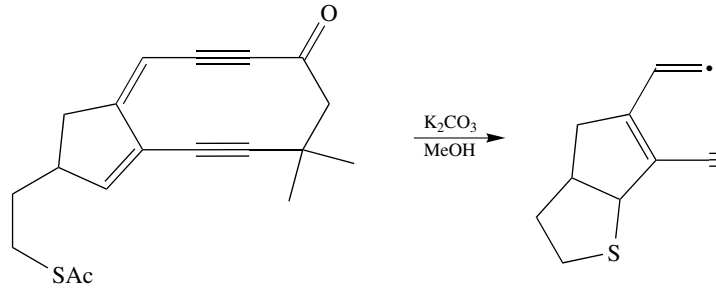
(86)

R = Et, *t*-Bu

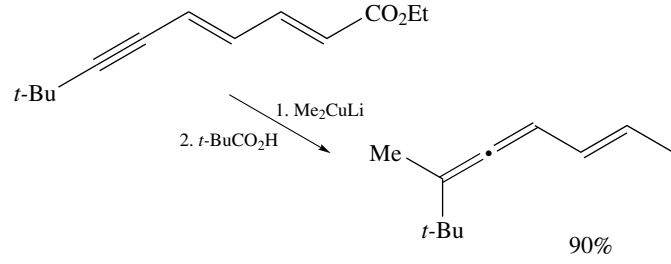
protonation with pivalic acid occurred at C-2 of the enolate, giving the 1,8-adduct as the only isolable regioisomer with 90% yield (equation 89)[38,158]. This vinylallene is well-suited as a diene in regio- and stereoselective Diels–Alder reactions. Analogously, ethyl 2,4,6-decatrien-8-ynoate reacted in a 1,10-fashion to give the 3,5,7,8-tetraenoate (equation 90), and even the 1,12-adduct could be obtained from a Michael acceptor



(87)



(88)

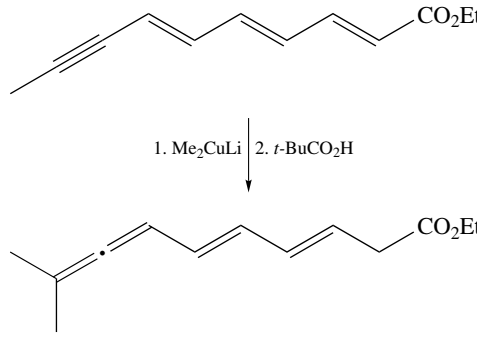


(89)

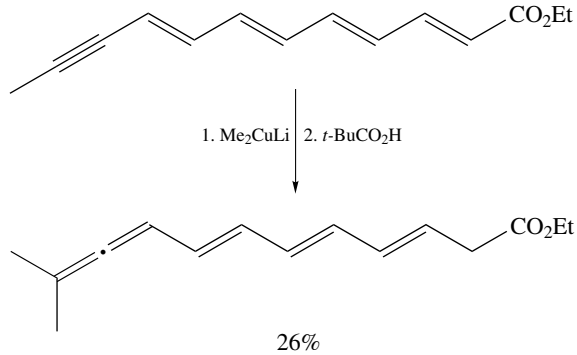
which contains four double bonds between the triple bond and the acceptor substituent (equation 91). In the latter case, however, the yield was only 26%; this is probably due to the reduced thermal stability of the addition products with increasing length of the conjugated π-system (the 1,12-adduct was the only isolable reaction product, apart from polymeric compounds)[38,158].

These transformations and those summarized in Section III.A make clear that Michael acceptors containing any combination of double and triple bonds undergo regioselective addition reactions with organocopper reagents. The following rule holds: *Michael acceptors with any given arrangement of conjugated double and triple bonds react regioselectively with organocuprates at the triple bond closest to the acceptor substituent*. Similar to the 1,6-cuprate addition to acceptor-substituted enynes (Scheme 4), these reactions start with the formation of a cuprate π-complex at the double bond neighboring the acceptor group[162] and may then proceed via an allenic σ-copper(III) intermediate which produces

the addition product by reductive elimination of RCu[38].



68% (90)



26% (91)

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