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High Pressure and Selectivity in Organic Reactions.

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1. Introduction

Selectivity is eventually the most determining parameter in organic and, even more acutely, in applied chemistry. A chemical reaction rarely leads to a single product for thermodynamic and kinetic reasons. In the field of asymmetric synthesis, the chemical yield may be high and the optical yield low.

If two or more products are formed during the course of the reaction, they may derive from :

- distinct competitive reaction pathways (chemoselectivity)
- structurally distinct transition states within the same reaction (regioselectivity)
- spatially distinct transition states within the same reaction (stereoselectivity)
- distinct chiral transition states within the same reaction yielding different enantiomers (enantioselectivity).

The course and fate of a reaction and, accordingly, selectivities with respect to products are influenced by physical (pressure, temperature, ultrasound), chemical (catalyst) and physicochemical (solvent, additives such as adsorption materials or host-guest compounds) parameters . The present review article has its aim at reporting the effect of pressure on selectivity in organic reactions and emphasizing the usefulness of this parameter to improve it. It should be noted that the field has been relatively little explored as indicated by the rather short reference list at the end of this review.[1]

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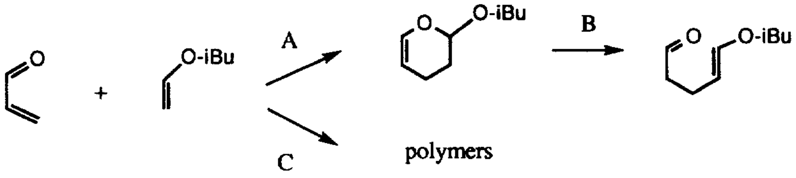
The first simple example stresses the importance of experimental conditions in controlling selectivity in thermally sensitive reactions. In the Diels-Alder addition of isobutyl vinyl ether (IBVE) to acrolein, several reactions are observed depending on pressure and temperature conditions (Table 1).[2]



Scheme 1

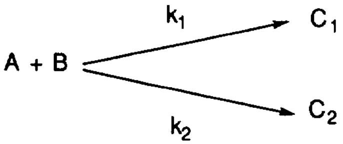
At ambient pressure (120° C and higher), cycloaddition takes place to a limited extent only since polymerization is the dominant reaction. Lower temperatures disfavour the formation of polymers, but also drastically reduce the yield of cycloadduct. At the same temperature, an increase of pressure induces a further reaction leading to unsaturated open-chain products (process B). Raising the pressure to 1300 MPa (1 MPa ~ 10 bar) and lowering the temperature considerably results in a very selective reaction affording the desired cycloadduct in 80 % yield. In this example, the pressure effect is highly beneficial for the chemoselective formation of dihydropyrans which are useful starting compounds for the synthesis of sugars. The pressure procedure is very general as amply demonstrated in the synthesis of furan cycloadducts which are produced as sole products in the high pressure addition of ethylenes to heterocyclic dienes.[3]

Table 1. Chemoselectivity in the [4+2] addition of IBVE to acrolein.

T (°C)	P(MPa)	REACTION
150	0.1	C
120	0.1	A + C
120	200	A + B + C
37	1300	A

2. Quantification of the pressure effect on selectivity

We shall discuss from a quantitative point of view the pressure effect on the chemoselectivity of bimolecular chemical systems. Obviously, the same reasoning holds for regio-, stereo- and enantioselectivity. The influence of pressure on the following pathways can be expressed in terms of Evans and Polanyi's relationship :



$$\partial / \partial P\,[\ln(k_1 / k_2)] = -1 / RT\,(\Delta V_1^{\neq} - \Delta V_2^{\neq})$$

With the help of an integrated form approximated by El'yanov,[4] the quantified relation becomes :

$$\ln [(k_1 / k_2)_p / (k_1/k_2)_o] = - \Phi / RT (\Delta V_1^{\neq} - \Delta V_2^{\neq})$$

k_p , k_o : rate constants at P and ambient pressure respectively

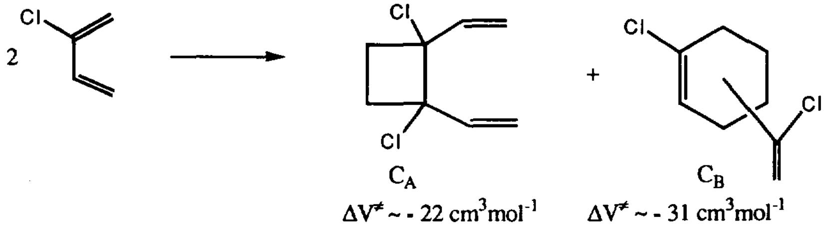
Φ : complex function only depending on pressure

A kinetic study in a modest pressure range (0 - 100 MPa for example) yields the values of the volumes of activation $\Delta V_1^{\neq}$ and $\Delta V_2^{\neq}$. Consequently, the chemoselectivity (C_1 / C_2) can be deduced at high pressure. For instance, at 20° C with the assumption of a C_1 / C_2 ratio of 50 : 50 at atmospheric pressure, this ratio takes following values at 1200 MPa :

75 : 25 if $\Delta V_1^{\neq} - \Delta V_2^{\neq} = - 10\ cm^3.mol^{-1}$
88 : 12 if $\Delta V_1^{\neq} - \Delta V_2^{\neq} = - 20\ cm^3.mol^{-1}$
18 : 82 if $\Delta V_1^{\neq} - \Delta V_2^{\neq} = + 15\ cm^3.mol^{-1}$

Accordingly, the pressure effect on chemoselectivity depends on the sensitivity to pressure of the competitive reactions. The following thermal dimerizations, each yielding several products, were studied under pressure: chloroprene,[5] 1,3-cyclohexadiene[6] and the crowded 1,1,2,2,3,3-hexamethyl-4,5-bis(methylene)-cyclopentane.[7]

a) Chloroprene : (Scheme 2)

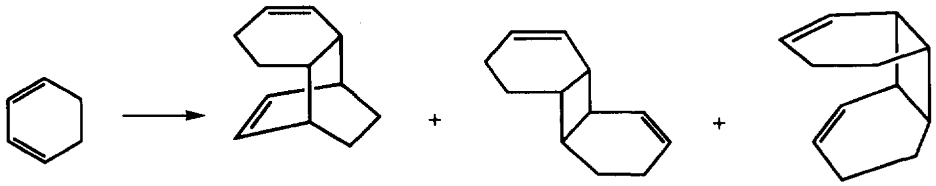


Scheme 2

Table 2. Pressure effect on [2+2] and [4+2] dimerization of chloroprene.

Pressure (MPa)	Distribution (%)		$C_B : C_A$	
	C_A	C_B	observed	calculated
0.1	54	30	0.56	
500	25	68	2.7	3.2
1000	8	89	11.1	4.4

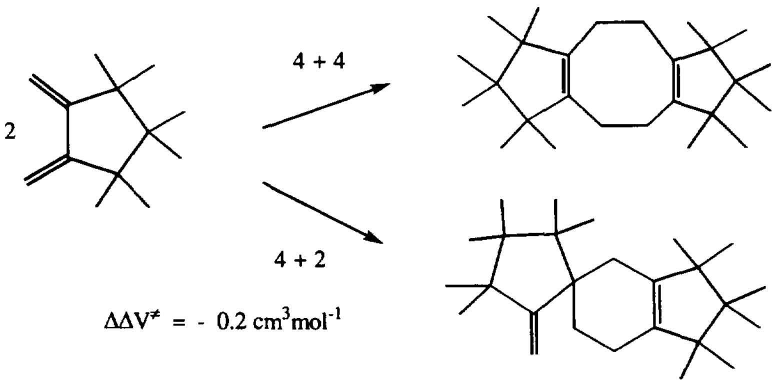
b) 1,3-Cyclohexadiene : (Scheme 3)



	endo [4 + 2]	anti [2 + 2]	syn [2 + 2]
$\Delta V^{\neq}$ (cm^3mol^{-1})	~ − 28	~ − 18	~ − 22

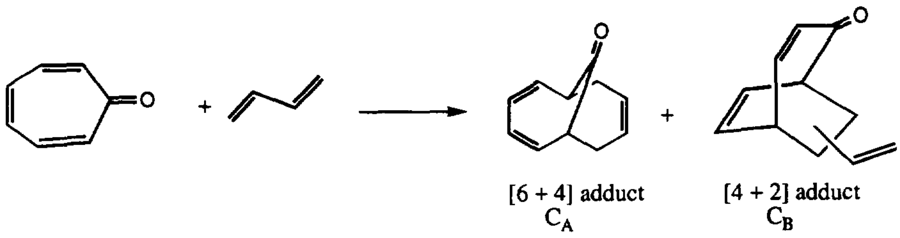
Scheme 3

c) Hexamethylcyclopentane compound : (Scheme 4)



Scheme 4

In the two cyclodimerizations (a) and (b) (Schemes 2 and 3), the observed changes of the C_B/C_A ratio and the distribution of [4+2] and [2+2] isomers originate from an alteration of the mechanism: [4+2] cycloadditions proceed according to a concerted pathway whereas the [2+2] process is featured with an acyclic transition state with the involvement of possible diradical intermediates. In example (c), there is no change in mechanism ($\Delta\Delta V^{\neq}$ # 0) and therefore, no pressure effect on chemoselectivity. This is also the case in the reaction of tropone with 1,3-butadiene (Scheme 5) for which $\Delta\Delta V^{\neq}$ = - 0.3 $cm^3.mol^{-1}$ (Table 3).[8] These results also emphasize the prominent role of high pressure kinetics in mechanistic discriminations.[9,10] As an example, the activation volume proved to be a powerful criterion in evaluating the carbanionic character in elimination reactions[11] : E_1cB processes are featured by negative $\Delta V^{\neq}$ -values whereas E_2 routes are retarded by pressure ($\Delta V^{\neq} > 0$). The mechanistic aspect will not be examined further here.



Scheme 5

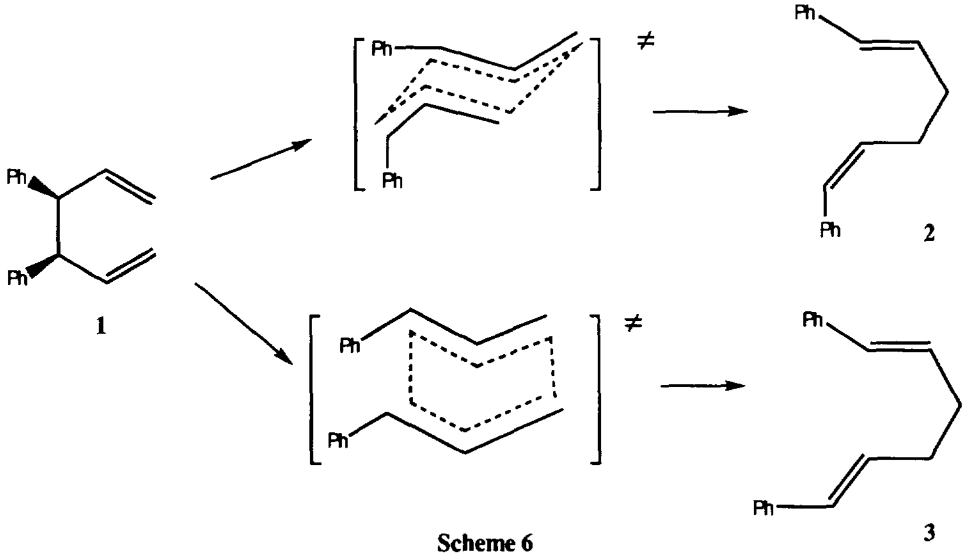
Table 3. Pressure effect in the reaction of tropone with butadiene

Pressure (MPa)	$C_A : C_B$
90	10.0 : 1
540	10.3 : 1
690	10.8 : 1

The result is that the pressure effect, e.g. the magnitude of $\Delta\Delta V^{\neq}$, is in relation with :

- the reaction mechanism
- the thermal stability of the adducts
- the solvation effect
- the bulk of the substituting groups and, more generally, the crowding of the transition state.

To illustrate the latter effect, a recent paper[12] reports the Cope rearrangement of diene **1** yielding rearranged products E,Z (**2**) and E,E (**3**). The $\Delta\Delta V^{\neq}$ between both pathways is 4.5 $cm^3.mol^{-1}$ in favour of (**2**) which is formed via the more sterically demanding chair-like transition state compared to the boat-like transition state leading to (**3**) (Scheme 6).



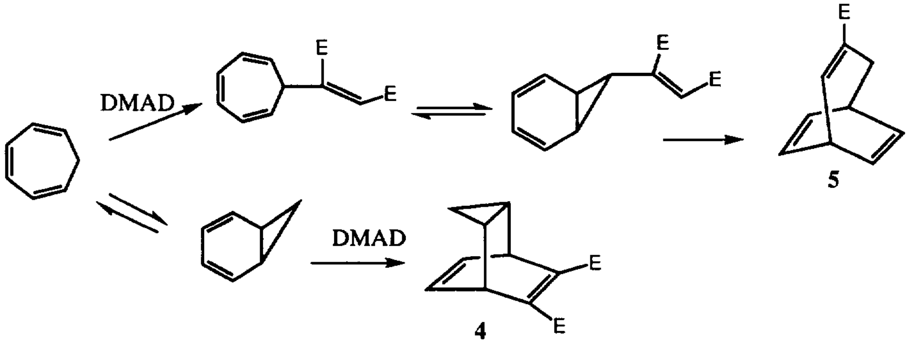
Scheme 6

3. Examples

The examples which will be detailed below refer to the pressure effect on selectivity in a very general sense. The influence of pressure on asymmetric induction is reported in the second part of the review article.

3.1 Chemo- and Regioselectivity

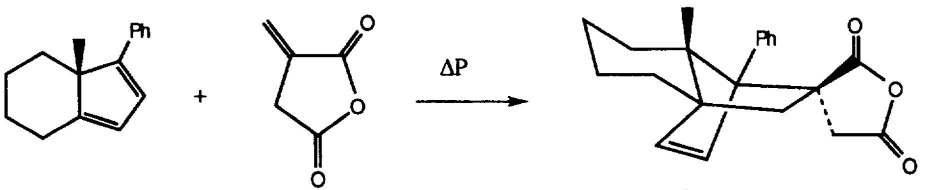
Dimethylacetylene dicarboxylate adds to cycloheptatriene yielding two products **4** and **5** in a 2 : 1 ratio at atmospheric pressure. When the pressure is raised, **5** gradually diminishes compared to **4** and eventually vanishes at a sufficiently high pressure.[13] **4** is formed via a typical [4+2] addition of norcaradiene valence tautomer and, therefore, is promoted by pressure. Product **5** results from an initial ene reaction followed by [3,3] sigmatropic shift. The ene and the Diels-Alder additions are promoted equally by pressure.[9] The formation of **4** as a single product could be explained through the pressure promoted cyclotautomerization (disrotatory electrocyclic process).[9] This is an illustrative example of a highly selective process under pressure (Scheme 7).



DMAD is E—≡—E (E = CO_2CH_3)

Scheme 7

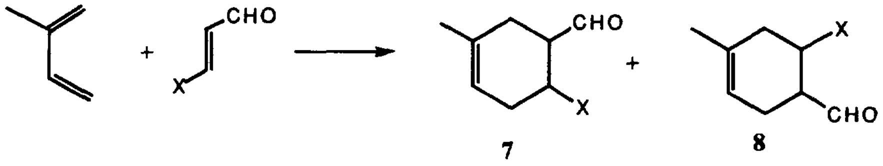
The reactions between rigid dienes and dienophiles are strongly chemo- and regioselective yielding only one adduct under high pressure. An example is provided in the synthesis of **6** (Scheme 8). In this particular case, high pressure serves mainly to stabilize adduct **6** which otherwise decomposes at ambient pressure.[14]



6

Scheme 8

Diels-Alder reactions involving isoprene and acrylic dienophiles are not regioselective. At 20° C under high pressure, acrolein adds in a fully regioselective manner whereas in the case of crotonaldehyde, one isomer is preferred when pressure is raised, probably due to a change to more kinetic product[15] (Scheme 9).

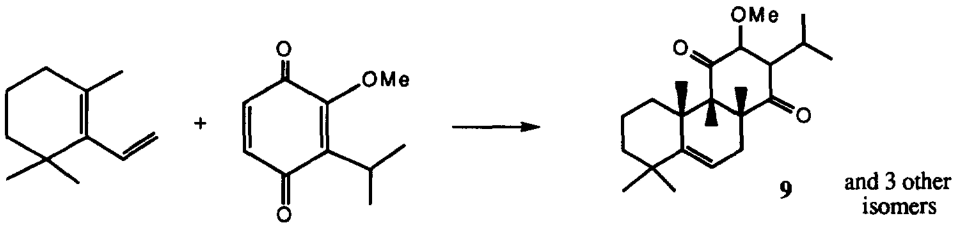


Scheme 9

If X = H, only 7 is formed

If X = CH_3, 7 increases from 60 % (600 MPa) to 72 % (1000 MPa).

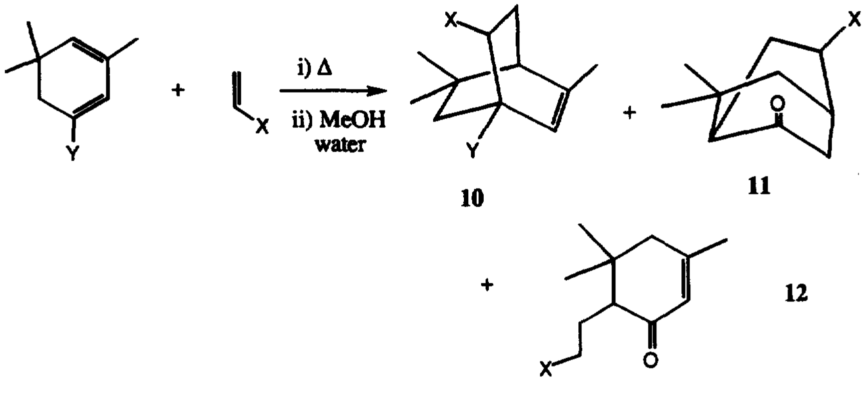
In the synthetic route to antitumor abietone diterpenes such as (±)-taxodione and (±)-royleanone, the combination of high pressure and Lewis acid catalysis leads to a significant increase of regioselectivity (Table 4, Scheme 10). The cycloadditions are also highly stereoselective.[16] New approaches towards useful higher triterpenes considered the reaction of 1,3,3-trimethyl-2-vinylcyclohexene with sterically demanding 2-cyclohexenones. Under high pressure and with $ZnBr_2$, the reaction takes place yielding either Diels-Alder or Michael adducts in a selective way.[17]



Scheme 10

Table 4. Regioselective formation of 9

Pressure (MPa)	Catalyst	Selectivity of 9 (%)
600	none	37
1200	none	59
1200	$ZnBr_2$	81



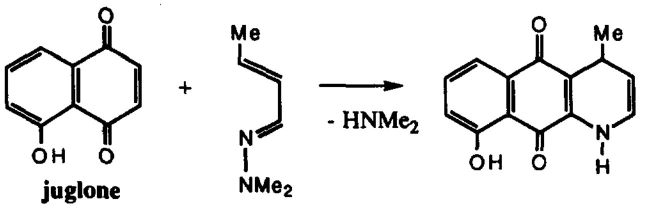
Scheme 11

An excellent chemoselectivity was observed in the cycloaddition of acrylic dienophiles to hindered enamines[18] (Table 5, Scheme 11).

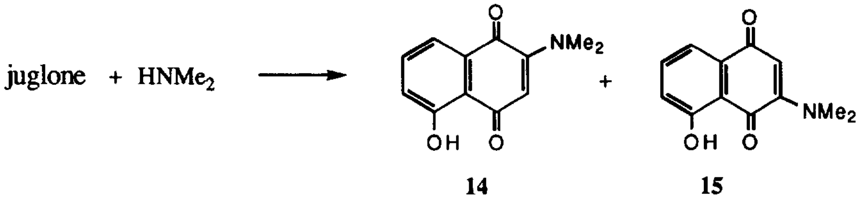
Table 5. Addition of acrylic dienophiles to enamines

Y	X	Conditions	10 (%)	11 (%)	12 (%)
Morpholino	CO_2CH_3	pressure	53	0	0
		thermal	0	29	23
Piperidino	CN	pressure	90	0	0
		thermal	0	10	20

Cycloadditions of azadienes to quinones usually afford several products in addition to polymers due to the versatile reactivity of azadienes. For example, crotonaldehyde-*N*,*N* -dimethylhydrazone adds to juglone yielding the [4+2] adduct **13** together with **14** and **15**[19] (Scheme 12). Under high pressure (and short reaction times) the cycloadduct **13** is formed in 48 % yield free from **14** and **15**, whereas at ambient pressure under sonication, the yields are respectively 52 % (**13**), 15 % (**14**), 15 % (**15**). Although the yield of **13** cannot be considered satisfactory, the result regarding selectivity is of interest, since such hetero-Diels-Alder processes present a real complexity due to their extreme sensitivity to the nature of the pair of azadiene-dienophile and experimental conditions. Pressure appears to provide a mean for keeping improved control over the reaction.

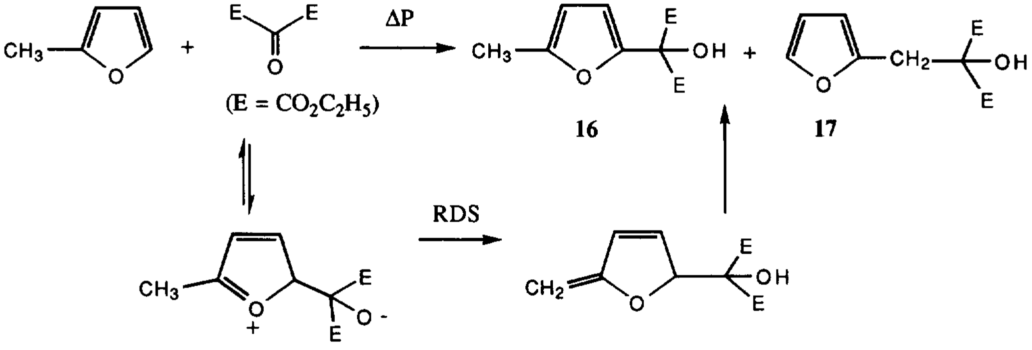


13



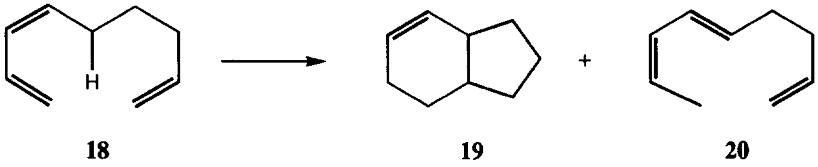
Scheme 12

The unusual reaction of 2-methylfuran with diethyl mesoxalate is strongly promoted by pressure[20] (Scheme 13). The effect is very evident in the composition of the isomeric mixture of **16** and **17**. The proportion of **17** varies from 28 % at 250 MPa (no reaction at atmospheric pressure) to 77 % at 1200 MPa. The exact reason why pressure promotes **17** vs **16** is not clear. In particular the mechanism leading to **17** seems to reflect a complex process, probably involving electrophilic attack at the C-2 carbon adjacent to the oxygen, proton transfer from the methyl group at C-5 and a [1,5]-sigmatropic rearrangement.[21] (Scheme 13)



Scheme 13

Thermolysis of (Z)-1,3,8-nonatriene **18** gives products **19** and **20**, both according to pericyclic processes[12]: an intramolecular [4+2] addition yielding **19** and a [1,5]-sigmatropic shift affording **20**. At 0.1 MPa, **20** is preferred whereas high pressure reverses the selectivity in favour of the Diels-Alder product **19**. $\Delta\Delta V^{\neq}$ has been estimated to 10-12 cm^3.mol^{-1} (Scheme 14).

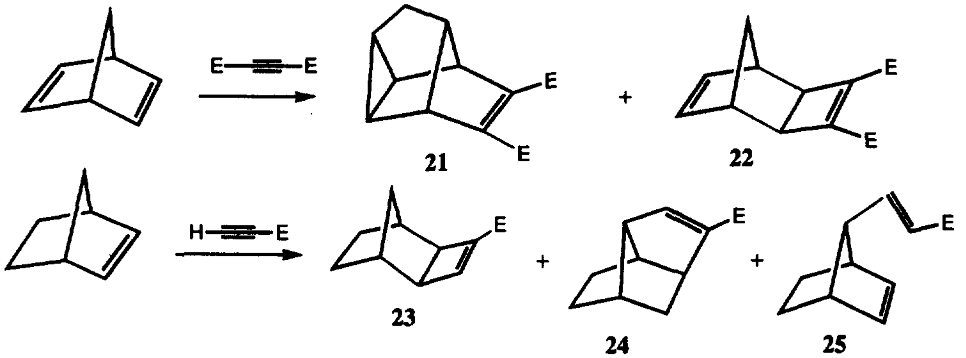


	19	20
0.1 MPa	31	69
770 MPa	73	27

Scheme 14

High pressure can also reverse the chemoselectivity of catalyzed addition reactions versus uncatalyzed analogs (Table 6, Scheme 15).[22]

In reaction A, in the ruthenium-catalyzed process, pressure affects considerably the chemoselectivity whereas it remains unchanged in the $AlCl_3$ catalyzed reaction B. In the latter case, **23**, **24** and **25** originate from a common zwitterionic intermediate.[23] The reversal of chemoselectivity in the ruthenium-catalyzed reaction with a pressure increase of only 300 MPa is seemingly surprising. In fact, in this case, the catalytic cycle is probably complex involving several steps which may be affected by pressure in antagonistic directions as a general property of transition metal catalyzed reactions.



Scheme 15

Table 6. Addition of acetylenic esters to norbornadiene and norbornene

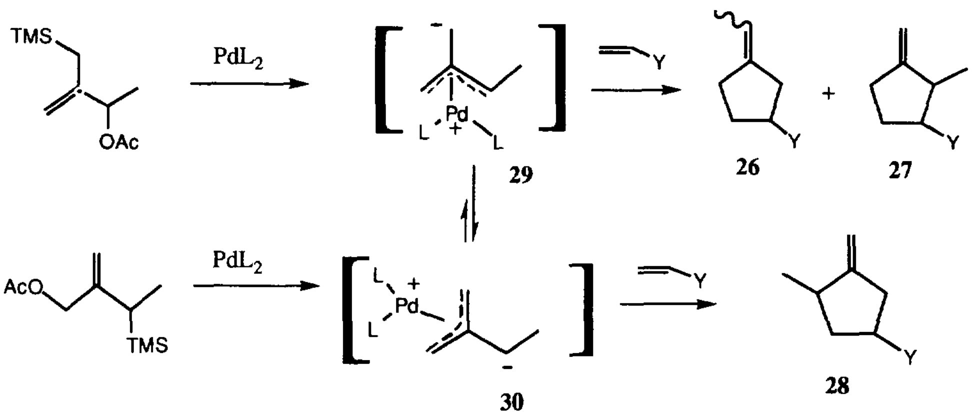
Reaction	Catalyst	P(MPa)	Selectivity (%)				
			21	**22**	**23**	**24**	**25**
A	none	0.1	100	0			
	none	300	100	0			
	Ru*	0.1	31	69			
	Ru*	300	87	13			
B	$AlCl_3$	0.1			71	18	11
	$AlCl_3$	300			74	18	8

* : $RuH_2CO(PPh_3)_3$

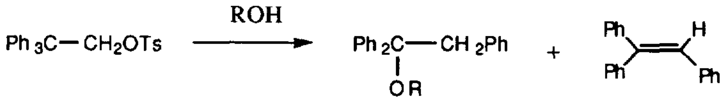
At this point, it may be mentioned that strong Lewis-acid catalysts often perturbs the course of reactions involving sensitive dienes prone to polymerization. In this respect, it has been asserted[24] that $LiClO_4$ in diethyl ether acting either as a Lewis acid-like catalyst or as a medium of high internal pressure[25] is a substitute for the pressure methodology. In fact, in most cases, operation under pressure not only improves yields, but leads to higher chemoselectivity .[26]

High pressure was shown to exert a dramatic effect on regioselectivity in palladium-catalyzed trimethylenemethane (TMM) cycloadditions.[27] Such reactions occur via Pd-TMM complexes yielding three regioisomeric adducts **26**, **27**, **28** (Scheme 16).

Under standard conditions, **28** predominates via the thermodynamically favored complex **30**. However, it was recently found that high pressures reversed the regioselectivity in promoting **26** and/or **27**.[27] For example, in the cycloaddition of TMM to coumarone, the ratio **26** + **27** : **28** changed from 1 : 9 to (3.2-3.8) : 1. Similarly, with benzylideneacetone, this ratio (1 : 3) was reversed to 3.6 : 1. In the case of dimethyl benzylidenemalonate, only **26** was formed at high pressure (**26** : **28** was 1 : 3.3 under standard conditions). The same trend was also found in [6+4] cycloadditions. The proposed explanation considered that in Scheme 16 pressure increased the rate of the bimolecular addition to the acceptor (favoring **26**) versus the unimolecular interconversion of Pd-TMM complexes **29** and **30**. Another interesting observation was the fact that pressure decreased the rate of these reactions, a result in relation to the detrimental pressure effect on ligand dissociation which necessarly is involved in such multistep catalytic cycle.



Scheme 16



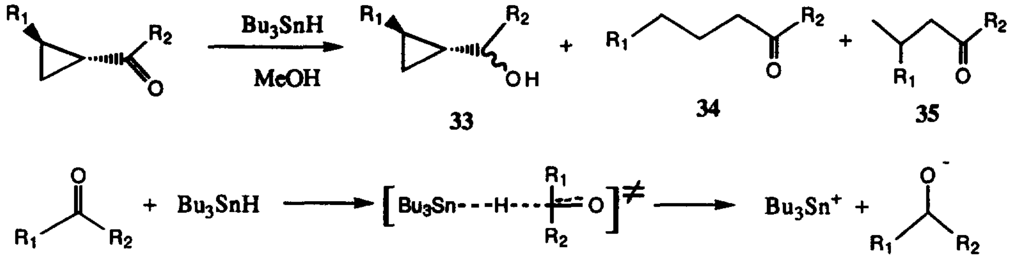
Scheme 17

Pressure improves chemoselectivity in solvolysis reactions. Alcoholysis of 2,2,2-triphenylethyl tosylate yields an ether via nucleophilic substitution with rearrangement and triphenylethylene via an elimination process[28] (Scheme 17). Pressure promotes nucleophilic substitution (92 % ether is formed at 500 MPa vs 55 % at ambient pressure when ROH is methanol). Substitution implies the reaction of one molecule of solvent with the carbenium ion so that the volume of the system in the transition state is decreased whereas elimination would occur with a positive activation volume. Similarly, hydrolysis of esters proceeds chemo- and regioselectively under high pressure.[29]

$$\mathrm{ArCl} + \mathrm{Me_2NR} \longrightarrow \underset{\mathbf{31}}{\mathrm{ArN(Me)R}} + \underset{\mathbf{32}}{\mathrm{ArNMe_2}}$$

Scheme 18

Nucleophilic aromatic dealkylation of heteroaromatic chlorides takes place under 800 MPa at 100° C in a very selective way (Scheme 18). Product 31 represents 80-90 % of the product mixture.[30]



Scheme 19

As stated above, chemoselectivity is largely influenced by steric requirements. It has been demonstrated that the effect of pressure on sterically demanding reactions is very significant,[31] producing late transition states and, accordingly, is a revelator of high negative $\Delta V^{\neq}$-values. This is highlighted in the reduction of sterically hindered ketones by tributyltin hydride[32] (Table 7, Scheme 19). Alkylcyclopropylcarbinols are selectively produced under 1400 MPa pressure in nearly quantitative yields whereas open-chain ketones are formed predominatly at ambient pressure. The result can be understood when considering that pressure would favour a polar hydrostannation pathway over the radical mechanism, as much as steric strain is introduced in the ketone.[31] This means that electrostriction will contribute to the magnitude of the activation volume (Scheme 19).

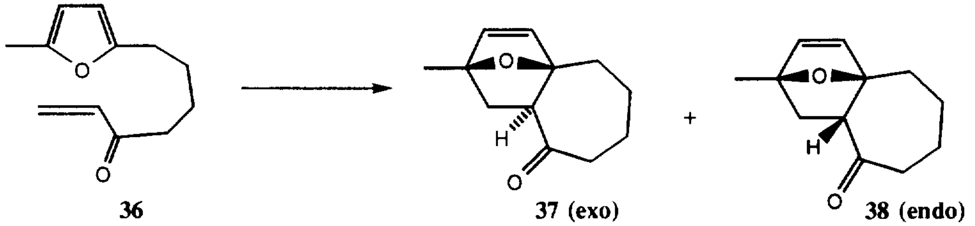
Table 7. Distribution of products in the reduction of cyclopropylketones.

R_1	R_2	P(MPa)	Selectivity (%)		
			33	34	35
H	Me	0.1	50	50	0
		1400	87	13	0
H	Ph	0.1	50	50	0
		1400	87	13	0
Me	iPr	0.1	33	33	33
		1400	100	0	0
--$(CH_2)_3$--		0.1	42	0	58
		1400	94	0	6

3.2 Stereoselectivity

The stereochemistry in Diels-Alder reactions is predominantly endo (endo rule). It was shown some time ago that pressure influences the endo cycloadduct only moderately.[33] More recently, a significant pressure effect was detected in the homo-Diels-Alder reaction of norbornadiene and maleic anhydride.[34] The endo content varied from 81 % at ambient pressure to 92 % at 1000 MPa pointing to $\Delta V^{\neq}$endo - $\Delta V^{\neq}$exo = - 3.4 cm^3.mol^{-1}. This result could be accommodated in terms of enhanced rigidity of the transition state arising from geometrical factors favoring attractive secondary orbital interactions. As a general rule, pressure acts beneficially on the formation of endo isomer, as demonstrated in the thermal dimerization of 1,3-cyclohexadiene[6] . The endo : exo stereoisomer ratio changes from 8 : 1 at atmospheric pressure to 24 : 1 at 700 MPa ($\Delta\Delta V^{\neq}$ = - 6 cm^3.mol^{-1}).

In the intramolecular Diels-Alder reaction of compound **36** (Scheme 20), the endo adduct **38** is kinetically promoted by high pressure. At 1200 MPa, the endo : exo ratio changes from 47 : 53 (90 % yield) to 72 : 28 (92 % yield) for a reaction time of 10 h and 50 h respectively.[35] This is presumably caused by a difference of 5 cm^3.mol^{-1} in the partial molar volumes of **37** and **38**.



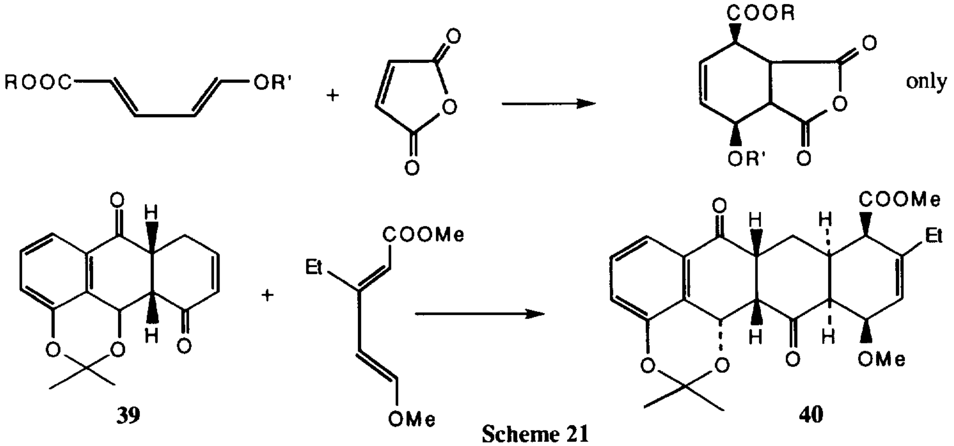
36 $\overline{V}$ = 183 cm^3.mol^{-1}

37 (exo) $\overline{V}$ = 169 cm^3.mol^{-1}

38 (endo) $\overline{V}$ = 164 cm^3.mol^{-1}

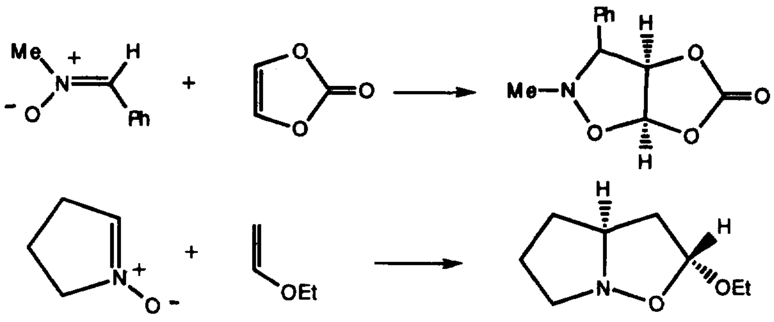
Scheme 20

In high pressure Diels-Alder reactions involving cyclic dienophiles and push-pull substituted dienes, only one regio- and stereoisomer is observed.[36] High regio- and endo- stereoselectivity is reached in the [4+2] cycloadditions shown in Scheme 21.[37,38] These reactions may be of importance in synthetic organic chemistry, particularly the condensation of **39** leading to product **40**, a precursor of the antibiotic aklavinones[36] (Scheme 21).



Scheme 21

High pressure alters the stereoselectivity in the [3+2] dipolar cycloaddition of nitrones with vinyl ethers and esters[39] (Scheme 22). At ambient pressure the ratio **41** : **42** is 50 : 50 whereas it changes to 33 : 67 under 200 MPa. A more striking example is provided by the exclusive formation of **43** at a pressure of 200 MPa in 83 % yield, whereas no reaction occurs at ambient pressure.



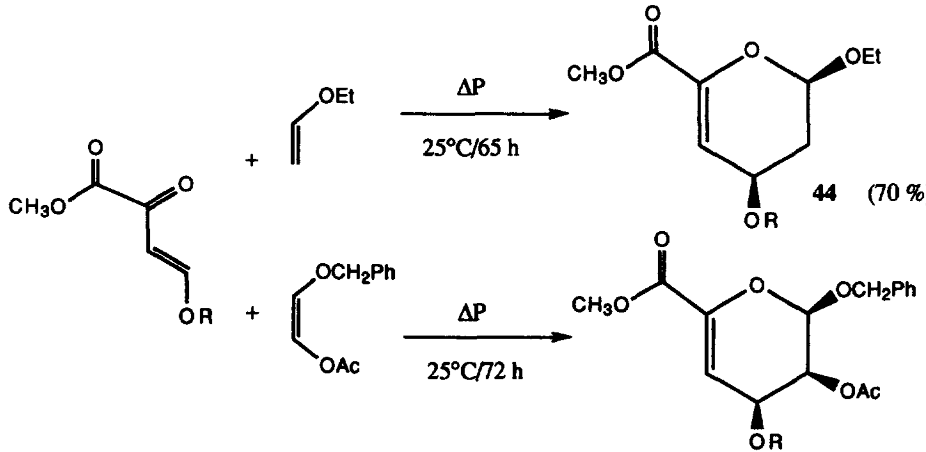
41 (cis)

42 (trans)

43 only

Scheme 22

In the inverse electron demand [4+2] cycloaddition of 1-oxa-1,3-butadienes with electron rich dienophiles, the endo adducts **44** and **45** are produced preferentially[40] (Scheme 23). The endo selectivity increases noticeably as the pressure increases. At 1300 MPa, the endo : exo ratio is 5.7 : 1.0 in the case of ethyl vinyl ether and > 45 : 1 with the cis 1,2-disubstituted dienophile. The substantial increase with pressure in the diastereoselectivity of the cycloaddition of the above oxobutadiene with the latter dienophile can be attributed to the additional differences in $\Delta V^{\neq}$ between the reaction paths leading to the endo and exo diastereoisomers because of the additional cis C-2 dienophile substituent.

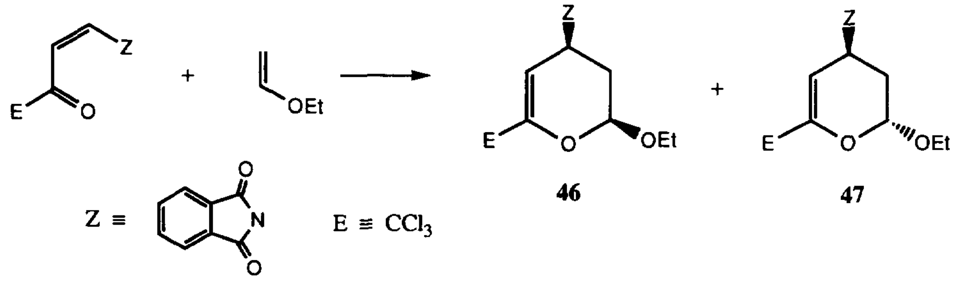


44 (70 %)

Scheme 23

45 (50 %)

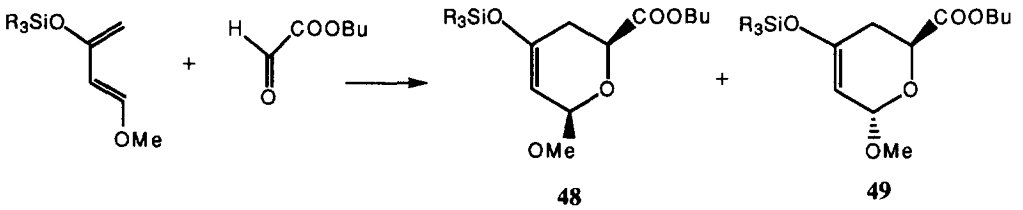
A significant pressure effect on diastereoselectivity has been detected in Diels-Alder reactions of enaminoketones and vinyl ethers[41] (Scheme 24). If Z is a benzomaleimido group and E = CCl_3, $\Delta\Delta V^{\neq}$ = -5.9 $cm^3.mol^{-1}$, resulting in a ratio (**46** : **47**) of 1.67 at 0.1 MPa and 13.6 at 600 MPa. The result has been confirmed in a further study demonstrating that high cis diastereoselectivity can be achieved by operating at pressures as high as possible with partners possessing adequate electronic requirements.[42]



Scheme 24

An even higher $\Delta\Delta V^{\neq}$ -value has been found in the photoinduced cyclodimerization of 1,3-cyclohexadiene $\Delta\Delta V^{\neq}$ (endo - exo) ~ - 9 to -12 cm^3.mol^{-1} in relation to the involvement of solvated ion pairs.[43] The $\Delta\Delta V^{\neq}$ -value refers to two types of mechanisms depending on the solvent used and the triplet energy of the sensitizer. The pressure-induced diastereoselectivity in the photochemical [2+2] addition of cyclopentenones with cyclopentene and 3,3-dimethyl-1-butene has been studied recently.[44]

Diastereoselectivity is influenced by pressure in organometallic reactions. The cis-diastereoisomer **48** is promoted by pressure in the Diels-Alder cycloaddition of trialkylsilyloxy substituted dienes and glyoxalates[45] (Table 8, Scheme 25). The selectivity of the thermal reaction is poor.

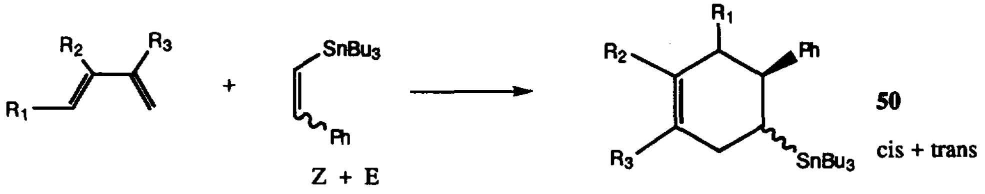


Scheme 25

Table 8. Pressure effect on diastereoselectivity (Scheme 25)

R_3	P(MPa)	48 : 49
$(CH_3)_3$	0.1	1 : 1
	1000	5 : 1
$(CH_3)_2Bu^t$	0.1	7 : 3
	1000	10 : 1

An interesting case of reverse diastereoselectivity has been observed in the following addition reaction involving a trialkyltin dienophile[46] (Table 9, Scheme 26). The reversal of diastereoselectivity is explained by a thermal isomerization of the starting diene at 180° C (temperature needed to observe the reaction at ambient pressure) prior to addition.

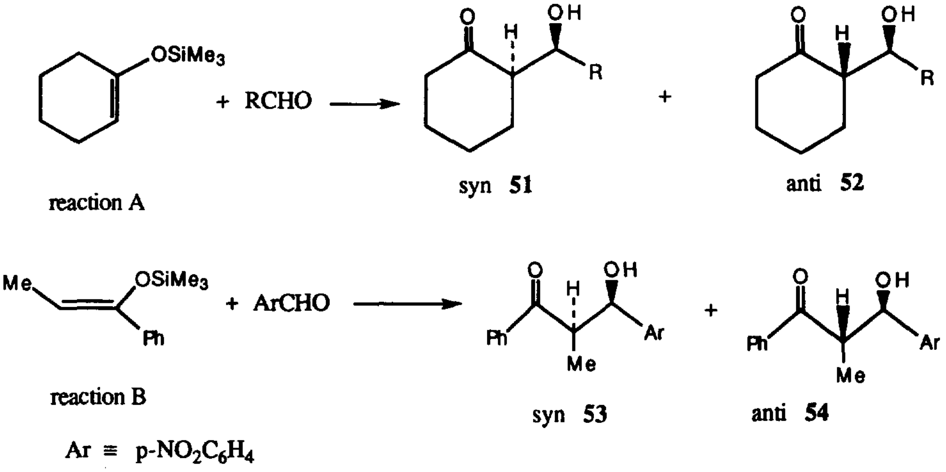


Scheme 26

Table 9. Pressure effect on diastereoselectivity (Scheme 26)

R_1	R_2	R_3	Z : E	P(MPa)	T (°C)	Cis : Trans
H	CH_3	CH_3	70 : 30	0.1	180	19 : 81
				2300	70	90 : 10
OCH_3	H	H	75 : 25	0.1	180	22 : 78
				2000	70	70 : 30

Aldol reactions of silyl enol ethers with aldehydes are noticeably accelerated by the application of pressure[47] (Scheme 27). Diastereoselectivity is also significantly influenced (Table 10). In addition, it should be noted that the stereoselectivity reverses in comparison with that of the $TiCl_4$-catalyzed (Mukaiyama) reaction. For reaction A, the ratio **51** : **52** changes from 3 : 1 (Mukaiyama) to 1 : 3 (high pressure), whereas in reaction B the corresponding values for the ratio **53** : **54** are 2 : 3 (Mukaiyama) and 3 : 1 (high pressure). The stereoselectivity results are explained by the existence of a cyclic chair transition state at low pressure. The anti preference (**52** in reaction A) or syn preference (**53** in reaction B) with increasing pressure are rationalized by considering that high pressure induces a crossover from a chair- to a boat preferred transition state which exhibits a more compact structure.

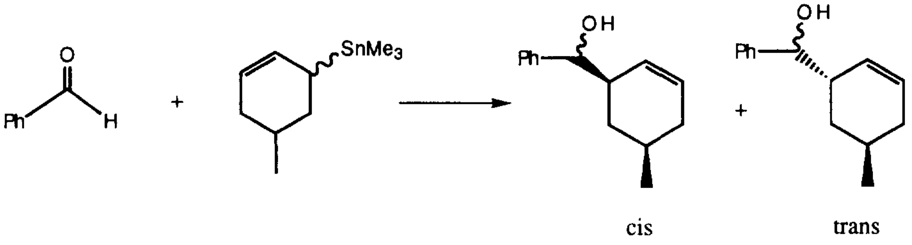


Scheme 27

Table 10. Pressure effect on diastereoselectivity in the aldol reaction of silyl enol ethers with aldehydes

Pressure (MPa)	% anti	
	52	54
300	20	57
500	31	51
800	67	41
1000	76	29
1200	80	-

A recent paper underlines the good erythro diastereoselectivity in the high pressure (900 MPa) addition of benzaldehyde to allylstannanes[48] (Table 11, Scheme 28). The addition occurs stereospecifically via syn approach of the electrophile. The diastereoselectivity results are consistent with a cyclic S_Ei' transition state with an unfavorable pseudo 1,3-diaxial interaction between the phenyl and the methyl group (in $SnMe_3$) leading to the threo product.



Scheme 28

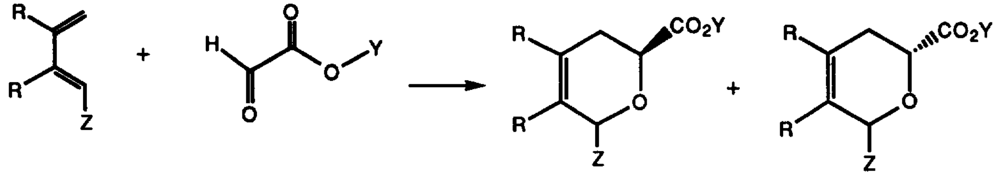
Table 11. Diastereoselectivity in the high pressure addition of benzaldehyde to an allylstannane (Scheme 28)

Cis : Trans	T°C	cis, erythro*	trans, erythro*
67 : 33	30	62	30
35 : 65	30	36	54
58 : 42	60	46	43
33 : 67	60	24	62

* : Remainder : cis and trans, threo

4. High pressure asymmetric synthesis

There are only a few reports in the field of high pressure asymmetric induction. The first experiments date back to two examples in the late 1970's. The Wagner-Meerwein rearrangement of 1,1-diphenyl-2-methyl-2 (4-methoxyphenyl) oxiran was examined in chiral solvents.[49] Whereas an optically inactive product was formed under normal pressure conditions, asymmetric induction was observed at 1000 MPa pressure, pointing to an enantioselective reaction. In the other work, (R)(-) menthyl glyoxalate was reacted with 2,3-dimethyl-1,3-butadiene and 1-methoxy-1,3-butadiene (Reaction B in Fig. 1)[50] (Scheme 29).



Y is $C_{10}H_{19}$

Scheme 29

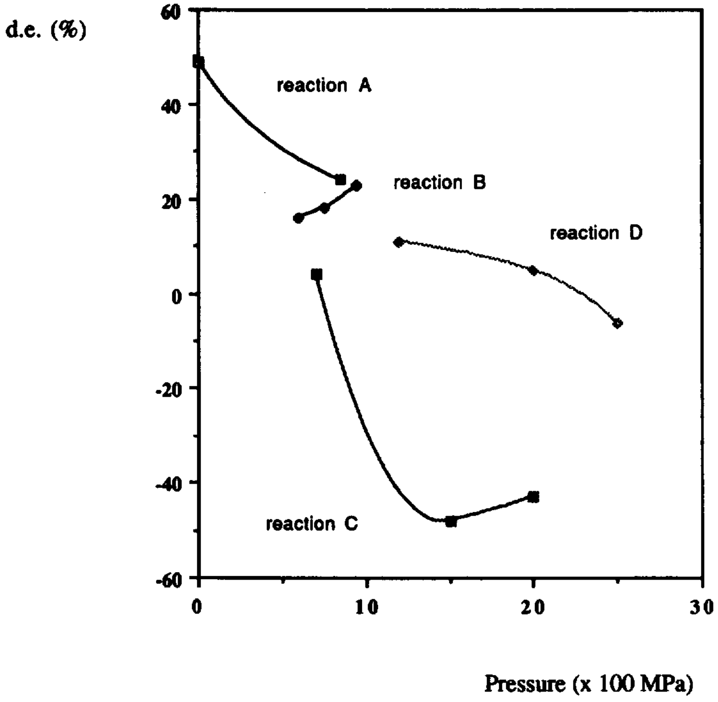
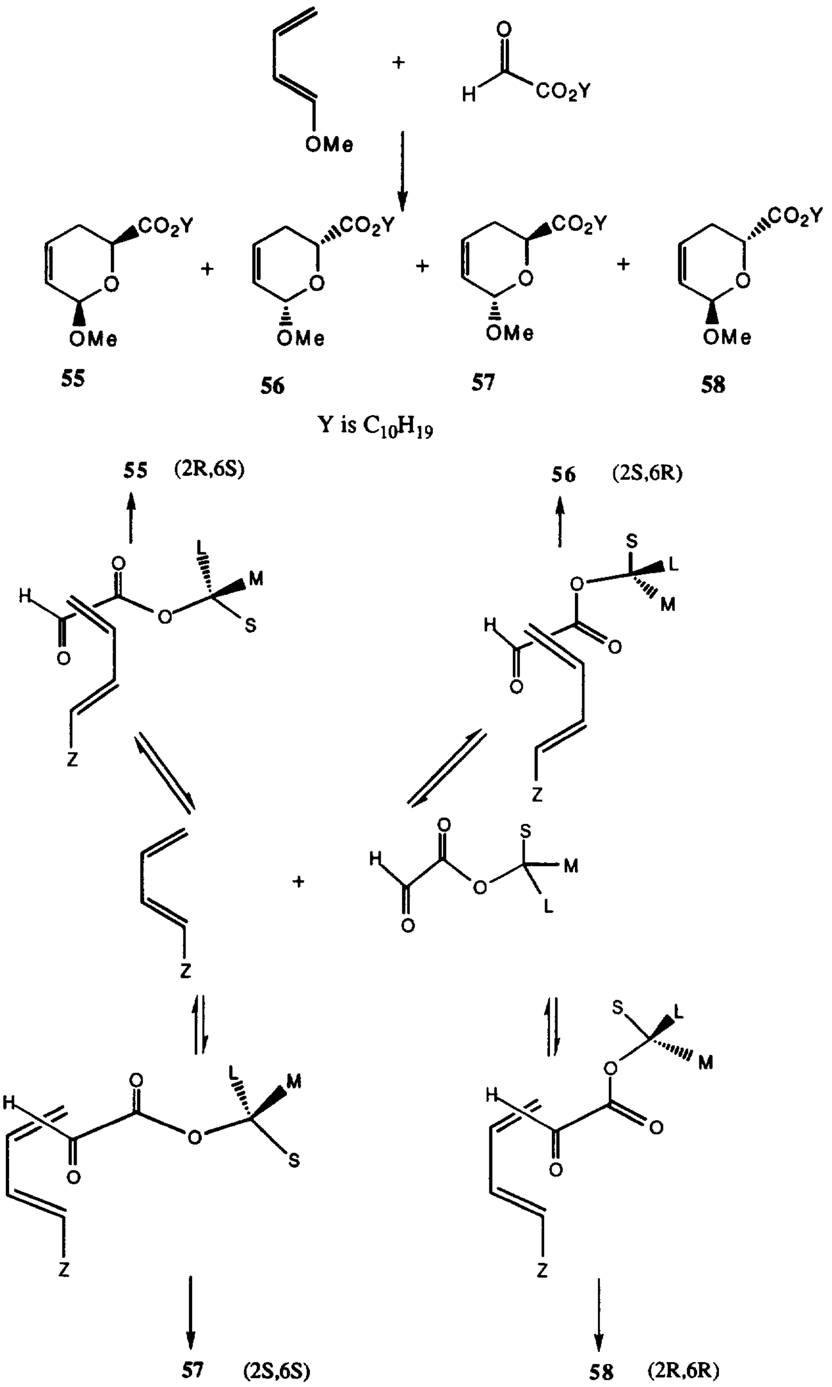


Figure 1

For both Diels-Alder reactions, the diastereoisomeric excess was raised by pressure, regardless of the solvent. The increase in optical activity was moderate, but perceptible (Fig. 1). The results were rationalized by taking into account the concept of parallel transition states (TS). Four TS may be envisaged depending on the conformation of the glyoxalate ester when entering the transition state (Scheme 30).[51]



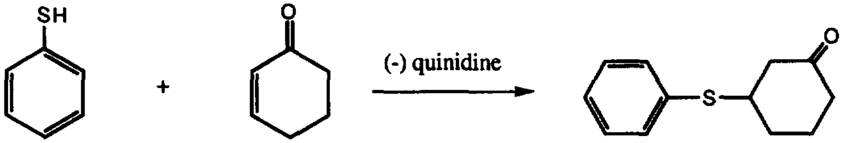
Scheme 30

(Reproduced with permission from High Pressure Chemical Synthesis, J. Jurczak and B. Baranowski Eds., Elsevier, Amsterdam (1989) p. 217)

According to Scheme 30, the glyoxalate ester which has adopted a cisoid conformation with absolute configuration (R) leads predominantly to adducts with a chiral center (6S) (*endo* and *exo)* (via TS leading to **55** and **57**). The magnitude of asymmetric induction was supposed to result from the relative TS probabilities leading to **55-56** and **57-58** , which obviously, depend on reaction parameters such as pressure, temperature and nature of solvent. Combinations of pressure and type of solvent can give a preference for a particular transition state. For example, the highest increase in optical yield under pressure is reached when the cycloaddition is carried out in toluene. Toluene is a non polar solvent, leading to electrostriction under pressure for ionogenic reactions.[52]

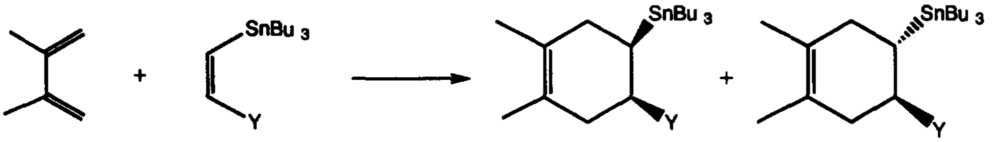
Subsequent studies on the effect of pressure on asymmetric induction lead to the general conclusion that asymmetric cycloadditions should be performed under very high pressure in solvents such as toluene that are characterized by a high freezing pressure and solvation properties in association with the effect of pressure.[50] A detailed review analyzes the pressure effect on asymmetric induction in the case of the synthesis of monosaccharides.[53]

The effect of pressure, however, may be puzzling. As illustrative examples, in the quinine- and quinidine-catalyzed Michael addition of benzenethiols to cyclohexenones (reaction A in Fig. 1) (Scheme 31) and methyl oxoindancarboxylate to methyl vinyl ketone, the enantiomeric excesses are decreased by pressure[54] (Fig. 1). The explanation makes use of the tightness of the different transition states. Steric requirement is the most determining stereodifferentiating parameter which causes a free energy difference between the two possible structures of TS leading to the R or S product. As pressure has been shown to promote the more congested transition state, the more compact enantiomer is favoured.



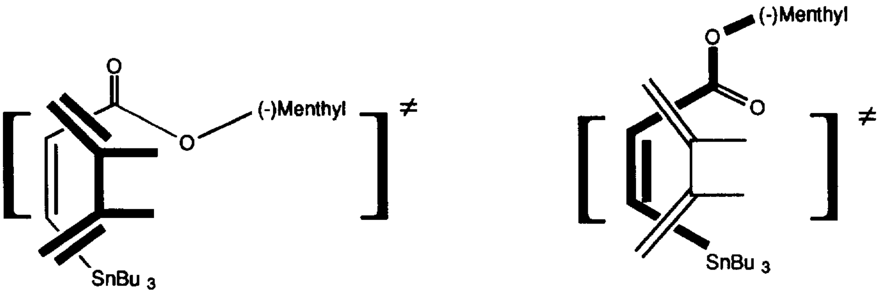
Scheme 31

The same result is obtained in the Diels-Alder reaction of 2,3-dimethylbutadiene with a (Z)-stannyl acrylic acid (-)menthyl ester[55] (reaction D in Fig. 1) (Scheme 32). The diastereoisomeric excess is decreased by pressure and, eventually, is reversed under very high pressure (Fig. 1). The result is accounted for by the shift of a S-trans transition state to the more compact S-cis TS, a result in harmony with the common pressure effect on steric congestion[31] (Scheme 33).



Y is CO_2(-)Menthyl

Scheme 32



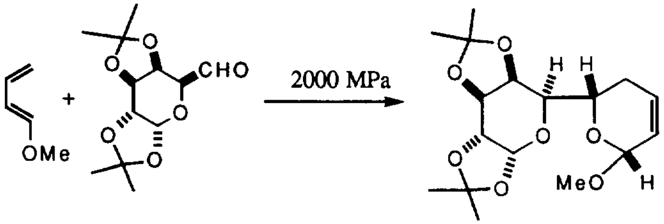
S - trans

S - cis

Scheme 33

An even more complex situation is encountered in the asymmetric condensation of 1-methoxy-1,3-butadiene and 2,3-di-O-benzyl-D-glyceraldehyde.[56] A change in the direction of induction occurs between the thermal and the lanthanide-catalyzed reaction (reaction C in Fig. 1). A minimum for optical activity is detected at a given pressure for the catalyzed reaction.

A remarkable example of 100 % asymmetric induction is provided by the very high pressure (2000 MPa) uncatalyzed Diels-Alder reaction of sterically hindered sugar aldehydes with 1-methoxybutadiene.[57,58] (Scheme 34).

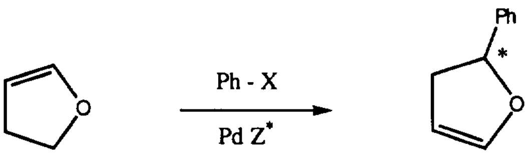


(exclusively)

Yield : 72 %
de ~ 100 %

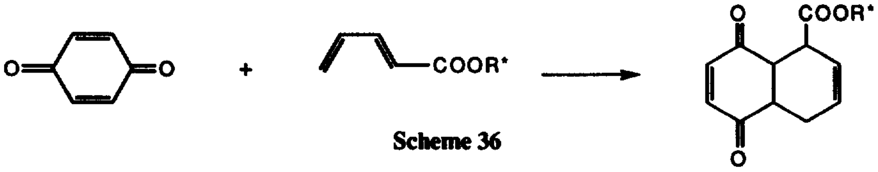
Scheme 34

The pressure effect on the palladium-catalyzed coupling of 2,3-dihydrofuran and phenylnonaflate was significant (Scheme 35). With a chiral Pd catalyst, 89 % ee was reached (only 47 % at ambient pressure).[59]



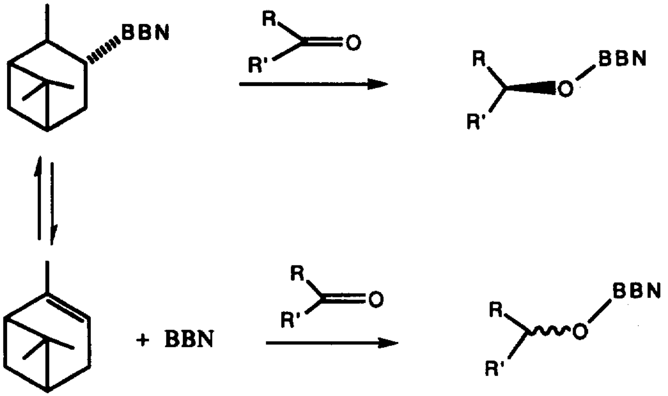
Scheme 35

Chiral induction is observed in the high pressure Diels-Alder reaction of p-benzoquinone and chiral 2,4-pentadienoic esters and amides[60] (Scheme 36). Interestingly, bulkier dienoic derivatives lead to higher optical yields, demonstrating the beneficial effect of pressure in overcoming steric hindrance.[61]



Scheme 36

The same effect is observed in the asymmetric induction of prochiral ketones with B-3-pinanyl-9-borabicyclo[3.3.1]nonane (Table 12, Scheme 37).[62] The process is characterized by two competing pathways : a bimolecular β-hydride elimination yielding an optically active product and a dehydroboration-reduction sequence leading to racemization. The results of Table 12 clearly indicate that the bimolecular process is promoted by pressure.

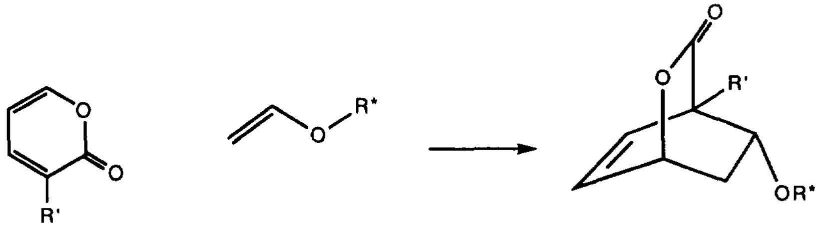


Scheme 37

Table 12. Enantiomeric excess in the reduction of prochiral ketones

Ketone	ee %	
	0.1 MPa	600 MPa
Me-CO-C_6H_{13}	44	63
Ph-CO-Me	78	100
Me-CO-CH=CHPh	58	71
Me-CO-isopropyl	57	90
α-tetralone	52	89
Cyclopropyl-CO-Me	no reaction	75
$Me_3SiC{\equiv}C$-CO-tert-butyl	no reaction	100

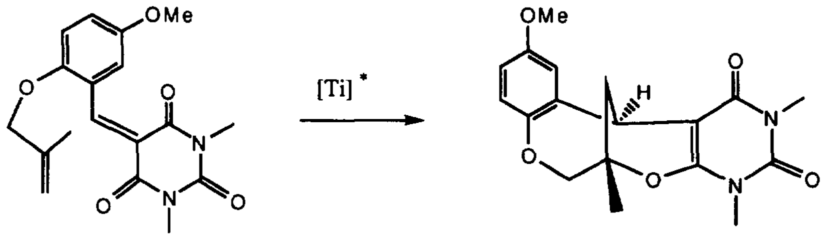
High pressure is the method of choice for preparing bis-adducts retaining the CO_2 fragment from the condensation of pyran-2-ones with chiral dienophiles.[63] Thermal or Lewis acid-catalysis conditions are not suitable, since decarboxylation occurs. Under high pressure excellent chemical yields and good levels of asymmetric induction are reached (Scheme 38).



Scheme 38

More examples of high pressure asymmetric conditions can be found in the recent literature : for example synthesis of abietanoid *o*-quinones[64] and enantioselective synthesis of β-aminoesters[65] (Scheme 39). An elegant study reported the remarkable increase in the enantioselectivity of the intramolecular Diels-Alder reaction shown in Scheme 40.[66] By the use of a chiral titanium Lewis acid, the enantiomeric excess progressed from 4.5 % at ambient pressure to 20.5 % at 500 MPa. The result may be explained by the difference in the bulkiness of the transition state leading to both enantiomers. In ref. 66, the authors made an interesting additional suggestion, e.g. the formation of complexes with different stoichiometry according to pressure.

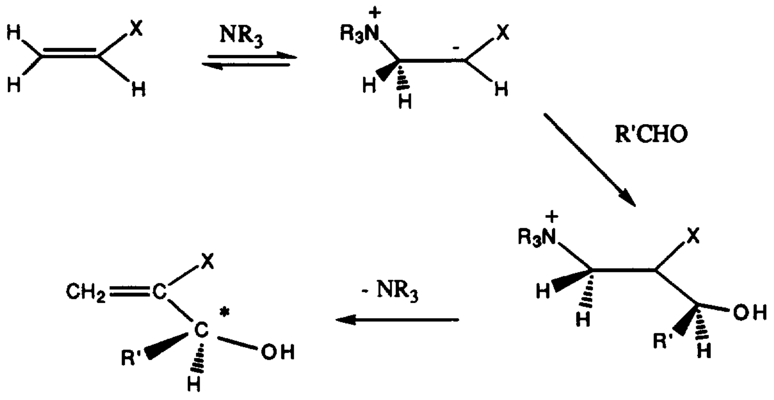
Scheme 39



d and l enantiomers

Scheme 40

In the last decade, the Baylis-Hillman reaction has been rediscovered because of its extreme sensitivity to pressure.[67] It consists of the addition of an acrylic compound to a keto derivative in the presence of a tertiary amine. In fact, it is a multistep process involving as a first step the conjugate addition of the amine to the acrylic compound followed by nucleophilic attack of the resulting enolate on the keto derivative[68] (Scheme 41). The product contains a new chiral center. Optical activity can be induced either by using chiral acrylic esters[67] or chiral substituted diazabicyclo[2.2.2]octanes (DABCO-catalysts).[69] In the first case, 100 % ee was obtained in the reaction of benzaldehyde with (-) menthyl acrylate at 750 MPa instead of 22 % at ambient pressure.[67] With chiral DABCO derivatives, a remarkable enhancement of enantioselectivity was observed when the pressure was raised from 0.1 to 500 MPa.[69]



Scheme 41

5. Conclusion

Since pressure influences organic reactions kinetically, it also has an effect on selectivity. Chemoselectivity is generally largely favored by high pressure because of the mildness of thermal conditions. The pressure control of regio- and stereoselectivity depends on the difference between the activation volumes of parallel reactions leading to regio- or diastereoisomers. The pressure effect on the direction of asymmetric induction is not predictable. The diastereoisomeric excess can be increased or adversely affected by pressure, depending on the steric requirements of the transition state specific to each configuration (the concept of parallel transition states). High pressure should be considered as a useful parameter for the synthesis of optically pure synthons especially when the reaction proceeds via a sterically congested transition state.

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Biographical Sketch

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Gérard Jenner received his PhD in 1966 from the University of Strasbourg . His scientific concern has been high pressure chemistry and thermodynamics covering various fields such as macromolecular science, P-V-T relationships, homogeneous catalysis, physical and synthetic organic chemistry. After two years spent as professor of physics in Tunisia, he joined the Centre National de la Recherche Scientifique where he is now director of research. He took a position as Research Associate at the State University of New York at Stony Brook with Prof. W. J. le Noble (1980-81). He was member of the Board of the International Association of High Pressure Science and Technology (AIRAPT), of the Board of the European Physical Society (Condensed Matter Division) and had the chairmanship of the European High Pressure Research Group (1988-91).

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