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Comparative activation modes in organic synthesis. The specific role of high pressure

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1. Introduction

While a number of reactions occur spontaneously, most require activation. The first basic premise of any organic chemist has been to use heat in order to increase molecular agitation as well as the frequency of efficient collision between molecules. In addition to thermal agitation, the traditional means of inducing reactivity are focused on photonic activation and chemical catalysis (general acid and base catalysis, Brönsted bases and Lewis acids). In recent years, however a range of new activation modes have emerged.

We shall classify these into physical activation modes (ultrasonic waves,[1] microwaves[2]), chemical modes (catalysis by novel mild Lewis acids[3] and transition metals[4]), physicochemical modes (activation through solvophobic effects[5]—including microemulsions[6] and vesicles,[7] host–guest chemistry such as the use of calixarenes,[8]

Keywords: high pressure; multiactivation; Diels–Alder reaction; cycloaddition; Michael reaction.

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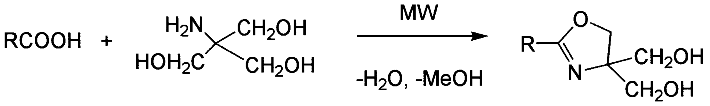


Scheme 1.

cyclodextrins…,[9] 'activation' in liquid crystals[10]), and biochemical catalysis (enzymatic[11] and antibody catalysis[12]).

Over several decades, the objective of many laboratories throughout the world has been the promotion of high-pressure chemistry as a powerful original, yet simple, physical activation method.[13] Whereas chemical activation has been considered as a tool in organic synthesis from the mid-19th century with a better knowledge of the phenomenon of catalysis, pressure was considered only from the beginning of this century.[14]

The present review article

(i) reports comparative results in preparative organic chemistry using some activation modes mentioned above vs pressure activation, and
(ii) highlights the specific effects making pressure a useful synthetic method.

The rate v of a chemical reaction as defined below (bimolecular process) is given by:

$$A + B \rightarrow C$$

$$v = -d[A]/dt = -d[B]/dt = d[C]/dt = k[A][B]$$

The equation indicates that the more concentrated the solution, the higher the rate. The rate, however, is also a function of the kinetic constant k. This constant is intimately dependent on various physical and chemical parameters. In the transition state theory, k is related to temperature and pressure by the well-known expressions:

$$k = A\exp(-E/RT) \qquad \text{(Arrhenius equation)}$$

with

$$E = \Delta H^{\neq} + RT \qquad \text{and} \qquad \Delta G^{\neq} = \Delta H^{\neq} - T\Delta S^{\neq}$$

$$\ln k = -1/RT \int \Delta V^{\neq}\, dP \qquad \text{(Evans–Polanyi equation)}$$

with

$$\Delta V^{\neq} = \partial \Delta G^{\neq}/\partial P \qquad (\Delta V^{\neq} = \text{activation volume})$$

$\Delta G^{\neq}$ is a measure of the height of the potential barrier that the reaction must overcome in order to proceed. Under standard conditions (P and T constant), every reaction possesses a well-defined activation energy. Under specific activation conditions $\Delta G^{\neq}$ can be modified so that the potential barrier is lowered to allow the system to reach the crest of the peak and, subsequently, to enter the transition state. Chemical reactions are influenced by pressure in several ways depending on the volume variations generated by the progression from the ground state to transition state ($\Delta V^{\neq}$).

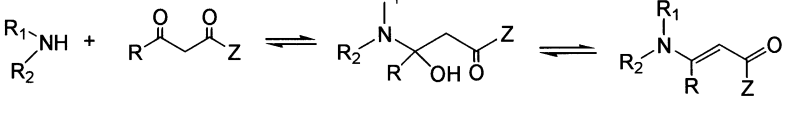
2. Comparison of pressure activation and other activation modes

2.1. Microwaves

Microwaves (MW) are electromagnetic waves (wavelength between 1 cm and 1 m). Polar molecules are subject to dipole orientation (dipolar polarisation) which alternates when the electric field is generated by a high-frequency alternative current. The resulting molecular friction leads to a rapid temperature increase depending on the dipole moment of the molecules. Although the intimate causes of microwave effects on chemical reactions contain some obscure facets, it has become clear in recent years that two effects are operative: (i) a merely thermal effect and (ii) an orientational effect due to polarization.[2b] The activation energy has been shown to decrease under microwave conditions in the formation of imides of polyamic acids ($\Delta G^{\neq}$=105 kJ mol^{-1} under simple heating and 57 kJ mol^{-1} under MW conditions).[15]

Microwaves have been found to be particularly suitable in most syntheses involving the elimination of water, volatile alcohols or carbon dioxide. This can be highlighted, for example, in the addition of carboxylic acids to tris(hydroxyl)-methylamine affording 80–100% oxazolines under microwave conditions (Scheme 1).[16]

Activation by microwaves is relatively recent. To our knowledge there is no comparative study with activation by high pressure. Two independent papers have reported the synthesis of hindered enaminoketones via condensation of amines and 1,3-diketones or 3-ketoesters (Scheme 2) either under high pressure[17] or assisted by microwave irradiation and clay catalysis.[18] Although the experimental conditions are not comparable, it is clear that microwave activation is particularly rewarding vs pressure which gives less efficient results probably due to the fact that operation under pressure requires closed systems retaining the water produced during the process.



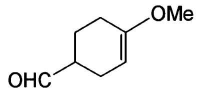
Scheme 2.

Table 1. Pressure and ultrasonic activation in reaction A[20]

Activation mode[a]	X	R_1	R_2	R_3	Yield (%)
Ultrasound	H	H	H	H	65
High pressure					67
Ultrasound	$SiMe_3$	H	H	H	57
High pressure					61
Ultrasound	H	H	$–O(CH_2)_2O–$		65
High pressure					75
Ultrasound	H	$–OC(CH_3)_2O–$		CH_3	76
High pressure					73

[a] Toluene, 45°C, 2 h (ultrasound conditions) and toluene, 1.1 GPa, 20°C, 2 h (high-pressure conditions).

Table 2. Pressure and ultrasonic activation in reaction B[21]



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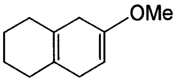


2

Enol ether	Activation mode	Conditions	Yield (%)
1	High pressure	MeCN, 1 GPa, 25°C, 18 h	85
1	Ultrasound	Neat, 0.1 MPa, 35°C, 46 h	78
2	High pressure	MeCN, 1 GPa, 25°C, 18 h	95
2	Ultrasound	MeCN, 0.1 MPa, 35°C, 10 h	83

2.2. Ultrasound

Ultrasounds are acoustic waves with frequencies ranging from 20 to 100 MHz. They are mechanical waves that are not absorbed by solids and, therefore, they do not induce heating. The propagation of ultrasonic waves through a liquid produces acoustic cavitation processes. The cavitational collapse occurring in the vicinity of a solid surface is responsible for the generation of instant and local high temperatures and pressures up to 100 MPa (pressure will be expressed throughout either in megapascal (MPa, 1 bar=0.1 MPa) or gigapascal (GPa, 10,000 bar=1 GPa). As a consequence, the effects of pressure and ultrasounds appear, in a first approximation, to be similar, albeit most authors would consider the so-called 'hot spot theory' only through its thermal effects. These effects have been used in organic synthesis.[1,19] The three examples given below underline the apparent similarity between high pressure activation and sonoactivation. These concern addition reactions characterised by a negative activation volume: Diels–Alder reaction (reaction A) (Table 1),[20] dipolar cycloaddition (reaction B) (Table 2),[21] aldol reaction (reaction C) (Table 3)[22] (Scheme 3).

Table 3. Pressure and ultrasonic activation in reaction C[22]

Activation mode	Yield (%)	*syn*/*anti*
Ultrasound (DME–H_2O, 0.1 MPa, 55°C, 2 days)[22a]	90	75:25
High pressure (CH_2Cl_2, 1 GPa, 60°C, 9 days)[22b]	68	73:23

In reaction C, the fact that the *syn*/*anti* ratio is not modified could be an additional argument to support the similar nature of both activation modes.

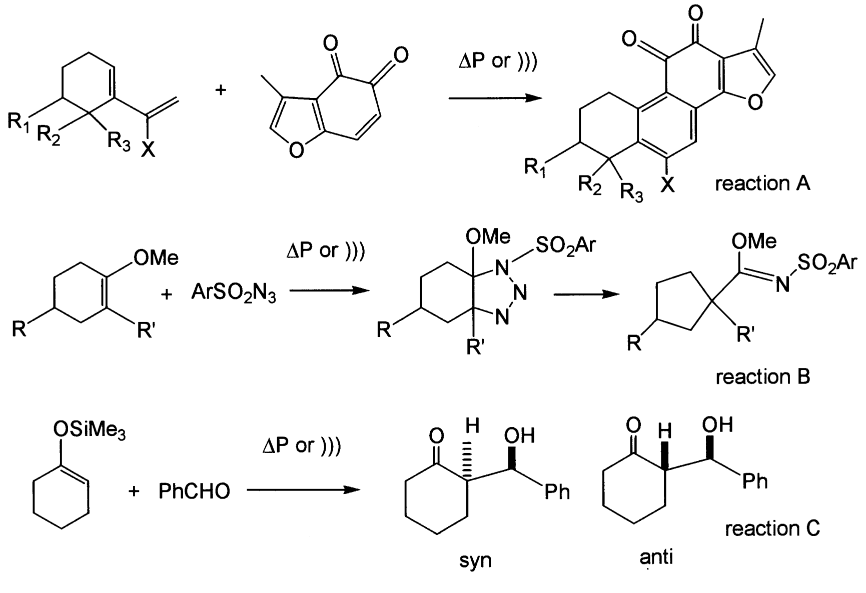
Differences may appear however, as exemplified in the synthesis of 1-azaanthraquinones via aza-Diels–Alder reactions. Crotonaldehyde-*N*,*N*-dimethylhydrazone cycloadds to juglone **3** yielding the [4+2] adduct **4** together with two undesired regioisomeric products **5** and **6** resulting from a consecutive reaction (Scheme 4 and Table 4).[23]

It is interesting to note that, after sonication or application of high pressure, and other conditions being equal, a higher yield of **4** is obtained via the pressure process since, under ultrasonic conditions, the cycloaddition is followed by the nucleophilic addition–oxidation of the liberated dimethylamine to **3**.

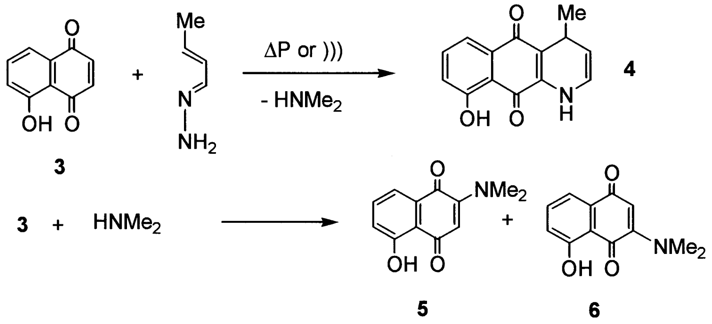
2.3. Chemical catalysis

2.3.1. Lanthanide catalysis.

Lanthanide and scandium compounds are expected to act as potent Lewis acids, particularly towards carbonyl oxygens and, to a lesser degree,



Scheme 3.



Scheme 4.

Table 4. Diels–Alder reaction of juglone **3**

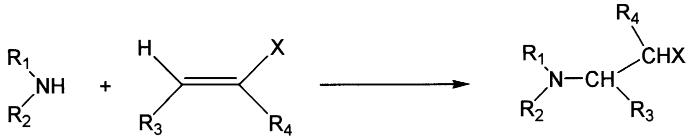
Activation mode	Conditions	Yield (%)		
		4	**5**+**6**	Polymers
High pressure	Toluene, 1 GPa, 20°C, 6 h	48	0	52
Ultrasound	Toluene, 0.1 MPa, 20°C, 6 h	32	20	48

nitrile or imine bonds. The most appropriate counterions from the viewpoint of electroattractivity and solubility in water and organic solvents are the fod (tris[2,2-dimethyl-6,6,7,7,8,8,8-heptafluoro-3,5-octanedionato]) and the triflate (Otf) anions. Lanthanide and scandium catalysis is compatible with aqueous reactions, permitting the use of commercial aqueous solutions of organic compounds such as formaldehyde and phenyl glyoxal which have important uses in industrial reactions.[24] They can be recovered and re-used without significant loss of catalytic activity. There are several reports comparing pressure activation and lanthanide catalysis[25–27] and the conjugate Michael-like addition of amines to α,β-ethylenic derivatives to yield β-amino compounds is shown in Scheme 5 and Table 5.

Table 5 merits the following comments. As long as the reaction centres are relatively uncrowded, lanthanide catalysis is as efficient as pressure (300 MPa) activation (entries 1 and 5). Intrusion of steric hindrance in either the amine or the acrylic compound, however, gives a decisive advantage to pressure activation (entries 2–4, 6 and 7). The difference in yields for both methods increases with increasing steric hindrance of the reaction centres (compare entries 3 and 4 with entry 2 and entries 6 and 7 with entry 5). This is discussed later (Section 3.3) and may be related to the general pressure effect on steric hindrance.[28]

2.3.2. Catalysis by lithium salts. Novel Lewis acid catalysts have appeared in recent years and include $BiCl_3$,[29] $InCl_3$,[30] lithium compounds such as lithium trifluoromethanesulfonamide,[31] lithium benzenethiolate,[32] lithium tetrafluoroborate.[34] One of the most utilized compounds is lithium perchlorate despite the difficulties with its handling.[33] It was recently shown, however, that the perchlorate can be advantageously replaced by the safer lithium tetrafluoroborate and lithium triflate.[34]

When lithium perchlorate is progressively dissolved in diethyl ether (other organic solvents may also be used[35]), high internal pressures P_i are developed which are seemingly comparable to hydrostatic pressures in excesses of 200–1000 MPa.[36] As a logical deduction, the rate enhancement observed in some organic reactions carried out in lithium perchlorate/diethyl ether (LPDE) solutions was first ascribed to the high P_i values.[37] It was shown later, however, that the accelerating effect of LPDE is in fact due to catalysis through ionic aggregates containing the cation Li^+ complexed by ether,[38,39] although a recent paper argues against lithium catalysis and emphasizes electrostatic stabilization of the transition state by LPDE.[40] In particular, Li^+ readily binds to a carbonyl bond leading to an exaltation of the electrophilicity of C=O bonds by complexation with Li^+. This was demonstrated in the reaction of mesityl oxide with isoprene.[39] The [4+2] cycloaddition competed with the cyclodimerization of isoprene. The yield ratio of adduct vs cyclodimers varied from 1.9:1 in carbon tetrachloride to 2.7:1 in 3 M LPDE solution (Table 6 and Scheme 6).



Scheme 5.

Table 5. Michael-like addition[26] of amines to α,β-ethylenic compounds

Entry	R_1	R_2	R_3	R_4	X	Yields (%)	
						With catalyst[a]	At 300 MPa[b]
1	*i*Pr	*i*Pr	H	H	CO_2Me	17	13
2	*t*Bu	H	H	Me	CO_2Me	4	11
3	*i*Pr	Me	Me	H	CO_2Me	6	55
4	*i*Bu	*i*Bu	Me	H	CO_2Me	7	20
5	*t*Bu	H	H	H	CN	35	62
6	*i*Pr	*i*Pr	H	H	CN	2	8
7	$-(CH_2)_5-$		H	Me	CN	5	19

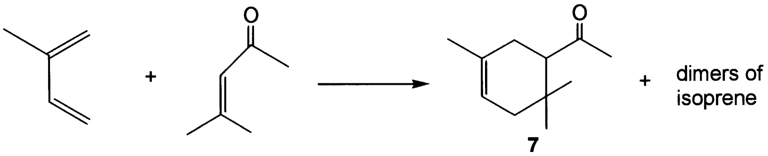
Solvent MeCN, 24 h, temperature 30–50°C depending on run.

[a] 0.1 MPa, $Yb(Otf)_3$ (5 mol%).

[b] No catalyst.

Table 6. Cycloaddition of mesityl oxide to isoprene[39] (20 MPa, 100°C, 24 h)

Medium	Yield (%)	
	Cyclodimers of isoprene	**7**
CCl_4	15	27.5
3 M LPDE	19	52



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Scheme 6.

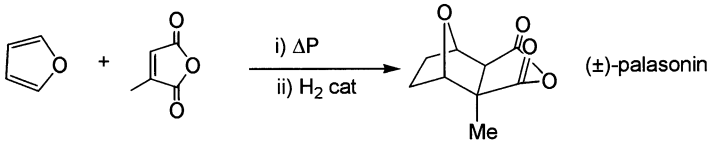
Table 7 illustrates the comparative effect of LPDE catalysis and high pressure in Diels–Alder addition reactions (entries 1 and 2), homo-Diels–Alder cycloaddition (entry 3), ene reaction (entry 4) and electrophilic addition (entry 5).[39] The yields, clearly, depend on the mode of activation and in addition, LPDE is able to modify the stereoselectivity. In entry 2, for example, the *exo*/*endo* ratio is 33:67 in 3 M LPDE and 74:26 in dichloromethane at 300 MPa. This is also an argument for the Lewis acid character of LPDE.

Table 7. Comparison between LPDE catalysis and pressure activation

Entry	Reaction	Conditions	Yield (%)	
			In LPDE[a]	At 300 MPa[b]
1	Isoprene+toluquinone	20°C, 24 h	89[b]	29
2	Furan+methyl vinyl ketone	20°C, 16 h	4	17
3	Norbornadiene+DMAD	80°C, 24 h	30	61
4	1-Hexene+diethylketomalonate	80°C, 24 h	40[b]	14
5	2,5-Dimethylfuran+diethylketomalonate	25°C, 24 h	39	100

[a] LPDE: 1 M (entry 1), 3 M (entries 2, 3 and 5), 2.5 M (entry 4).

[b] Solvent: acetone (entry 1), dichloromethane (entries 2 and 3), ether (entries 4 and 6) and chloroform (entry 5).



Scheme 7.

The synthesis of cantharidine can be successfully achieved either under high pressure (about 1000 MPa) or in 5 M LPDE solution via cycloaddition of 2,5-dihydrothiophene-3,4-dicarboxylic anhydride to furan followed by hydrogenation.[41] (±)-Palasonin is obtained by cycloaddition of citraconic anhydride to furan followed by catalytic hydrogenation (Scheme 7).[42] The attempted synthesis at ambient pressure in 5 M LPDE gives <10% yield, a result explained by the rapid retro-Diels–Alder reaction promoted in the highly polar medium (see also Section 4.2). Under 0.8 GPa in furan solution, palasonin is obtained nearly quantitatively provided that an adequate furan/anhydride ratio is used.

The same reason prevails, at least in part, in the conjugate addition of amines to α,β-unsaturated nitriles in LPDE medium[39] (Table 8).

Finally, LPDE may induce polymerization of sensitive unsaturated compounds. This has been demonstrated in norbornadiene reactions.[43]

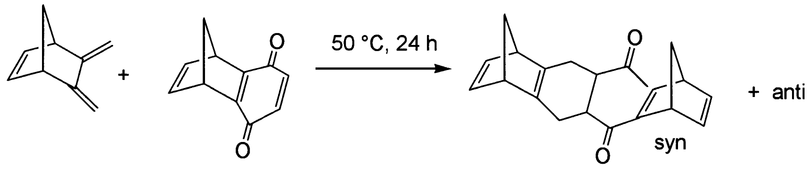
2.4. Physicochemical activation

Physicochemical activation results from interactions between the medium and the reactive molecules, and should be taken in a very general sense. The activation can arise from the solvent itself or from added complexing molecules. In our presentation of the activation modes, we have included host–guest activation and specific activation in liquid crystals. As these chemistries are still in their infancy

Table 8. LPDE catalysis and pressure activation[39] in amine-unsaturated nitrile addition

Reaction (see Scheme 5)	Yields (%)	
	1 M LPDE (0.1 MPa)	*P* (0.3 GPa)
R_1=*i*Pr R_2=*i*Pr R_3=H R_4=H (50°C)	21	20
R_1=Me R_2=*i*Pr R_3=Me R_4=H (30°C)	6	7

Ether is the solvent in the pressure reactions (24 h).



Scheme 8.

and lie at the boundary of what we understand here by activation, they will not be developed further. Host–guest activation is in actual fact the chemistry of cavities serving to harbour the reactive system in order to concentrate or to orient the reactive species or to stabilise them by specific interactions such as hydrogen bonding. Complexing molecules include cyclodextrins,[9] metalloporphyrins,[44] cryptands,[45] catenands[46] and calixarenes.[8] There is no doubt that this list will be extended in the near future. Liquid crystals, especially smectic phases, exhibit structured states which may affect the rigidity of transition states and, accordingly, the reaction rates.[10]

In the last few years numerous studies have revealed that aqueous media are capable of inducing dramatic rate accelerations in some reactions.[5,47] The fact that reactions characterized by negative activation volumes are also accelerated in water has prompted the proposal that the high cohesive energy density of water (δ^2= 554 cal mol^{-1} K^{-1}) is the driving force which was loosely interpreted to a pressure effect. There is no doubt, however, that hydrophobic packing of the reactive molecules is operative. Water is a highly-structured liquid in which molecular bonding is established through strong and oriented bonds such as hydrogen bonds.[48] There exist cavities in the available space able to host hydrophobic molecules. A reaction proceeds via the small amount of dissolved reactants in water. If there is no affinity of an organic molecule for selecting such cavities, there is no dissolution and, consequently, no hydrophobic effect and no reaction. On the other hand, if the compounds are completely soluble in water, no true hydrophobic effects can be expected, and the only effect of water is then manifested through the usual solvent properties. As a consequence of the generally limited solubility, organic synthesis in water proceeds in a heterogeneous way.

Table 9. Comparative water effects[50] vs pressure effects

Entry	Reaction	Yields (%)	
		Water[a]	At 300 MPa[b]
1	Isoprene+*p*-benzoquinone	21	12
2	Isoprene+toluquinone	15	2
3	Isoprene+2,6-dimethylbenzoquinone	12	8
4	Acrylonitrile+diisopropylamine	69	8
5	Crotononitrile+piperidine	95	15
6	Methacrylonirile+piperidine	100	19
7	Methacrylonitrile+methylisopropylamine	72	0
8	Acrylamide+di-*n*-propylamine	96	67
9	Methacrylamide+piperidine	70	12
10	Methacrylamide+*t*-butylamine	11	0
11	Methyl crotonate+diisopropylamine	0	55
12	Methyl methacrylate+methylisopropylamine	0	28

Ambient temperature, except in entries 4, 7, 11 and 12 (50°C); Reaction time 24 h except in entries 1 and 2 (5 h).

[a] Ambient pressure; concentration of each reactant is 1 mmol; due to their limited solubility, it is clear that the final yields depend upon their concentration.

[b] Organic solvent: acetone (entries 1–3) or acetonitrile (entries 4–12).

In some cases, activation through hydrophobic effects can be very strong compared to pressure. This is illustrated in Scheme 8.[49] In dichloromethane at 0.3 GPa, the yield is 6% whereas it amounts 41% in water at ambient pressure. Addition of a hydrogen bond generator (*p*-nitrophenol) increases the yield at atmospheric pressure to 72%, demonstrating the efficiency of the physicochemical activation mode.

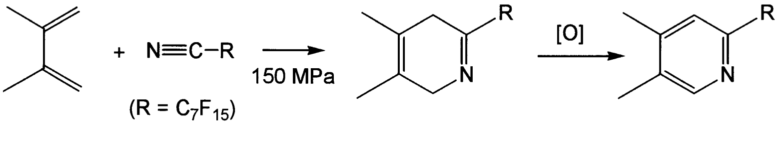
Recent papers from our laboratory have reported comparative studies of pressure activation vs hydrophobic effects in Diels–Alder (entries 1–3) and Michael-like reactions (entries 4–12),[50] these significant results being listed in Table 9.

The three Diels–Alder cycloadditions involving quinones are, remarkably, promoted at ambient pressure in aqueous solution. The effect is even stronger than with pressure activation in organic solvents. This may be related to the complexing ability of the two carbonyl bonds of the quinones to form hydrogen bonds with water.[51]

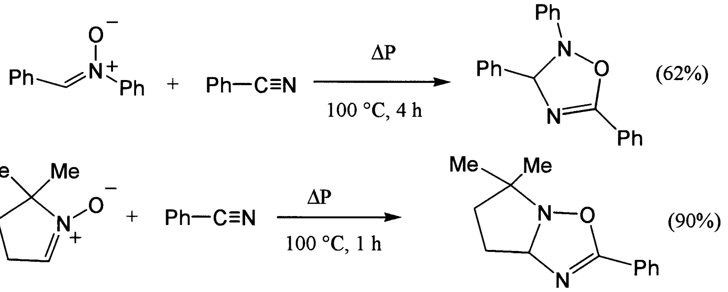
Excellent yields of β-aminonitriles are obtained in water in the conjugate addition of amines to α,β-unsaturated nitriles (entries 4–10). They are higher than those reached at 300 MPa in acetonitrile. In some cases, the reaction does not occur at all under pressure whereas it proceeds smoothly in aqueous solution. As the mechanism involves zwitterions, polar media such as water favour their formation, with a concomitant rate increase.[52] When substituting acrylic esters for nitriles (entries 11 and 12), there is apparently no reaction in aqueous solution, at variance with the pressure-assisted reaction. Actually, water accelerates the forward reaction involving acrylates as much as for acrylonitriles. The zero yield is simply explained by the fast reversibility of β-aminoesters in highly polar media whereas β-aminonitriles are quite stable in water.

3. Specific pressure activation

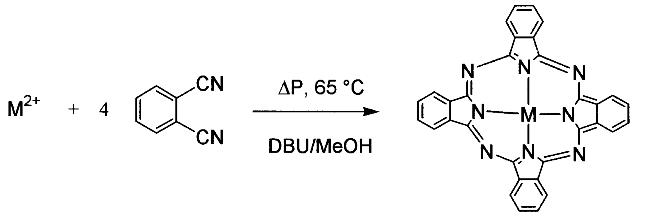
Pressure represents a mild non-destructive activation mode, generally respecting the molecular structure by limiting decomposition or further evolution of the products. The specific effects of high pressure can be of important value for organic synthesis.



Scheme 9.



Scheme 10.



Scheme 11.

3.1. Activation of functional groups

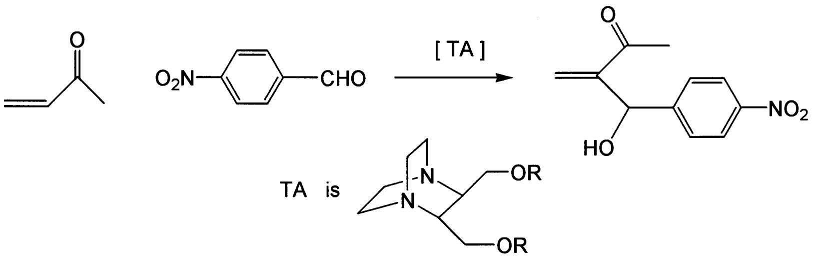
The cyano group in nitriles is chemically inert unless activated nitriles are involved. Perfluorooctanenitrile undergoes hetero Diels–Alder reaction with 2,3-dimethylbutadiene, leading to a fluorodihydropyridine[53] (Scheme 9). Pressure has a beneficial effect on the yields.

The 1,3-dipolar cycloaddition of saturated nitriles to nitrones is a rare reaction owing to the relatively low chemical reactivity of the nitrile group. Under high-pressure conditions, geminal dinitriles react regioselectively with nitrones to give access to Δ^4-1,2,4-oxadiazolines.[54] Simpler common nitriles serving usually as solvents such as acetonitrile and benzonitrile undergo 1,3-dipolar cycloaddition with nitrones under 1 GPa, affording oxadiazoles in fair to excellent yields (Scheme 10).[55]

An improved synthesis of phthalocyanines has been reported involving the reaction between 1,2-dicyanobenzene and a metal salt M^{2+} at 1 GPa with 1,8-diazabicyclo[5.4.0]undec-7-ene as catalyst (Scheme 11).[56] The yields are in the range 10–15% depending on the nature of *M* and the experimental conditions. They may appear to be modest, but are comparable to those obtained by other routes. The yield can be increased (up to 50%) by adding a reducing agent such as hydroquinone.

3.2. Solvation effect

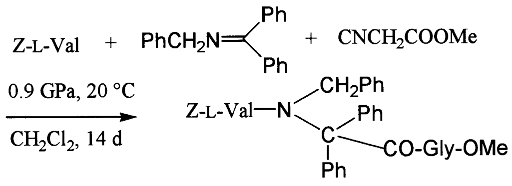
The kinetic pressure effect is, usually, primarily determined by the variation in volume due to changes in the nuclear positions of the reactants during the formation of the transition state. Reactions subjected to solute–solvent interactions in the process, however, undergo an additional activation volume change $\Delta V_e^{\neq}$ called electrostriction. According to the Drude–Nernst theory, the pressure dependence of the dielectric constant of the solution is largest in non-polar media. Accordingly, electrostriction may induce pressure kinetic effects which can be considerable so that pressure emerges as a powerful activation method in syntheses involving the creation of charged species in the transition state.[57] As an illustrative example, optically active α-methylene-β-hydroxyalkanones were prepared via the Baylis–Hillman reaction of methyl vinyl ketone and *p*-nitrobenzaldehyde catalysed by chiral substituted DABCO catalysts (Scheme 12).[58] A remarkable enhancement of the reaction rate and enantioselectivity occurred under 0.5 GPa. The Baylis–Hillman reaction is a highly pressure-dependent reaction, mostly for electrostriction reasons, since it involves the formation of successive



Scheme 12.

Table 10. Pressure effect in reactions involving polar transition states

Reaction	Estimated range for $\Delta V_e^{\neq}$ ($cm^3 mol^{-1}$)	Ref.
Baylis–Hillman	−40 to −50	59
Menshutkin	−10 to −30	60
[2+2]	−10 to −30	61
Michael-like reactions	−5 to −40	52



Scheme 13.

ionic steps. Table 10 reports ionogenic reactions featuring electrostriction phenomena.

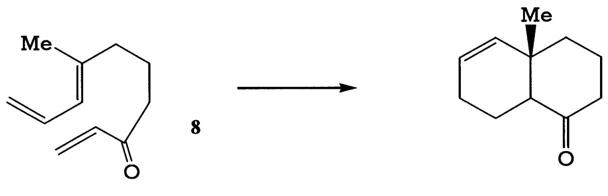
Ugi reactions belong to the rare class of four-component systems. They are related to the synthesis of peptides. The Ugi-like reaction depicted in Scheme 13 does not occur at ambient pressure. Under high-pressure conditions the yield reaches 63% with dichloromethane as the solvent, but only 19% if methanol is used.[62] Clearly, charge separation occurs in the transition state of the reaction.

The ongoing chemistry of host–guest compounds requires multistep syntheses. Diaza-coronands and -cryptands can be synthesized in excellent yields under pressure via double Menshutkin reactions.[63,64]

With regard to the Baylis–Hillman reaction, a recent study reports the high-pressure formation of polyacetals from ketones.[65]

3.3. Effect on sterically hindered or strained transition states

Steric effects are intimately related to volume requirements as the bulkiness of the molecules involved in the transition state conditions the magnitude of the steric interactions. As an important consequence, pressure affects volume changes and should have an effect on steric congestion. A steric perturbation imposes rate deceleration and is associated with a shift of the transition state towards the products along the reaction axis. In terms of pressure activation this presupposes a more negative activation volume, and therefore, an enforced pressure effect in such way that pressure may remove steric inhibition in sterically hindered reactions.[28] The same considerations apply to strained molecular systems.[66]



Scheme 14.

Some recent examples include the cycloaddition of Danishefsky's diene to a sterically hindered dienophile angularly substituted by a trifluoromethyl group,[67] and the cycloaddition of acyclic dienes to cycloalkenones which are totally unreactive at normal pressure.[68] The cycloaddition of methyl palustrate with anhydrides cannot occur at ambient pressure due to significant steric hindrance, and under 1 GPa, the Diels–Alder reaction with maleic anhydride yields the adducts in 27% yield.[69] In an approach to the total synthesis of brassinosteroids, the intramolecular Diels–Alder reaction of the unsaturated ketone **8** occurs only under 1 GPa (Scheme 14).[70]

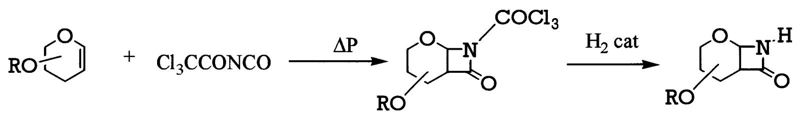
The asymmetric conjugate Michael addition of amines to chiral bulky crotonates is basically possible only under pressure,[71] and the reactions are quantitative. Interestingly, efficient stereo- and enantioselectivity are achieved at 1.4 GPa since the diastereoisomeric excess increases from 10% at ambient pressure to 98% at high pressure. A very recent article reports the nucleophilic addition of alcohols to acrylic compounds.[72] The yields are strongly increased by pressure, the increase being more pronounced when either the bulkiness of the alcohol and/or the steric hindrance around the reactive centres in the activated alkenes are higher.

Concerning strained systems, some recent literature mentions the construction of molecular lego via repetitive Diels–Alder reactions.[73–75] High pressure is a remarkable activation tool in effecting the synthesis of strained polycycles. The chemistry of rigid organic three-dimensional structures serving as linkers has been examined.[76] The complex building blocks were best synthesised at hyperbaric pressures via cycloaddition reactions.[77]

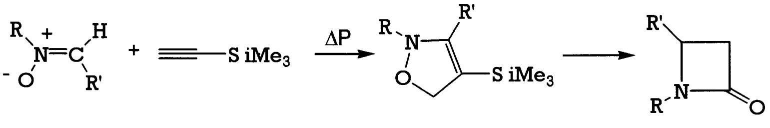
4. Pressure activation as an alternative for the synthesis of sensitive molecules

4.1. Synthesis of heat-sensitive molecules

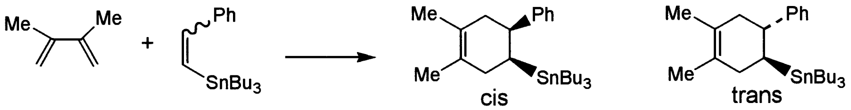
As a mild activation mode, pressure may be of considerable value in the synthesis of thermally fragile molecules, allowing a lowering of the temperature. In addition, under such conditions, selectivity is generally preserved or even



Scheme 15.



Scheme 16.



Scheme 17.

improved. There are countless examples, some of which are now described.

The synthesis of β-lactams can be achieved via [2+2] cycloaddition of isocyanates to vinyl compounds (Scheme 15). Some β-lactams, however, are not stable under normal conditions, and undergo a retro reaction upon heating or even upon standing at room temperature. Glycals react with acyl isocyanates under 1.2 GPa to afford in fair to excellent yields cycloadducts which are readily transformed into the desired β-lactams (Scheme 15).[78]

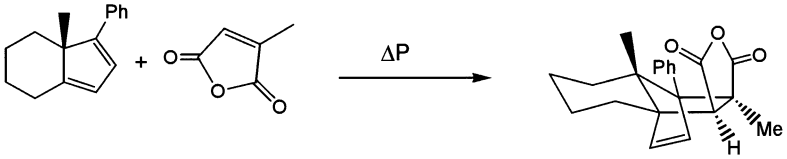
The high pressure [2+2] cycloaddition of phenyl isocyanate to 2,3-dihydrofuran and other vinyl ethers leads to β-lactams[79] ($\Delta V^{\neq}$ is estimated to have a value of $-28\ \mathrm{cm^3\,mol^{-1}}$). Another way to synthesise β-lactams consists of a two-step process. The first step involves the high pressure dipolar cycloaddition of nitrones and trimethylsilylacetylene to give Δ^4-isoxazolines in excellent yields which are subsequently converted to β-lactams by known procedures (Scheme 16).[80]

The [4+2] cycloadditions remain the privileged high pressure reactions. An interesting report of reverse diastereoselectivity is the Diels–Alder reaction of a trialkyltin dienophile (Scheme 17).[81] At ambient pressure it is necessary to thermally activate the reaction system and, whereas at 2 GPa and 70°C the *cis/trans* ratio is about 20:80, at 180°C it reverts to 90:10 due to thermal isomerisation of the starting dienophile.

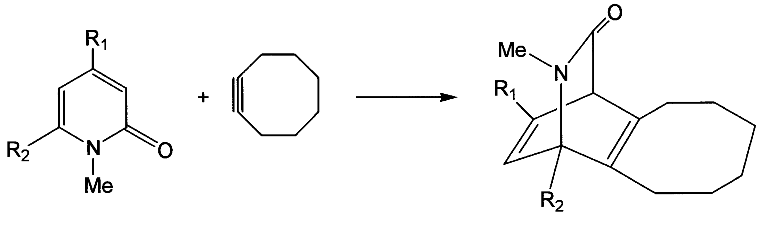
A highly selective high pressure reaction has been reported.[82] Itaconic and citraconic anhydride cycloadd to homochiral cyclopentadienes in a completely regio- and face-selective manner. High pressure serves mainly to stabilise the adducts which otherwise decompose at ambient pressure. Scheme 18 portrays the reaction involving citraconic anhydride.

The high-pressure (0.8 GPa) Diels–Alder reaction of *N*-methyl-2(1*H*)-pyridones with cyclooctyne at 90°C affords 1:1 cycloadducts in 60–80% yield (Scheme 19).[83] No adduct is recovered at normal pressure due to the extrusion of methyl isocyanate.

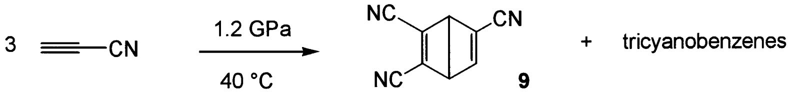
Tropone reacts with buckminsterfullerene (C_{60}) according to a [4+2] cycloaddition at 0.3 GPa and 100°C.[84] High pressure impedes the retro-Diels–Alder process. Pressure



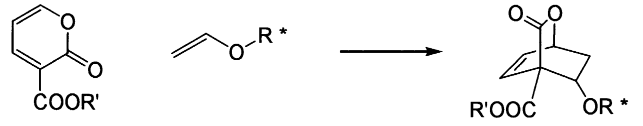
Scheme 18.



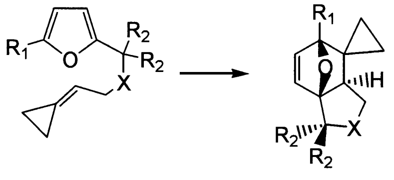
Scheme 19.



Scheme 20.



Scheme 21.



Scheme 22.

induces strong acceleration in the trimerisation and Diels–Alder reaction of cyanoacetylene, allowing substantial decrease of the reaction temperature (Scheme 20).[85] At 1.2 GPa, the tricyano Dewar benzene **9** can be isolated as the major product (**9**/other isomers=16:7). The same laboratory succeeded in synthesising, at 9 GPa, fused norbornene analogues bearing silicon and oxygen atoms in bridgehead positions from the cycloaddition of siloles to oxanorbornenes.[86] At atmospheric pressure, these reactions proceeded only marginally upon heating which caused partial decomposition of the starting materials.

Pyrones are another class of heat-sensitive molecules as they easily extrude CO_2 upon heating, and in recent years, several papers have reported their Diels–Alder reactions. 2-Pyrone undergoes cycloaddition with α,ω-dienes at 1.85 GPa yielding bicyclic bridged lactones which can be converted into useful polyoxygenated cyclohexane derivatives.[87] Under high pressure, excellent chemical yields and good levels of asymmetric induction were obtained in the addition of esters of 3-hydroxypyran-2-one to vinyl ethers (Scheme 21).[88]

Pyrroles do not undergo Diels–Alder addition due their aromaticity. High pressure appears not to favour diene behaviour unless adequately *N*-substituted pyrroles are reacted, in which case it is possible to obtain Diels–Alder adducts.[89] Epibatidine analogues (which are potent analgesics) have been synthesised via [4+2] cycloaddition of vinylsulphone to 3-phenothioxy-*N*-carbomethoxypyrrole.[90] Similarly, pyrrole *S*,*S*-dioxides containing terminal olefin substituents undergo facile intramolecular cycloaddition at 1.2 GPa.[91]

Table 11. Diastereoselectivity of spiroaziridine synthesis at 20°C

Pressure	Time (days)	Yield (%)	**11/12**
0.1 MPa	60	85	1.7:1
1.1 GPa	4	83	10:1

Much attention has been devoted to the high pressure intramolecular Diels–Alder reaction. A keenly sought synthesis concerns the bicyclic framework of taxol. Progress has been made in using pressure activation to effect intermolecularly the stereoselective construction of the taxane ring system with the requisite *trans*-B/C ring fusion.[92] In a synthetic approach to phorbols, furan tethered with a skeleton possessing a (*Z*)-vinylogous ketoester affords two cycloadducts at 1.9 GPa.[93] Epimerisation leads to the formation of a carbotricycle having the stereochemistry required for the construction of phorbol derivatives. The intramolecular cycloaddition of furans with bicyclopropylidene moieties is possible only under high pressure conditions to yield diastereoselective adducts as spirocyclopropane-annellated tricyclic structures in excellent yields at 1 GPa (Scheme 22).[94,95] The adducts do not resist a temperature increase.

To close this section, although the Michael reaction does not afford heat sensitive products stricto sensu, it is an elegant example of pressure-induced diastereoselectivity. The addition of benzylamine to the methylene cyclohexane **10** yields two spiroaziridines **11** and **12** having a diastereoisomeric excess of 91% at 1.1 GPa (Table 11 and Scheme 23).[96]

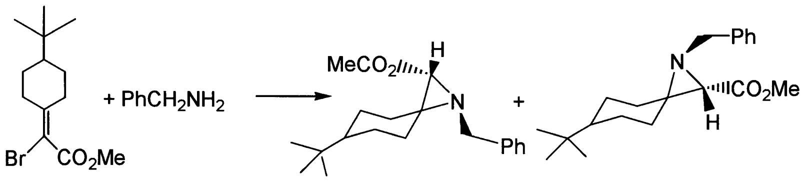
4.2. Pressure as an alternative to Lewis acid catalysis

Besides their catalytic role, Lewis acids may induce undesirable reactions such as polymerisation, degradation of substrates and products, isomerisation and/or dehydration. Some functional groups are additionnally vulnerable to strong Lewis acids. It is therefore, interesting to consider pressure as an alternative synthetic method.

Citraconic anhydride adds to furan, producing a palasonin precursor,[42] and to alkylated furans to afford CD-ring precursors of paclitaxel.[97] Sulphur containing furans undergo, under high pressure, facile [4+2] cycloadditions with cycloalkenones to give the corresponding cycloadducts which can be stabilised upon oxidation of the vinyl sulfide groups (Scheme 24).[98]

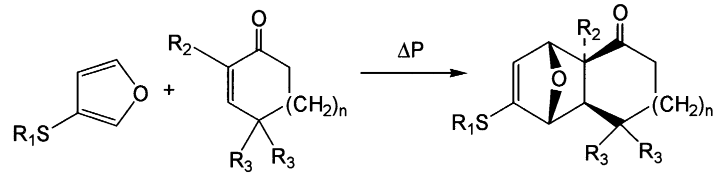
It should be emphasised that these Diels–Alder reactions of furans are best achieved under high pressure since Lewis acids or LPDE lead exclusively to ether cleavage and polymerisation.

Bi- and tricyclic *N*-oxy-β-lactams are synthesised in two steps from enol ethers and β-nitrostyrene. The first step



10 **11** **12**

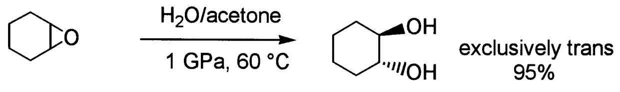
Scheme 23.



Scheme 24.

$$\mathrm{RCOOR'}\ \xrightarrow[\mathrm{MeCN\text{-}H_2O,iPr_2NH}]{\mathrm{1\ GPa,\ 30\ ^\circ C}}\ \mathrm{RCOOH} + \mathrm{R'OH}$$

Scheme 25.



Scheme 27.

involves high pressure tandem [4+2]/[3+2] cycloadditions without Lewis acid catalysts and the second step is a base-catalysed rearrangement of the resulting adduct.[99]

A number of recent papers report on the advantage of using high pressure in cleavage reactions. Hydrolysis and solvolysis of esters usually proceeds in the presence of acids. Under such conditions, selectivity may be a problem since the cleavage is always accompanied by side reactions. A mild procedure based on high pressure methodology with tertiary amines as catalysts enables the smooth hydrolysis at room temperature, affording the corresponding carboxylic acids in high yield and complete selectivity (Scheme 25).[100] Even selective hydrolysis of two ester groups can be achieved using this approach. An important application disclosed was the pressure-assisted hydrolysis of biologically-related molecules such as aminoesters and peptides.

The cleavage of ethers under acidic conditions is a well-known reaction. If acid-sensitive functional groups are present, it is worthwhile carrying out the reaction under pressure using neutral or quasi-neutral conditions. The ether cleavage by acyl halides is very efficient at 1 GPa under neutral conditions due to electrostriction effects (enhanced formation of the oxonium complex) (Scheme 26).[101] Under high pressure conditions, epoxides are hydrolysed to diols (Scheme 27).[102]

5. Multiactivation based on pressure

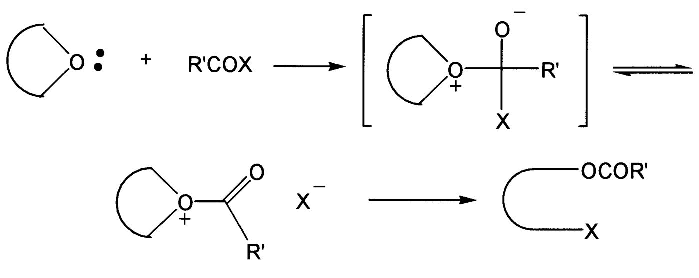
The association of several activation modes emerges as a powerful synthetic strategy when the respective kinetic effects are convergent. As an illustrative example, in an unusual Diels–Alder reaction, an acceleration of 10^6 was observed by a combination of Lewis acid catalysis, micellar catalysis and activation by hydrophobic interactions.[103] In this regard, pressure has been combined with chemical activation (hard Lewis acids, lanthanides, lithium salts, transition metals or biocatalysis) or with physicochemical activation.

5.1. Pressure and chemical catalysis

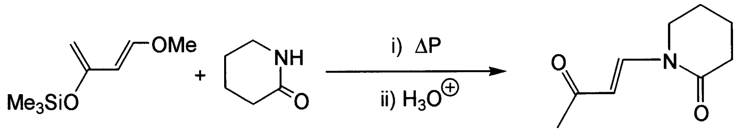
5.1.1. Pressure and traditional Lewis acid catalysis. Combinations of high pressure and hard Lewis acid catalyst effects have been envisaged for some time in organic synthesis, the catalysts used being essentially $AlCl_3$,[104] $EtAlCl_2$[105] or zinc halides.[106] The presence of the catalysts in the reaction system does not alter the overall kinetic effect of pressure since the activation volume is hardly modified, but this has been demonstrated to be valid for [4+2] cycloadditions only.[107]

Some examples using zinc halides are highlighted in the synthesis of antitumour abietone diterpenes, for which a combination of pressure and $ZnBr_2$ catalysis leads to a simultaneous significant increase in yield and regioselectivity.[108] Zinc halides are also excellent catalysts in the inverse electronic demand Diels–Alder reactions of pyrones and electron-rich alkenes, affording under pressure (1–1.2 GPa) valuable bicyclic lactones in a regio- and stereoselective manner.[109] Novel 4-alkoxy-β-lactams derived from aminoesters could be synthesised via $ZnCl_2$-catalysed high pressure [2+2] cycloadditions.[105]

Novel Lewis acid catalysts for use in high pressure experiments have been designed from bismuth compounds. A recent paper reports the $BiCl_3$-catalysed addition of poorly reactive lactams to Danishefsky's diene (Scheme 28).[110] The reaction is strongly promoted by pressure since the



Scheme 26.



Scheme 28.

Table 12. High pressure (300 MPa) syntheses in LPDE solution

Reaction	Conditions	Yield (%)
Isoprene+benzoquinone	Acetone, 20°C, 24 h	32
	LPDE (1 M), 20°C, 24 h	100
Isoprene+2,6-dimethylbenzoquinone	Acetone, 20°C, 24 h	8
	LPDE (1 M), 20°C, 24 h	68
Cycloheptatriene+acrylonitrile	CH_2Cl_2, 80°C, 24 h	0
	LPDE (2.5 M), 80°C, 24 h	11
Furan+methyl vinyl ketone	Ether, 20°C, 16 h	17
	LPDE (3 M), 20°C, 16 h	83
1-Hexene+diethyl ketomalonate	$CHCl_3$, 80°C, 24 h	14
	LPDE (2.5 M), 80°C, 24 h	58

yield of the *N*-substituted lactam increases from 0 to 46% when the pressure is raised from ambient to 100 MPa.

5.1.2. Pressure and lithium salts. Two papers have been reported on this multiactivation mode. Ethereal solutions of lithium perchlorate (LPDE) catalyse pericyclic reactions and Table 12 portrays some examples.[39] Both activation types contribute to higher yields of adducts. In the cycloaddition of cycloheptatriene and acrylonitrile, LPDE makes the reaction amenable to occur.

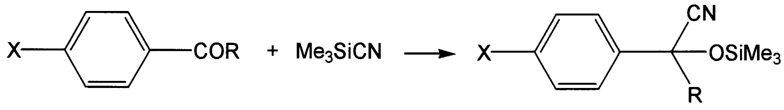
In a more recent study, it has been shown that a combination of pressure and catalysis by lithium salts (LPDE and LTFBA (lithium tetrafluoroborate in acetonitrile)) is an interesting synthetic strategy to activate poorly reactive aromatic ketones in cyanosilylation reactions (Scheme 29 and Table 13).[111]

5.1.3. Pressure and lanthanide catalysis. The use of lanthanides for catalysis has become increasingly popular due to their commercial availability, facile recovery and tolerance to atmospheric agents. The pressure multiactivation mode is introduced in 1994 for the synthesis of bicyclic lactones via cycloaddition of pyrones and vinyl ethers under 1.2 GPa and $Yb(tfc)_3$ catalysis.[112] Cycloadditions could be successfully achieved by means of the combined influence of pressure and catalytic amounts of lanthanide catalysts.[113] Under such biactivation conditions, epoxides add to amines,[114] particularly indoles.[101,115,116]

In the same field, 1,1-cyclopropanedicarboxylic esters react with indoles (Scheme 30).[117]

A recent article reports the $Yb(Otf)_3$-catalysed homoconjugate addition of β-ketoesters with diethyl cyclopropanedicarboxylate at high pressure.[118] In a more general sense, Michael reactions are the candidates of choice for the application of the biactivation method. The addition of β-ketoesters to α,β-unsaturated carbonyl compounds proceeds efficiently under 0.8 GPa and $Yb(Otf)_3$ catalysis.[119] The conjugate addition of bulky amines to hindered acrylates is strongly accelerated by pressure and lanthanide catalysis.[17]

5.1.4. Pressure and transition metal catalysis. Organometallic catalysts have the general formula M_xL_n where M is the transition metal and L is an organic ligand. There is complexation between M_x and the ligands L_n. The catalyst effectiveness is related to the ligating ability of L and catalysis occurs when M has a vacant coordination site,

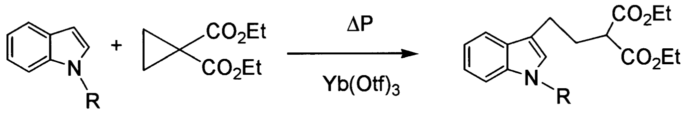


Scheme 29.

Table 13. Cyanosilylation of aromatic ketones catalysed by LPDE and LTFBA

X	R	Pressure (MPa)	Time (h)	Yield (%)	
				LPDE	LTFBA
H	Ph	0.1	8	14	61
		300	4	65	100
Me	Ph	0.1	8	61	47
		300	4	100	61
NH_2	Ph	0.1	24	4	10
		300	24	26	51
Me	Me	0.1	8	64	–
		300	4	100	–

Ketone (0.2–0.4 mmol), TMSCN (0.3–0.5 mmol), 3 M solution of lithium salt, *T* (20°C).



Scheme 30.

$$Bu_3Sn\text{-}Ph + ClCOOR \xrightarrow{PdL_4} PhCOOR + Bu_3SnCl$$

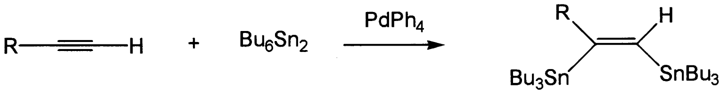
Scheme 31.

allowing the coordination of M_xL_n to an organic molecule. The application of pressure to transition metal-catalysed reactions is relatively recent,[120] and these concern almost exclusively palladium catalysis. Ruthenium catalysis has also been used in high pressure cycloadditions.[121] A recent paper reports the high pressure hydroboration of various functionalised olefins catalysed by Wilkinson rhodium catalysts.[122] Although both modes of activation can be efficient when used separately, their combination can bring significant improvements relative to the reactivity and selectivity.

Organopalladium compounds catalyse a myriad of coupling reactions. Typical high pressure variants are

(i) the cross coupling between substituted aryl- and vinyltins and chloroformates,[123] the Pd-induced decomposition of chloroformates not occurring under pressure (Scheme 31).

(ii) the Pd-catalysed addition of hexabutylditin to alkynes which yields under 0.9–1.3 GPa (*Z*)-1,2-bis(tributylstannyl)-alkenes (Scheme 32).[124]



Scheme 32.

In the Pd-catalysed trimethylenemethane cycloadditions, pressure drastically improves the regioselectivity.[125] A typical Heck reaction is the Pd-catalysed arylation and alkenylation of alkenes. The rate-determining step in the catalytic cycle is the oxidative addition of a zerovalent palladium species to the halide, this step being promoted by pressure. The other steps can be either accelerated or decelerated by pressure. The net volume balance, however, has a negative sign in such way that pressure may be a very useful parameter to activate Heck reactions which otherwise would not occur or would take place only sluggishly. Notable examples are the syntheses of isoquinolines and benzazepines[126] as well as isochromanes.[127] The Pd-catalysed coupling of 2,3-dihydrofuran and iodobenzene is also promoted by pressure.[128] In addition, the activity of the palladium catalyst does not decrease at high pressure which is capable of stabilising PdL_n by enforcing ligand coordination.

Table 14. Yields (%) in the multiactivation of furan cycloadditions in solvophobic media

Dienophile	Water[a]		Ethylene glycol	
	0.1 MPa	300 MPa	0.1 MPa	300 MPa
Methyl vinyl ketone	27	87	18	86
Acrylonitrile	–	–	4	80
Methyl acrylate	–	–	0	72
Acrolein	–	–	2	30
Methacrolein	–	–	0	32
Crotonaldehyde	–	–	0	35

20°C, 60 h (16 h in the vinyl ketone reaction).

[a] No reaction in organic solvents.

5.2. Pressure and solvophobic effects

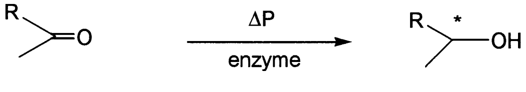
The effect of pressure on organic reactions in aqueous solution has been examined only recently.[129] Coupling of pressure and hydrophobic activation means operation in heterogeneous conditions since, from the synthetic point of view, high reactant concentrations are desired. Furan cycloadditions were investigated under pressure in aqueous solution and in ethylene glycol, a water-like solvent, leading to solvophobic effects (Table 14).[129] Remarkably, in solvophobic media, pressures as modest as 300 MPa are sufficient to reach yields which are obtained only >1 GPa in hydrocarbon solvents, making the biactivation method synthetically useful. Pressure does not alter the stereoselectivity. This is in contrast with the catalytic effect of Lewis acids which induce a reversal of the *endo*/*exo* ratio.[130] More results relative to Diels–Alder and Michael reactions can be found in two further papers.[52,131]

The effect of pressure on organic reactions in aqueous solutions is complex. The reason stems from antagonistic effects, eg the activation volume relative to hydrophobic effects is positive—meaning deceleration by pressure—whereas the activation volume due to hydrogen bonding is negative.[51] In addition, electrostatic effects may also be involved for many reactions (negative activation volume). Nevertheless, the combination of pressure and solvophobic activation may be an interesting method to increase the reactivity of reluctant polar molecules.

5.3. Pressure and enzymatic catalysis

Enzymes are proteins having catalytic activity in transformations of biomolecules (reactions in vivo). They may also catalyse some reactions which occur in vitro. Enzymes reduce the activation energy and stabilise the transition state of the catalysed reaction. As enzymes are chiral host molecules, they are able to discriminate between enantiomers of a racemic substrate.[132] The most extensively investigated reactions catalysed by enzymes are hydrolyses, esterifications, reductions and oxidations. Addition reactions such as aldol condensations can be catalysed by aldolases.[133]

Such multiactivation is still in its infancy. The results are



Scheme 33.

Table 15. Activation methods used in organic synthesis

Activation mode	Advantages	Drawbacks
Pressure	Simple non-destructive method No or little work-up Excellent reproducibility	Low volume reactions Cost of equipment Limited to homogeneous reactions (difficulty of mixing)
Ultrasound	Simple method Large volume reactions No or little work-up Adaptable to heterogeneous reactions	No generality Cost of equipment Hazardous temperature control
Photons	Flexible, selective method Method based only on the reactivity Of the excited state	Energy cost Low volume reactions Parallel reactions
Microwaves	Large volume reactions Fast reactions (elimination of volatile products) Adaptable to heterogeneous and sterically hindered reactions	Hazardous temperature control Safety problems (reactions in solution) No reproducibility Thermal stability of the products
Lanthanide catalysis	Mild, non-agressive method Insensitive to air and water Recovery of catalyst with constant catalytic properties	No generality (catalysis limited to some bonds) Work-up necessary Cost of catalyst, if not recovered
LPDE catalysis	Efficient and selective catalytic method	No generality (not adapted to acid-sensitive reactions) Necessity of large amounts of LPDE (serves as the solvent) Preparation of LPDE and work-up necessary Sensitive to water Hazards of lithium perchlorate Cost of LPDE
Transition metal catalysis	Synthesis of specific reactions not available by traditional catalysis	No generality (method adapted to specific reactions) Cost of catalysts
Solvophobic interactions	Considerable acceleration of rate constant Cheap, environmentally safe method (extraction of products, however, needs organic solvents)	No generality Possibility of hydrolysis Work-up necessary
Enzymatic catalysis	Low temperature efficient method Highly selective method	No generality (limited to a few specific reactions) Cost of enzymes Sensitive to temperature

difficult to analyse in relation to the complexity of the activation processes in enzyme reactions and the enzyme survival during pressure application.[134] In general, pressure stabilises hydrogen bonds in enzymes, induces reversible changes such as dissociation of protein–protein complexes, binding of ligands and conformational changes. The microbial reduction of prochiral ketones by *Saccharomyces cerevisiae* and *Yarrowia lipolytica* has been attempted under pressures up to 150 MPa (Scheme 33).[135] The results show that pressure increases the enantioselectivities, but leads to lower yields.

6. Conclusions

The diversity of activation methods has grown noticeably in recent years. Table 15 summarises their main advantages and drawbacks. In the context of such an armoury, pressure activation may represent in many cases a very interesting synthetic method. When traditional synthetic strategies appear forbiddingly difficult or fail utterly, the pressure parameter, possibly associated with other activation methods, may be considered. It should be emphasised that operation under pressure is an inocuous method, respecting the stability of the reactants and products (with the notable exception of some enzymes in the corresponding enzymatic reactions). Other salient features include:

(i) the extreme simplicity of the method
(ii) the capacity to induce ionogenesis
and (iii) the capacity to remove steric inhibition.

It is now hoped that the notable advantages of this method materialise in new or improved synthetic routes, and it adds another important dimension to the existing synthetic activation modes. In this context, a recent paper reports high-pressure promoted tandem [4+2]/[3+2] cycloadditions on a solid support, opening a pathway to high pressure combinatorial chemistry.[136]

References

1. Einhorn, C.; Einhorn, J.; Luche, J. L. *Synthesis* **1989**, 787–813.
2. (a) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathé, D. *Synthesis* **1998**, 1213–1214. (b) de la Hoz, A.; Diaz-Ortiz, A.; Moreno, A.; Langa, F. *Eur. J. Org. Chem.* **2000**, 3659–3673. (c) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199–9223.

3. (a) Kobayashi, S. *Synlett* **1994**, 689–701. (b) Kobayashi, S. *Eur. J. Org. Chem.* **1999**, 15–27.
4. (a) Lautens, A.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49–92. (b) Ojima, I.; Tzarmarioudakis, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635–662.
5. Lubineau, A.; Augé, J.; Queneau, Y. *Synthesis* **1994**, 741–760.
6. (a) Schwuger, M. J.; Stickdorn, K.; Schömaker, R. *Chem. Rev.* **1995**, *95*, 849–864. (b) Tascioglu, S. *Tetrahedron* **1996**, *52*, 11113–11152.
7. Fendler, J. H.; Tundo, P. *Acc. Chem. Res.* **1984**, *17*, 3–8.
8. Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1994**, *34*, 713–745.
9. Takahashi, K. *Chem. Rev.* **1998**, *98*, 2013–2033.
10. Leigh, W. J.; Mitchell, D. S. *J. Am. Chem. Soc.* **1992**, *114*, 5005–5010.
11. (a) Wong, C. H. *Chemtracts-Org. Chem.* **1989**, *3*, 91–111. (b) Kvittingen, L. *Tetrahedron* **1994**, *50*, 8253–8274.
12. List, B.; Shabat, D.; Barbas, C. F.; Lerner, R. A. *Eur. J. Org. Chem.* **1998**, *4*, 881–885.
13. (a) *High Pressure Chemical Synthesis*; Jurczak, J., Baranowski, B., Eds.; Elsevier: Amsterdam, 1989. (b) *High Pressure Chemistry, Biochemistry and Materials Science*; Winter, R., Jonas, J., Eds.; Kluwer Academic: Dordrecht, 1993. (c) *High Pressure Molecular Science*; Winter, R., Jonas, J., Eds.; Kluwer Academic: Dordrecht, 1999. (d) *High Pressure Chemistry*; van Eldik, R., Klärner, F. G., Eds.; Wiley: Weinheim, 2002; pp. 305–347.
14. Bridgman, P. W.; Conant, J. B. *Proc. Natl Acad. Sci. USA* **1929**, *15*, 680–688.
15. Lewis, D. A.; Summer, J. D.; Ward, T. C.; Mc Grawth, J. E. *J. Polym. Sci., Part A* **1992**, *30*, 1647–1653.
16. Marrero-Terrero, L.; Loupy, A. *Synlett* **1996**, 245.
17. Jenner, G. *Tetrahedron Lett.* **1996**, *37*, 3691–3694.
18. Rechsteiner, B.; Texier-Boullet, F.; Hamelin, J. *Tetrahedron Lett.* **1993**, *34*, 5071–5074.
19. (a) Lindley, J.; Mason, T. *Chem. Soc. Rev.* **1987**, *16*, 275–311. (b) Luche, J. L. *Synthesis* **1989**, 787–813.
20. Lee, J.; Snyder, J. K. *J. Am. Chem. Soc.* **1989**, *111*, 1522–1524.
21. Goldsmith, D.; Soria, J. J. *Tetrahedron Lett.* **1991**, *32*, 2457–2460.
22. (a) Lubineau, A. *J. Org. Chem.* **1986**, *51*, 2142–2144. (b) Yamamoto, Y.; Maruyama, K.; Matsumoto, K. *J. Am. Chem. Soc.* **1983**, *105*, 6963–6965.
23. (a) Bouaziz, Z.; Nebois, P.; Fillion, H.; Luche, J. L.; Jenner, G. *Tetrahedron* **1995**, *51*, 4057–4064. (b) Jenner, G. *Tetrahedron* **1997**, *53*, 2669–2695.
24. Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3590–3596.
25. Jenner, G. *High Pressure Res.* **1995**, *13*, 321–326.
26. Jenner, G. *Tetrahedron Lett.* **1995**, *36*, 233–236.
27. Jenner, G. *Tetrahedron* **1996**, *52*, 13557–13568.
28. Jenner, G. *J. Chem. Soc., Faraday Trans. 1* **1985**, *81*, 2437–2460.
29. Le Roux, C.; Gaspard, H.; Dubac, J.; Jaud, J.; Vignaux, P. *J. Org. Chem.* **1993**, *58*, 1835–1839.
30. Loh, T. P.; Pei, J.; Koh, K. S.; Cao, G. Q.; Li, X. R. *Tetrahedron Lett.* **1997**, *38*, 3465–3468.
31. Tamio, R.; Mineur, C.; Ghosez, L. *Tetrahedron Lett.* **1995**, *49*, 8977–8980.
32. Ono, M.; Nishimura, K.; Nagaoka, Y.; Tomioka, K. *Tetrahedron Lett.* **1999**, *40*, 1509–1512.
33. Sankararaman, S.; Nesakumar, J. E. *Eur. J. Org. Chem.* **2000**, 2003–2011.
34. Jenner, G. *Tetrahedron Lett.* **1999**, *40*, 491–494.
35. Ayerbe, M.; Cossio, F. P. *Tetrahedron Lett.* **1995**, *36*, 4447–4450.
36. Kumar, A. *J. Org. Chem.* **1994**, *59*, 4612–4617.
37. Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990**, *112*, 4595–4596.
38. Forman, M. A.; Dailey, W. P. *J. Am. Chem. Soc.* **1991**, *113*, 2761–2762.
39. Jenner, G.; Ben Salem, R. *Tetrahedron* **1997**, *53*, 4637–4648.
40. Shtyrtin, Y. G.; Murzin, D. G.; Luzanova, N. A.; Ishkakova, G. G.; Kiselev, V. D.; Konovalov, A. I. *Tetrahedron* **1998**, *54*, 2631–2646.
41. Dauben, W. G.; Kessel, C. R.; Takemura, K. H. *J. Am. Chem. Soc.* **1980**, *102*, 6893–6894.
42. Dauben, W. G.; Lam, J. Y.; Guo, Z. R. *J. Org. Chem.* **1996**, *61*, 4816–4819.
43. Jenner, G. *High Press. Res.* **1993**, *11*, 257–262.
44. Gradillas, A.; del Campo, C.; Sinisterra, J. V.; Llama, E. F. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2611–2613.
45. Lehn, J. M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 89–112.
46. Sauvage, J. P. *Acc. Chem. Res.* **1990**, *23*, 319–327.
47. Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 164–170.
48. Blake, J. F.; Lim, D.; Jorgensen, W. L. *J. Org. Chem.* **1994**, *59*, 803–805.
49. Jenner, G.; Klärner, F. G. Unpublished results.
50. Ben Salem, R.; Jenner, G. *Rev. High Pressure Sci. Technol.* **1998**, *7*, 1268–1270.
51. Jenner, G.; Ben Salem, R. *Rev. High Pressure Sci. Technol.* **1998**, *7*, 1265–1267.
52. Jenner, G. *J. Phys. Org. Chem.* **1999**, *12*, 619–625.
53. Junge, H.; Oehme, G. *Tetrahedron* **1998**, *54*, 11027–11032.
54. Plate, R.; Hemkens, P. H.; Smits, J. M.; Nivard, R. J.; Ottenheijm, H. C. *J. Org. Chem.* **1987**, *52*, 1047–1051.
55. Yu, Y.; Fujita, H.; Ohno, M.; Eguchi, S. *Synthesis* **1995**, 498–500.
56. Edmondson, S. J.; Hill, J. S.; Isaacs, N. S.; Mitchell, P. C. *J. Chem. Soc., Dalton Trans.* **1990**, 1115–1118.
57. Jenner, G. *New J. Chem.* **1995**, *19*, 173–178.
58. Oishi, T.; Ozuri, H.; Hirama, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1241–1244.
59. Hill, J. S.; Isaacs, N. S. *Tetrahedron Lett.* **1986**, *27*, 5007–5010.
60. Brauer, H. D.; Kelm, H. *Zeit. Phys. Chem. NF* **1971**, *76*, 98–107.
61. Fleischmann, F. K.; Kelm, H. *Tetrahedron Lett.* **1973**, *14*, 3773–3776.
62. Yamada, T.; Yanagi, T.; Omote, Y.; Miyazawa, T.; Kuwata, S.; Sugiura, M.; Matsumoto, K. *J. Chem. Soc., Chem. Commun.* **1990**, 1640–1641.
63. Jurczak, J.; Ostaszewski, R.; Salanski, P.; Stankiewicz, T. *Tetrahedron* **1993**, *49*, 1471–1477.
64. Ostaszewski, R.; Jurczak, J. *Tetrahedron* **1997**, *53*, 7967–7974.
65. Jenner, G. Submitted.
66. (a) Jenner, G. *High Pressure Res.* **1992**, *11*, 107–118. (b) Jenner, G. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 929–933.
67. Bégué, J. P.; Bonnet-Delpon, D.; Lequeux, T.; d'Angelo, J.; Guingant, A. *Synlett* **1992**, 146–148.
68. Minuti, L.; Taticchi, A.; Gacs-Baitz, E.; Wenkert, E. *Tetrahedron* **1995**, *51*, 10033–10040.

69. Kotsuki, H.; Kataoka, M.; Matsuo, K.; Suetomo, S.; Shino, M.; Nishizawa, H. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2773–2776.
70. Tahri, A.; Uguen, D.; De Cian, A.; Fischer, J. *Tetrahedron Lett.* **1994**, *35*, 3945–3948.
71. Dumas, F.; Mezrhab, B.; d'Angelo, J.; Riche, C.; Chiaroni, A. *J. Org. Chem.* **1996**, *61*, 2293–2304.
72. Jenner, G. *Tetrahedron Lett.* **2001**, *42*, 4807–4810.
73. Jenner, G. In *Molecular Systems Under High Pressure*; Pucci, R., Piccitto, G., Eds.; North-Holland: Amsterdam, 1991; pp. 361–380.
74. Warrener, R. N.; Margetic, D.; Tietink, E. R.; Russell, R. A. *Synlett* **1997**, 196–198.
75. Benkhoff, J.; Boese, R.; Klaerner, F. G.; Wigger, A. E. *Tetrahedron Lett.* **1994**, *35*, 73–76.
76. Warrener, R. N.; Butler, D. N.; Russell, R. A. *Synlett* **1998**, 566–573.
77. (a) Warrener, R. N.; Margetic, D.; Russell, R. A. *Synlett* **1998**, 585–587. (b) Butler, D. N.; Warrener, R. N.; Malpass, J. R.; Russell, R. A.; Sun, G. *Synlett* **1998**, 588–590. (c) Warrener, R. N.; Johnston, M. R.; Schultz, A. C.; Houghton, M. A.; Gunter, M. J. *Synlett* **1998**, 590–591.
78. Chmielewski, M.; Kaluga, Z.; Salanski, P.; Jurczak, J. *High Pressure Res.* **1992**, *11*, 171–176.
79. Taguchi, Y.; Tsuchiya, T.; Oishi, A.; Shibuya, I. *Bull. Chem. Soc. Jpn* **1996**, *69*, 1667–1672.
80. Kennington, J. W.; Li, W.; Deshong, P. *High Pressure Res.* **1992**, *11*, 163–166.
81. Jurczak, J.; Rahm, A. In *High Pressure Synthesis*; Jurczak, J., Baranowski, B., Eds.; Elsevier: Amsterdam, 1989; pp. 322–348.
82. Winterfeldt, E.; Wray, V. *Chem. Ber.* **1992**, *125*, 2159–2161.
83. Matsumoto, K.; Ciobanu, M.; Yoshita, M.; Uchida, T. *Heterocycles* **1997**, *45*, 15–18.
84. Takeshita, H.; Lu, J.; Kato, N.; Mori, A. *Chem. Lett.* **1993**, 1697–1698.
85. Breitkopf, V.; Hopf, H.; Klärner, F. G.; Witulski, B.; Zimny, B. *Liebigs Ann.* **1995**, 613–617.
86. Kirin, S. I.; Klärner, F. G.; Eckert-Maksic, M. *Synlett* **1999**, 351–353.
87. Marko, I. E.; Seres, P.; Swarbrick, T. M.; Staton, I.; Adam, H. *Tetrahedron Lett.* **1992**, *33*, 5649–5652.
88. Prapansiri, V.; Thornton, E. R. *Tetrahedron Lett* **1991**, *32*, 3147–3150.
89. Keijsers, J.; Hams, B.; Kruse, C. G.; Scheeren, H. W. *Heterocycles* **1989**, *29*, 79–86.
90. Aben, R. W.; Keijsers, J.; Hams, B.; Kruse, C. G.; Scheeren, H. W. *Tetrahedron Lett.* **1994**, *35*, 1299–1300.
91. Suzuki, T.; Takayama, H. *J. Chem. Soc., Chem. Commun.* **1995**, 807–808.
92. Winkler, J. D.; Holland, J. M.; Peters, D. A. *J. Org. Chem.* **1996**, *61*, 9074–9075.
93. Harwood, L. M.; Jackson, B.; Jones, G.; Prout, K.; Thomas, R. M.; Witt, F. J. *J. Chem. Soc., Chem. Commun.* **1990**, 608–610.
94. Heiner, T.; Kozhushkov, S. I.; Noltemeyer, M.; Haumann, T.; Boese, R.; de Meijere, A. *Tetrahedron* **1996**, *52*, 12185–12196.
95. Heiner, T.; Michalski, S.; Gerke, K.; Kuchta, G.; Buback, M.; de Meijere, A. *Synlett* **1995**, 355–357.
96. Rulev, A. Y.; Maddaluno, J.; Plé, G.; Plaquevent, J. C.; Duhamel, L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1397–1401.
97. Beusker, P. H.; Aben, R. W.; Seerden, J. P.; Smits, J. M.; Scheeren, H. W. *Eur. J. Org. Chem.* **1998**, 2483–2492.
98. Rao, H. S.; Murali, R.; Taticchi, A.; Scheeren, H. W. *Eur. J. Org. Chem.* **2001**, 2869–2876.
99. Kuster, G. J.; Kalmoua, F.; de Gelder, R.; Scheeren, W. H. *J. Chem. Soc., Chem Commun.* **1999**, 855–856.
100. Yamamoto, Y.; Furuta, T.; Matsuo, J.; Kurata, T. *J. Org. Chem.* **1991**, *56*, 5737–5738.
101. Kotsuki, H.; Ichikawa, Y.; Iwasaki, M.; Kataoka, M.; Nishizawa, M. I. *High Pressure Res.* **1992**, *11*, 107–118.
102. Kotsuki, H.; Kataoka, M.; Nishizawa, H. *Tetrahedron Lett.* **1993**, *34*, 4031–4034.
103. Otto, S.; Engberts, J. B.; Kwak, J. C. *J. Am. Chem. Soc.* **1998**, *120*, 9517–9525.
104. Levina, I. S.; Kukikova, L. E.; Kemernitski, A. V.; Elyanov, B. S.; Gonikberg, E. M. *Izv. Akad. Nauk SSR, Ser. Khim.* **1992**, 1622–1623.
105. Gacs-Baitz, E.; Minuti, L.; Scheeren, H. W.; Selvaggi, R.; Taticchi, A. *Nat. Prod. Lett.* **1993**, *2*, 91–95.
106. Aben, R. W.; Limburg, E. P.; Scheeren, H. W. *High Pressure Res.* **1992**, *11*, 167–170.
107. Jenner, G. *New J. Chem.* **1997**, *21*, 1085–1090.
108. Engler, T. A.; Sampath, U.; Van der Velde, D.; Takusagawa, F. *Tetrahedron* **1992**, *48*, 9399–9416.
109. Posner, G. H.; Hutchings, R. H.; Woodward, B. T. *Synlett* **1997**, 432–434.
110. Jenner, G. *High Pressure Res.* **2000**, *18*, 239–244.
111. Jenner, G. *Sci. Technol. High Pressure* **2000**, *2*, 951–953.
112. Posner, G. H.; Ishihara, Y. *Tetrahedron Lett.* **1994**, *35*, 7545–7548.
113. Vandenput, D. A.; Scheeren, H. W. *Tetrahedron* **1995**, *51*, 8383–8388.
114. Meguro, M.; Asao, N.; Yamamoto, Y. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2597–2601.
115. Kotsuki, H.; Teraguchi, M.; Shimomoto, N.; Ochi, M. *Tetrahedron Lett.* **1996**, *37*, 3727–3730.
116. Harrington, P.; Kerr, M. A. *Can. J. Chem.* **1998**, *76*, 1256–1265.
117. Harrington, P.; Kerr, M. A. *Tetrahedron Lett.* **1997**, *38*, 5949–5952.
118. Kotsuki, H.; Arimura, K.; Maruzawa, R.; Ohshima, R. *Synlett* **1999**, 650–652.
119. Kotsuki, H.; Arimura, K. *Tetrahedron Lett.* **1997**, *38*, 7583–7586.
120. de Meijere, A.; Bräse, S. In *Transition Metal Catalyzed Reactions*; Davies, S. G., Murahashi, S. I., Eds.; Blackwell Science: Oxford, 1998; pp. 1–16.
121. Jenner, G.; Papadopoulos, M. *High Pressure Res.* **1990**, *5*, 644–646.
122. Colin, S.; Vaysse-Ludot, L.; Lecouvé, J. P.; Maddaluno, J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4505–4511.
123. Jousseaume, B.; Jurczak, J.; Salanski, P.; Verlhac, J. B. *High Pressure Res.* **1991**, *7*, 162–164.
124. Mitchell, T. N.; Dornseifer, N. M.; Rahm, A. *High Pressure Res.* **1991**, *7*, 165–167.
125. Trost, B. M.; Parquette, J. R.; Marquart, A. L. *J. Am. Chem. Soc.* **1995**, *117*, 3284–3285.
126. Tietze, L. F.; Burkhardt, O.; Henrich, M. *Liebigs Ann.* **1997**, 1407–1413.
127. Tietze, L. F.; Burkhardt, O.; Henrich, M. *Liebigs Ann.* **1997**, 887–891.
128. Hillers, S.; Sartori, S.; Reiser, O. *J. Am. Chem. Soc.* **1996**, *118*, 2087–2088.

129. Jenner, G. In *High Pressure Chemistry*; van Eldik, R., Klärner, F. G., Eds.; Wiley: New York, 2002; pp. 305–347.
130. Jenner, G. *Tetrahedron Lett.* **1994**, *35*, 1189–1192.
131. Jenner, G.; Ben Salem, R. *New J. Chem.* **2000**, *24*, 203–207.
132. Schoffers, E.; Golebiowski, A.; Johnson, C. R. *Tetrahedron* **1996**, *52*, 3769–3826.
133. Wong, C. H.; Whitesides, G. M. *Enzymes in Organic Chemistry*; Pergamon: New York, 1994; pp. 195–251.
134. Balny, C.; Masson, P.; Travers, F. *High Pressure Res.* **1989**, *2*, 1–28.
135. Fantin, G.; Fogagnolo, M.; Guerzoni, M. E.; Lanciotti, R.; Medici, A.; Pedrini, A.; Rossi, D. *Tetrahedron: Asymmetry* **1996**, *7*, 2879–2887.
136. (a) Kuster, G. J.; Scheeren, H. W. *Tetrahedron Lett.* **1998**, *39*, 3613–3616. (b) Davies, A. G.; Kinart, W. J. *J. Chem. Soc., Perkin Trans. 2* **1993**, 2281–2284.

Biographical sketch

Gérard Jenner received his PhD in 1966 from the University of Strasbourg. His scientific interest has been high pressure chemistry and thermodynamics covering various fields such as macromolecular science, *P–V–T* relationships, homogeneous catalysis, and 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 and head of laboratory. He took a position as Research Associate at the State University of New York at Stony Brook with Professor W. J. le Noble (1980–81). He was a 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 chaired the European High Pressure Research Group (1988–91). His current interests focus on multiactivation processes with pressure as the basic parameter, mechanistic studies using pressure kinetics, correlations between pressure and steric inhibition, crystallisation of proteins under hyperbaric conditions.