Green Chemistry

TUTORIAL REVIEW

View Article Online
View Journal | View Issue

Cite this: *Green Chem.*, 2025, **27**, 7096

Green synthesis of building blocks, drug candidates and fine chemicals by barochemistry: application of high pressure in organic synthesis

Guoshu Xie,[a] Valerie Wright,[a] Alexander Lazarev,[b] Gary Smejkal,[b] Vera Gross[b] and Béla Török *[a]

While there are many areas of green chemistry that affect contemporary synthesis, the development of non-traditional activation methods, such as microwaves, ultrasound, mechanochemistry or high hydrostatic pressure (HHP) is considered as one the most important contributors to the development of green synthetic processes. Among these methods HHP, which, by analogy with the other methods, *e.g.* sonochemistry or mechanochemistry, can be referred to as barochemistry, is well-suited for industrial production; the large scale instrumentation is broadly available, at this time focusing on food processing applications. HHP instruments are safe and easy to handle, robust, and are a good fit for batch and (stopped)-flow operations. The same instruments could be used for large scale chemical synthesis as well, however, the high pressure synthesis of organic compounds, including Active Pharmaceutical Ingredients (APIs), is still in its infancy with extensive developments expected in the near future. HHP applies mechanical compression force to initiate transformations, such as the inactivation of pathogens and enzymes, or activation of chemical reactions. The pressure range of these reactions (2–20 kbar) significantly exceeds that of the typical chemistry using pressurized gases (0.01–0.1 kbar), such as hydrogenations. This tutorial review provides a succinct introduction to the theory and use of barochemistry, with particular emphasis on its current applications and great potential in green synthesis.

Received 28th February 2025,
Accepted 19th May 2025

DOI: 10.1039/d5gc01075f

rsc.li/greenchem

Green foundation

1. We discuss the use of high hydrostatic pressure (HHP) that applies mechanical compression force to activate chemical processes is an emerging field in chemistry. We describe the fundamentals of high pressure activation, give an overview of available equipment and survey representative green organic synthesis applications.

2. Non-traditional activation methods, such as microwaves, ultrasounds, mechanochemistry or high hydrostatic pressure (HHP) is considered as one the most important contributors to the development of green synthetic processes. High pressure activation utilizes high hydrostatic pressure (HHP) to apply mechanical compression force to activate chemical reactions, organic and inorganic alike. The physical closeness of the reacting partners can create favorable orientations for the active centers to react, resulting in improved yields and selectivity, often combined with shorter reaction times, and easier workup as compared to reactions activated by traditional convective heating.

3. The green benefits of high pressure activation in organic syntheses suggests that broader applications of the HHP or barochemistry would bring extensive benefits to the green synthesis of pharmaceuticals, building blocks, and fine chemicals at the laboratory and likely at the industrial scale.

1. Introduction

The industrial production of chemicals and pharmaceuticals has led to great achievements in fulfilling important societal needs. The 20th and 21st centuries can be called the golden age of chemical synthesis. However, these unprecedented developments can have a dark side such as environmental toxicity of the product itself, *e.g.* DDT, PFAS and other "forever chemicals", or the generation of highly toxic waste during manufacturing.[1] By the end of the 20th century a growing sentiment developed that the traditional methods of chemical synthesis were not sustainable, effectively initiating the green chemistry movement.[2] This movement resulted in unparalleled advances in this field developing effective green tools with the aim of reforming the effective but outdated protocols in the chemical and pharmaceutical industries to provide fine chemicals and pharmaceuticals safely at low cost with no, or

[a]*Department of Chemistry, University of Massachusetts Boston, 100 Morrissey Blvd, Boston, MA, USA. E-mail: Bela.Torok@umb.edu*
[b]*Pressure BioSciences Inc., 480 Neponset St, Unit 10B, Canton, MA 02021, USA*

minimal negative effects on the environment.[3] Today the environmentally benign synthesis of active pharmaceutical ingredients (APIs) and fine chemicals[4] is one of the most important pillars of Green Chemistry.[5,6] There are several major contributors to these developments, such as catalysis,[7] solvents, and the so-called nontraditional activation methods that offer new perspectives for the chemical industry and new advances in the activation of chemical reactions.[8] Often these nontraditional activation methods are utilized together with other green tools.[9]

1.1. Green synthesis by non-traditional activation methods

An overwhelming majority of chemical reactions require some sort of activation to proceed. Although the use of catalytic approaches brings down the activation energy barrier, the use of non-traditional activation methods offers further improvements compared to conventional convective heating in activating chemical processes. The term non-traditional activation methods, includes protocols that use energy forms other than simple heat. The major areas are microwave, ultrasound, photo-, electro-, mechanochemistry and high pressure.[8] These methods possess a wide variety of energy forms and transmission to a reaction system. However, despite the different modes of energy transfer, the common attribute of these methods is that they activate certain chemical reactions more specifically and more efficiently than convective heating.

High pressure activation, or barochemistry, the topic of this work, uses mechanical compression force to initiate reactions. Definition: The term **barochemistry** refers to the use of externally applied hydrostatic pressure to initiate or accelerate chemical transformations. The name is analogous to other non-traditional activation methods such as photochemistry, sonochemistry or mechanochemistry.

The major advantages and green benefits of barochemistry are multifaceted and will be illustrated in the work: (i) catalyst-free and solvent-free conditions eliminate catalyst and solvent handling, and can be used for a wide range of reactions from Diels–Alder reaction or cycloadditions, to multistep cyclizations, (ii) such conditions help achieve higher yields and selectivities, (iii) high atom economy and low waste generation (depending on the reactions), (iv) and guarantee energy efficiency (once pressurized, a system can hold pressure for an extended period of time without continued energy input, and many reactions occur at room temperature), (v) the tunable features of the pressure instruments (pressure, temperature, static pressure or cycling) allow broad applicability, (vi) water is used as a pressure transmitting fluid, (non-flammable, non-toxic, inexpensive, widely available, and has low compressibility), (vii) and finally, barochemistry offers scalability; unlike with many non-traditional activation methods, the large scale instruments are already available should the need for scale up arise. Definitions: (i) The term **static pressure** refers to a system being pressurized and kept at that constant desired pressure for a period of time, after which the system gets decompressed. (ii) The term **cycling** or **pressure cycling** refers to system being pressurized and kept at that desired pressure for a period of time, decompressed, kept decompressed for a period of time, and these action repeated for a number of desired times as illustrated in Fig. 1.

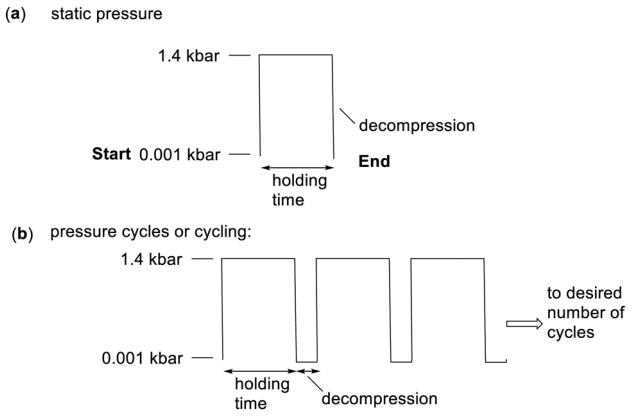


Fig. 1 HHP-initiated reactions under (a) static pressure and (b) pressure cycling used. Generally, the holding time are much longer under static pressure conditions than under cycling, however, holding time, decompression, pressure *etc*. can be set up as desired.

The pressure cycling (Fig. 1b) is a practical approach that often produces higher yields. While the exact nature of the cycling phenomenon is not fully understood, it is hypothesized that the pressure cycling protocol causes periodic change in the volume of the reaction vessel that could lead to some mass transfer and molecular re-alignments during compression and decompression steps that are beneficial for reaction kinetics.

The significance of organic synthesis in the preparation of pharmaceuticals, fine chemicals, and other consumer goods is indisputable. It is also vital that these synthetic operations are carried out in accordance with the green chemistry principles, to ensure that they have zero or negligible negative impact on the environment. In this tutorial, we will outline and discuss the beneficial features of high hydrostatic pressure for the synthesis of valuable products, including fine chemicals and APIs.

2. The theory and practice of high pressure reactions

High pressure activation utilizes high hydrostatic pressure (HHP) to apply mechanical compression force to activate chemical reactions, organic and inorganic alike. The physical proximity of the reacting partners can create favorable orientations for the active centers to react, resulting in improved yields and selectivity, often combined with shorter reaction times, and easier workup as compared to reactions activated by traditional convective heating. The application of HHP has more than a century of history. Röntgen's early work in 1892 appears to be the first use of high pressure.[10] Further applications followed in the early 1900s in food chemistry or general food science, and biology, including the preservation of milk,[11] or the denaturation of egg white albumin.[12,13] With

the development of reliable and safe high pressure equipment such applications have become a mainstream tool in the food industry.[14,15] Despite the early developments, the first HHP-activated synthetic procedure was only reported in the 1970s.[16] Since then, HHP-assisted synthesis has become more common, and has been the subject of regular reviews.[17–21]

A survey of the literature reveals that the number of publications in the high pressure area steadily increased since the 1970s. Fig. 2 illustrates the distribution of pressure-related publications based on gradually narrowing down the topic.

As shown, the search term "high pressure synthesis" finds 29 000 papers published, while an intersection of "high pressure" and "organic synthesis" keywords yields only 320 publications over the course of nearly a century. Fig. 2 also indicates that the publication frequency in both graphs significantly increased in the past few decades, perhaps suggesting that the commercial availability of reliable instrumentation accelerates new discoveries. Although these literature searches do not account for the exact numbers due to the occasional obscure mention of high pressure in synthesis (*e.g.* in medicinal chemistry synthesis of anti-hypertensive drugs), Fig. 2 still provides a comparison within different areas. Moreover, the vast majority of relevant publications to date are related to the application of high pressure in solid state reaction systems, both homogeneous and heterogeneous, for the preparation of inorganic compounds and materials, rather than applications in organic synthesis. The examples of typical inorganic/material science applications include gallium nitride semiconductors, perovskite solar cells, and low-temperature superconductors, just to name a few.[22] In contrast, high pressure organic synthesis often involves the use of HHP, *i.e.* utilizing liquids as pressure transmitting media. Compared to solid state applications, HHP-initiated organic synthesis, despite continuous developments,[17,18] is still in its comparative infancy.

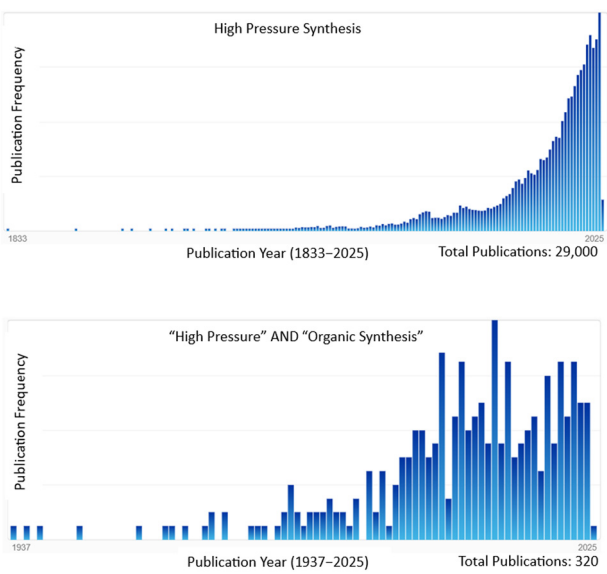


Fig. 2 Illustrations of the publication frequency over the years and total number of publications for generic search terms by SciFinder^n searches as of February 2025.

As one of the important thermodynamic parameters, pressure contributes to controlling the equilibrium and rate of chemical reactions.[23] Despite being a potentially useful tool, high pressure chemistry has been somewhat overlooked by organic chemists. Typical organic syntheses are carried out at or near atmospheric pressure (1 bar) or using pressurized gases (up to about 150 bar at the most), while under HHP conditions, reactions experience much higher pressures.[24] The typical pressure range of HHP reactions (2–20 kbar) is significantly higher than what is used in general organic synthesis, *e.g.* hydrogenations (0.01–0.1 kbar). Fig. 3 illustrates a logarithmic scale of the pressures encountered on Earth and elsewhere in the Universe, highlighting the relevant pressure range for organic synthesis (2–20 kbar). Pressure levels beyond this region (ultra-high pressure up to 7000 kbar) deal with materials in solid state and, while being routinely used in geology, material science, and engineering, and typically require Diamond Anvil Cells (DAC) instrumentation and specialized analytical approaches, are not applicable in organic chemistry and are not being covered in this work.

2.1. Understanding pressure effects: reaction volume ΔV and activation volume $\Delta V^{\ddagger}$

Although the beneficial effects of high pressure have been reported in several publications, the underlying phenomena of its effects on chemical reactions are still not fully understood.

The three major contributors that affect the rate of chemical reaction under high pressure conditions are (i) the increase in concentration of the reacting molecules in the medium; (ii) the change in the rate of molecular diffusion; and (iii) the compression of the reactants at the molecular level which can alter the shape of the "electron clouds" and thus change the rate of effective collisions, phase transitions and specific rearrangements of hydrogen bonding networks in solvents as well.

There is broad agreement that changes in the activation volume ($\Delta V^{\ddagger}$) and reaction volume (ΔV) are the main driving forces of the reactions under pressure. Definitions: (i) **Activation volume** – The term refers to the volume change between the total volume of the reactant molecules and the

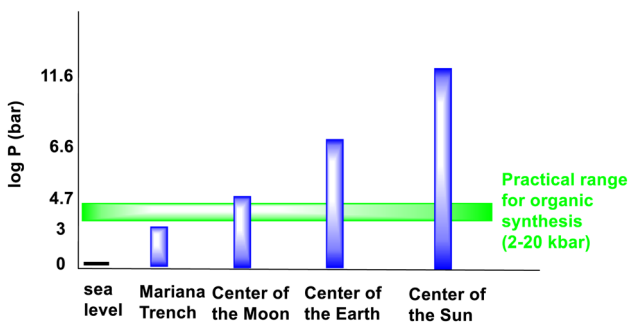


Fig. 3 A logarithmic scale of selected pressures in our Solar System (blue) as well as the pressure range used in organic synthesis (green).[25]

volume of the transition state ($\Delta V^{\ddagger} = V_{\text{transition state}} - V_{\text{starting materials}}$). (ii) **Reaction volume** – The term refers to the volume change between the total volume of the reactants and the total volume of the products ($\Delta V = V_{\text{products}} - V_{\text{starting materials}}$). The volume of starting materials and products include every participant (e.g. even minor byproducts) in the reaction scheme.

Negative values indicate that pressure is going to improve the reaction. In contrast, positive values point in the other direction, *i.e.*, slowing down the given reaction.[26] When the values are around zero, pressure is expected to have little effect on reaction rate. The activation volume ($\Delta V^{\ddagger}$) and reaction volume (ΔV) data can be predictive of reaction behaviour under pressurized conditions. Several theoretical methods are available to calculate these values, among these the XP-PCM (extreme pressure polarizable continuum model) method was specifically developed for high pressure conditions.[27]

2.2. Adiabatic compression heating

Adiabatic compression heating is a well-characterized phenomenon, which has a significant effect on the temperature of materials in gas phase, as the extent of heating is proportional to compressibility. In this tutorial, however, we are going to review compression of reagents in their liquid phase. Compressibility of most liquids is generally small, resulting in relatively insignificant adiabatic heat generation. Water, in particular, exhibits very low compressibility relative to most organic solvents (the bulk modulus of water at room temperature is about 22 kbar[28]). As a result, temperature rise (expressed in °C) due to compression heating in most aqueous systems typically does not exceed single digits if the starting temperature is near or at room temperature and the pressure is increased up to 7 kbar. Upon decompression the process is reversed and under ideal adiabatic (thermally insulated) conditions the system returns to the starting temperature. In real-world systems, however, compression heat tends to rapidly dissipate into the massive pressure vessel hardware surrounding the reaction mixture, thus reaching thermal equilibrium closer to the starting temperature than anticipated for the true adiabatic conditions.[29] It is also important to note that compression heat is being produced simultaneously within the entire volume of the pressurized liquid independent of the volume; therefore, it is possible to predict heat generation in any system, independent of its scale. However, large vessels tend to trap some heat in the middle, while heat dissipation occurs rapidly near the vessel walls, therefore, special engineering solutions may be necessary to ensure uniform temperature conditions in large scale equipment, if precise temperature control is important for the process at hand.[30]

3. Contemporary synthetic applications in barochemistry

3.1. High pressure technology in practice

HHP uses water as a pressure transfer medium that makes it possible to reach high pressures safely. Water is not very compressible, and the danger of pressure release in case of a sudden hardware failure is much lower compared to the gas-phase systems. Pressure cookers achieve significantly less pressure yet are far more dangerous as they rely on steam for pressure, which is highly compressible and could expand with explosive force. Water is about 20 000 times less compressible than air or steam, so it can be compressed to much greater levels of pressure without a risk of explosive decompression.[31] Accordingly, the high pressure technology is widely used, even at the industrial level, in food processing,[14,15] and in material science.[22]

A schematic description of a typical high pressure device is shown in Fig. 4. A relatively modest pressure is provided by a pneumatic or hydraulic source, which is amplified by an intensifier that, *via* a pressure medium, will generate the desired pressure for the pressure vessel, where the reaction occurs.

3.2. High pressure equipment

One of the most crucial parts of high pressure synthesis is the equipment itself. The first such equipment was reported in 1899 by Hite[11] to preserve milk in the dairy industry. The food industry is still the major user of large-scale high-pressure equipment. Similar reactors could be dedicated to barochemical synthesis as well, translating the laboratory protocols to large scale. There are several companies producing safe and reliable high-pressure equipment today.

High pressure in liquid phase is generated by high pressure intensifiers (Fig. 5). Low-to-moderate pressure levels are being applied to a larger piston, which, in turn, is pushing a smaller diameter piston to compress the pressure media. The cross-sectional ratio between the two pistons is equal to the pressure amplification factor. Intensifiers can be driven pneumatically or hydraulically. Small pneumatic intensifiers are less expensive; however, they rely on air compressors, which become

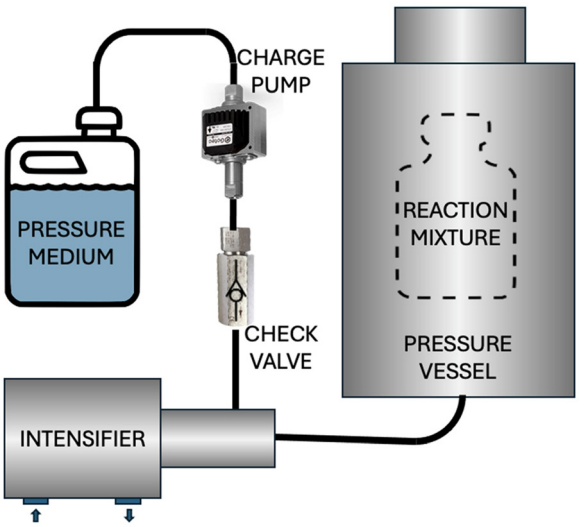


Fig. 4 Simplified fluidic diagram of a high hydrostatic pressure instrument.

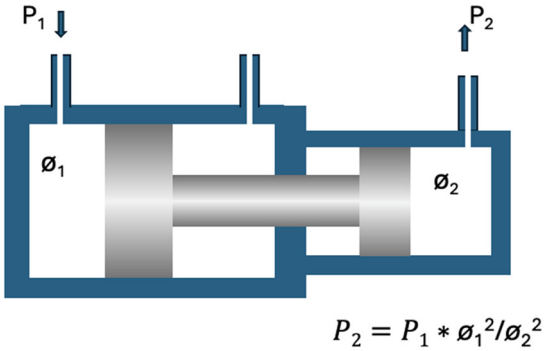


Fig. 5 High pressure intensifier amplifies pneumatic or hydraulic input pressure P_1 resulting in output pressure P_2 being greater by a factor determined as a ratio of piston areas (ϕ_1^2/ϕ_2^2).

increasingly expensive and difficult to maintain as their scale grows. Hydraulic intensifiers, on the other hand, typically require lower cross-sectional ratios and tend to scale much easier.

3.2.1. Commercial high pressure equipment. Commercialization of the high-pressure processing of food led to significant innovations and involved the efforts of several companies and Government agencies, leading to the birth of an entire new market.[32] Commercially existing equipment is currently available from several companies such as Hyperbaric (Spain),[33] JBT-Avure (USA),[34] Thissenkrupp-Uhde (Germany),[35] Kobelco (Japan),[36] as well as Baotou Kefa High Pressure Technology Co., Ltd (China),[37] although all of these companies are mainly focusing on food processing applications. Pressure BioSciences (USA)[38] offers a range of versatile benchtop research equipment for lab- to pilot-scale studies. Other vendors such as Graco/High Pressure Equipment,[39] Parker Hannifin Corp.,[40] and High Pressure Technologies, LLC[41] offer auxiliary components and consumables, such as reactor vessels, valves, tubing and pumps for those who are ambitious enough to build their own equipment.

3.2.2. Pressure vessels. High pressure vessels must withstand significant fatigue that accumulates over multiple pressurization and de-pressurization cycles. Smaller pressure vessels (up to 10 L) are typically machined from a single metal block. Larger pressure vessels are typically manufactured using relatively thin-wall stainless steel cylinders that are subsequently pre-compressed using multiple layers of a hard steel wire tightly wound around the cylindrical portion of the inner cylinder. In addition to a lower manufacturing cost compared to the machining a monoblock vessels of the similar dimensions, the wire-wound design has tremendous safety advantages: such pressure vessels tend to leak before they burst, since the steel wire shell keeps the vessel together even after it develops a crack through its wall.[43]

3.2.3. Pressure transmitting fluid. Older high-pressure systems were made of high-carbon steel and required organic solvents (kerosene, mineral oil, *etc.*) to be employed as pressure medium to prevent corrosion. Modern pressure vessels made from hot isostatically pressed austenitic stainless-steel alloys resist corrosion and can be used with water as the pressure transmitting medium. Water presents multiple advantages over organic solvents or oils. It is non-volatile, non-flammable, non-toxic, inexpensive, widely available, and also features one of lowest compressibility of liquids. In smaller high-pressure systems water can be used once and subsequently discarded, thus eliminating concerns of accumulating contaminants over time. However, large industrial systems tend to recycle water to save on overall process cost and also to save on pressurization times and preserve some energy by collecting most of the pressurized water in a secondary storage vessel at some intermediate pressure, before venting remaining pressure from the main vessel.

3.2.4. Batch reactors. Typical high-pressure equipment includes an air compressor or hydraulic pump as a source of pressure that is amplified by an intensifier as described in Fig. 4 above. The pressure medium, *e.g.*, water, is introduced into a pressure vessel *via* a charge pump that also purges air from a pressure chamber. The intensifier amplifies pressure provided by the air compressor or hydraulic pump to generate the desired pressure in the pressure chamber. Various complexity control solutions are available, from simple manually actuated valves to sophisticated computer- or programmable logic controller (PLC)-driven systems offering GMP-compliant data security and user management.

A specific model, a Barocycler 23020EXT (Pressure BioSciences) shown in Fig. 6, is a bench-top instrument which is a space-saving alternative to larger models. The stand-alone instrument is shown in Fig. 6(A), connected to an air compressor underneath (Fig. 6(B)). For small scale reactions, individually sealed fluoropolymer reaction vials (fluorinated ethylene propylene (FEP) 150 µl MicroTubes, Fig. 6(C)) are used, that are placed into metal sample cassettes which are then immersed in the pressure vessel. Up to 16 reactions (Fig. 6(D)) can be carried out under identical conditions, enabling the screening of a large set of reactions in a timely manner.

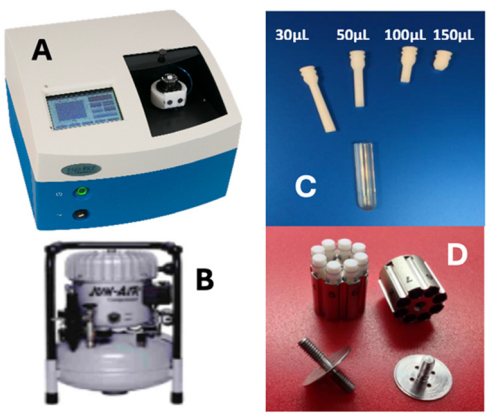


Fig. 6 Image of Barocycler 2320EXT (A); air compressor (B), fluorinated ethylene propylene (FEP) 150 µl MicroTubes (C); metal cassettes with 8 tubular openings each.

3.2.5. Stopped flow and continuous flow systems. While batch reactors are still predominant in high-pressure process equipment, there are several examples of the research-scale equipment designed to study reaction kinetics effects due to rapid changes of pressure, so-called "pressure-jump" systems. In principle, pressure jump equipment consists of the main reactor vessel typically equipped with optically transparent windows to facilitate spectroscopic analysis of the process, an intermediate accumulator vessel, and one or two high-speed valves that offer an ability to equilibrate pressure between the two vessels or vent the pressure media out to the atmospheric pressure level. Static high-pressure and pressure-jump kinetics experiments were successfully employed for studying protein conformational dynamics using UV-Vis,[44] fluorescence spectroscopy,[45] circular dichroism,[46] EPR,[47,48] NMR[46,49] and small angle X-ray scattering[50] techniques.

Continuous-flow systems have also been reported, which frequently consist of a modified HPLC-style pump, a flow-through reactor, *e.g.*, an aging tube or a capillary, and a downstream flow restrictor device capable of sustained restriction to the flow to maintain desired pressure level in the system.[51] All such systems are presently research-scale.[52]

A recently introduced manufacturing-scale "In-Bulk" HHP equipment by Hyperbaric SA[53] is a flow-through system that offers a semi-discontinuous treatment of fruit/vegetable juices and other pumpable liquids at a throughput of 4000 L per hour and pressure up to 7 kbar. The system is pressurized in a batch mode but filled and emptied in a flow-through manner, thus eliminating a need of manual handling of bags or bottles of packaged product.

3.2.6. Combination of high-pressure equipment with optical spectroscopy for mechanistic studies or real time monitoring. UV-Vis absorption and fluorescence are common analysis tools that are easily accessible, low-cost, simple, and reliable. Proteins and nucleic acids either directly absorb UV light, or are detected with sensitive and selective fluorescent dyes. For example, optical spectroscopy and HHP were combined into an experimental workflow named "High-Pressure Optical Spectroscopy" or HiPOS.[54] The most common use of HiPOS is for studying enzyme kinetics, or any chemical function that is influenced by HHP. The high pressure affects protein conformation, therefore high-pressure optical spectroscopy and microscopy can be used to study conformational dynamics, mechanisms of cell division, and macromolecular structure.[55] The HiPOS instrument is shown on Fig. 7.

The sample cuvette can be placed into the high pressure chamber and monitored using the AvaSpec Spectrophotometer attached *via* fiber optic cables. The spectrophotometer is coupled to a Barocycler HUB440, a compact, programmable high-pressure generator that can reach pressure of 4 kbar.[56]

The HiPOS system offers an ability to monitor the sample using optical spectroscopic techniques under HHP in real time. The system also has the benefit of being able to control the sample temperature. The HHP approach is safe and green, while the UV-Vis or fluorescence detection is sensitive, widely used, and well understood.

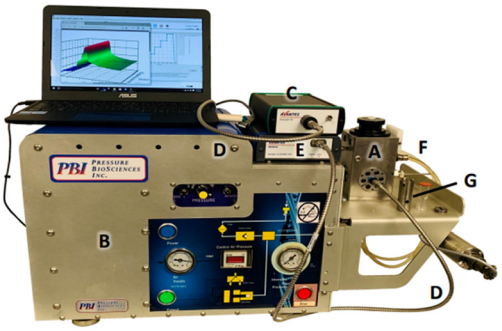


Fig. 7 Components of fiber optics-based HiPOS system. (A) The high-pressure optical cell interfaces with (B) the programmable HUB440 pressure generator (Pressure BioSciences, Inc., Canton, MA). (C) The xenon light source and the (E) AvaSpec photodiode array spectrophotometer (Avantes USA, Lafayette, CO) are coupled to the optical cell *via* the quartz (D) fiber optics cables. Three optical windows offer an easy conversion of the high-pressure cell from absorbance to fluorescence by simply re-positioning the detector fiber optics cable into an orthogonal position relative to the incident beam. (F) Operating temperature in the optical cell is controlled by an external circulating water bath. (G) Shows cuvette holder, semi-micro volume cuvette, and a silicone seal.

3.2.6.1. Mechanistic investigations of enzyme reactions by the HiPOS system. As enzyme-catalyzed reactions are strong contributors to green synthesis, thus mechanistic investigations by HiPOS could help the design of enzymatic synthetic processes. As Fig. 8 indicates, some enzymes exhibit dramatic increase of their activity, while others show significant inhibition as a function of pressure. Real-time kinetics of several proteolytic enzymes was studied in a HiPOS system as a function of temperature and pressure following the spectral change due to release of a chromophore the suitable chromogenic substrates. Trypsin showed consistent performance over a wide range of pressure and a marked increase in proteolytic activity with temperature. Both chymotrypsin and papainase (traditionally

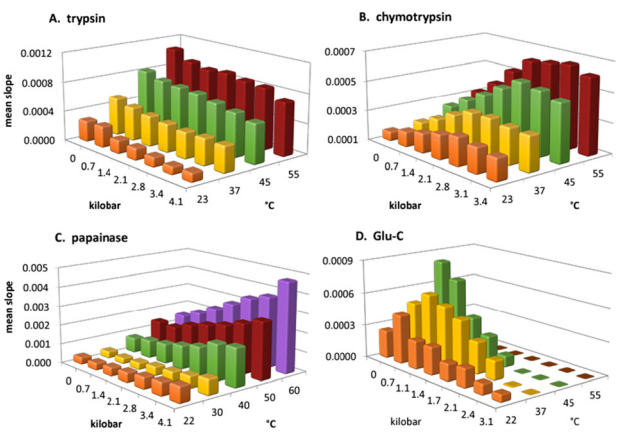


Fig. 8 Enzyme kinetic analysis as a function of pressure and temperature. Trypsin (A) and chymotrypsin (B) reaction rates were increased maximally at 55 °C at 2.8 kbar and 3.1 kbar, respectively. Papainase (C) activity increased nearly 10-fold at 4.1 kbar and 60 °C. Glu-C (D) inactivated at high pressure after reaching maximum activity at 0.7 kbar and 45 °C.

known as papain) showed marked activation with pressure and temperature, while endopeptidase Glu-C was rapidly inactivated with elevated pressure.[54]

Further, the HiPOS system has demonstrated the barosensitivity of several Good's buffers where high pressure induces a shift in pH. Such changes can be measured spectrophotometrically in real time using pH indicator dyes which undergo color transition (Fig. 9 and 10, original data, experimental details available in figure legends). Definition: **Barosensitivity** refers to the sensitivity of a system (such as a molecule, buffer, protein, or reaction) to changes in hydrostatic pressure, typically manifested as structural, functional, or physicochemical changes under elevated pressure.

3.3. Synthetic applications

Synthetic applications of high pressure were employed for several common types of reactions in organic synthesis. The following sections focus on some of the reaction types. In most cases a typical HHP instrument, as described in 3.1 and 3.2, was used, sometimes commercially available instruments, in some others, custom-made machines that were overwhelmingly used in following reactions. In a few examples an innovative use of water freezing was applied to circumvent the need for special apparatus, that could generate up to 2 kbar pressure, which is specifically noted at these examples.

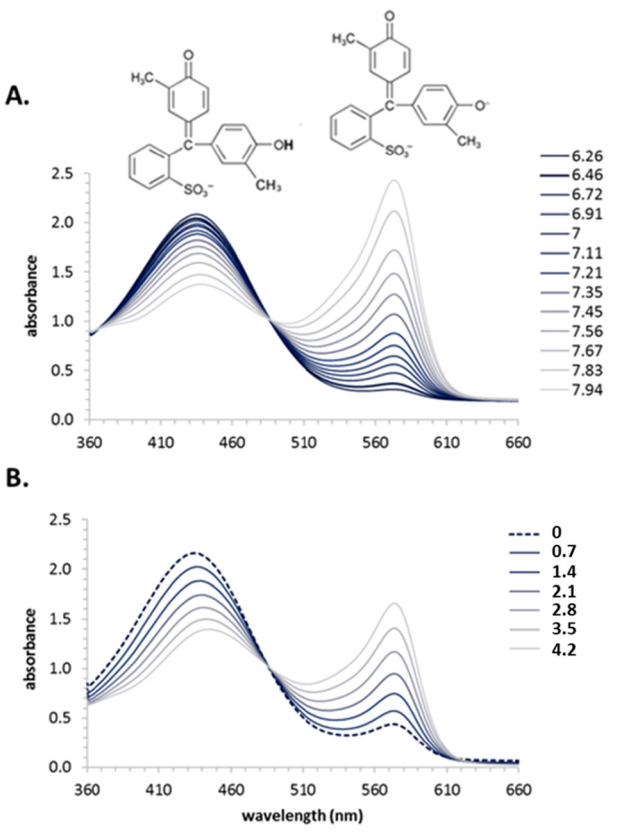


Fig. 9 (A) pH calibration curve showing changes in cresol red spectra in Tris solutions ranging from pH 6.2 to 8.0 performed at atmospheric pressure in the optical cell. Protonated and deprotonated forms of the dye are correlated to peaks at 434 and 573 nm, respectively. (B) Spectral changes of 100 mM Tris-HCl pH 6.86 solution at atmospheric (dashed line) and at high pressure. Cresol red indicated an increase in pH from 6.86 to 7.67 at 4.1 kbar. pH was 0.85 ± 0.05 pH units.

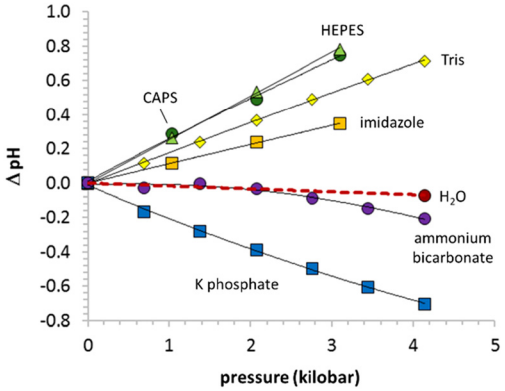
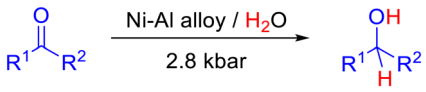


Fig. 10 Barosensitivity of some commonly used biological buffers.

3.3.1. Catalytic hydrogenation. Catalytic hydrogenation[57,58] is one of the most common reduction methods in synthetic chemistry facilitating the transformation of a broad array of functional groups. It is an example of a truly green protocol. The atom economy is perfect 100%, the catalysts are mostly recyclable, minimal or no waste generated, while applying alcohols that are the greenest organic solvents. The HHP version of hydrogenations carries multiple benefits, many are specific to these reactions, *e.g.* (i) the closed system ensures that the hydrogen formed *in situ* during the reactions will stay in the reaction vessel, (ii) the high pressure maintains higher H_2 concentration in the liquid phase, largely eliminating the gas-to-liquid mass transfer limitation. (iii) Parallel, it also improves the hydrogen coverage on the surface of the metal catalyst aiding reaction kinetics and ultimately yield. Due to the high H_2 coverage and the unfavorable hydrogen desorption kinetics under high pressure, (iii) also helps to maintain high selectivity by inhibiting overhydrogenation. Since it is experimentally very difficult to prepare a sealed vessel with hydrogen gas for the HHP experiments, the HHP hydrogenation protocol uses *in situ* generated hydrogen. As a representative example, the catalytic hydrogenation of a broad variety of ketones to alcohols has been developed under HHP conditions by Tomin *et al.*[59] This protocol was based on the use of Ni–Al alloy with water, using the reaction of the aluminum content with water as the hydrogen source, under HHP conditions at 2.8 kbar. A broad variety of acyclic, cyclic and aryl–alkyl ketones were hydrogenated to their appropriate alcohols with high yields and chemoselectivity as shown in Scheme 1.[59] The use of HHP allowed the removal of the traditionally used dilute base which ensured the high selectivity for the alcohols by eliminating common overhydrogenation.[60] Mechanistically, the Al content of the alloy reacts with water and generates H_2 *in situ*, while the Ni becomes a RANEY® Ni skeleton catalyst. The high pressure forces the hydrogen gas to remain in solution, increasing the hydrogen coverage on the surface of the catalyst.

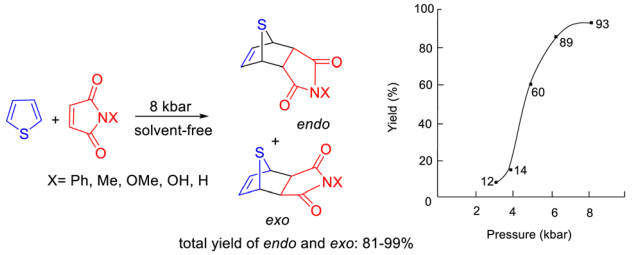


Scheme 1 Selective reduction of ketones under high hydrostatic pressure.

3.3.2. Cycloadditions. Cycloaddition reactions are of high importance in the synthesis of carbo- and heterocyclic products. Due to the nature of these reactions, they are prime targets for high pressure chemistry, since under HHP conditions the distorted electron cloud can lead to more effective overlaps of the orbitals that are involved in the cyclization. Representative examples of the Diels–Alder reaction and other cycloaddition and pericyclic reactions have been thoroughly investigated by Chen *et al.*[27] by using computational methods to provide more insight into the nature of the pressure effect in these reactions. It is reasonable to assume that similar effects are at play in these reactions, independently of the individual substrates. The calculations provided reaction paths and Gibbs energy profiles for the reactions under pressure. For example, the major observations revealed that the Gibbs free energy of the transition state as well as the overall reaction linearly decreased as the pressure increased. Most importantly, the activation energy of reaction also decreased with pressure, and the reaction became barrierless at 50 kbar and the product Gibbs energy is also significantly decreased. For comparison, the same reaction has an activation energy of 21 kcal mol^{-1} at ambient pressure, 1 bar. Although the in-depth interpretation of physics of the pressure effect is beyond the scope of this work, one can conclude that the pressure creates energetically highly favorable conditions for the reactions to occur with much lower activation energy barriers and improves the overall energetics of the products under pressure as well, compared to the ambient pressure alternative.

3.3.2.1. Diels–Alder reactions. Cyclization reactions generally benefit from high pressure conditions due to their activation volume $\Delta V^{\ddagger}$ and reaction volume ΔV values, that are sufficiently negative to ensure a beneficial contribution of pressure.

The Diels–Alder cycloadditions[61] are likely the most well-known cyclizations having high significance as a synthetic source of large variety of invaluable chemicals. A high-pressure protocol described the Diels–Alder reaction of thiophene[62] that was generally considered more as a heteroaromatic compound than a diene prohibiting its use in these reactions even with strong dienophiles such as maleic anhydride.[63] Kotsuki's group disclosed the use of high pressure as an activation method for this reaction, significantly improving the product yield. The authors carried out the reaction at 8 kbar under solvent-free conditions and obtained the products as a mixture of *endo* and *exo* isomers in good to excellent yields (81–99%) as shown in Scheme 2. Further investigations were also carried out to determine the dependence of the yield on the level of pressure (Scheme 2). At 100 °C, the yields considerably

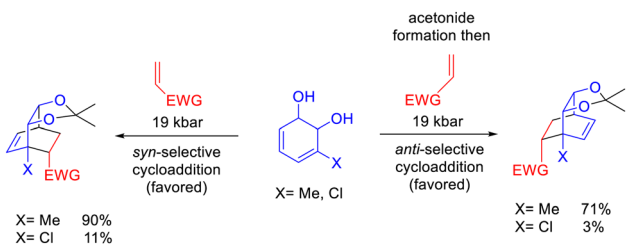


Scheme 2 High pressure-initiated Diels–Alder reaction of thiophene with maleimide dienophiles and the dependence of the yield on the applied pressure.

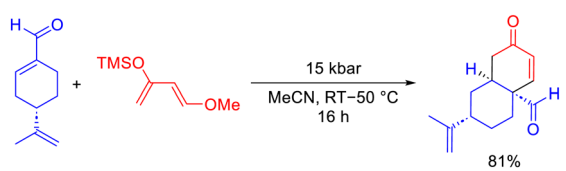
increased with pressure, suggesting high pressure improved the kinetics of the reaction.

The Diels–Alder reaction of *cis*-1,2-dihydrocatechols (X = Me and Cl) with a variety of activated alkenes as dienophiles is another successful example of HHP-initiated cyclization (Scheme 3). The reaction carried out at 19 kbar,[64] as described by Stewart *et al.*, provided two different bicyclo[2.2.2]octene products *via* *syn*-addition pathway and *anti*-selective addition pathway at the same pressure with good to excellent yields for the Me analog. Conversely, the Cl analog performed poorly in the reaction.

High pressure–assisted Diels–Alder reactions have shown promise in the synthesis of complex molecules such as antibiotics by the Rutjes group. Due to the quick adaptation of bacteria to resist antibiotics, these drugs are constantly being designed or modified to ensure their efficacy. An HHP-initiated Diels–Alder cyclization of sterically hindered substrates served as a key step for the synthesis of a new antibiotic, platencin (Scheme 4). Traditional methods of high heat or acid catalysis can only overcome steric hindrance when a compatible reagent is used. The Danishefsky's diene is not one of those reagents.



Scheme 3 High-pressure-promoted selective Diels–Alder reactions of *cis*-1,2-dihydrocatechols with electron-deficient dienophiles.



Scheme 4 High-pressure-promoted selective Diels–Alder reaction for the synthesis of a key intermediate of platencin.

Nevertheless, the high-pressure protocol produced good isolated yield of 81%.[65] It is hypothesized, that pressure caused molecular re-alignments during compression, that overcame the steric hindrance represented by the cyclic dienophile.

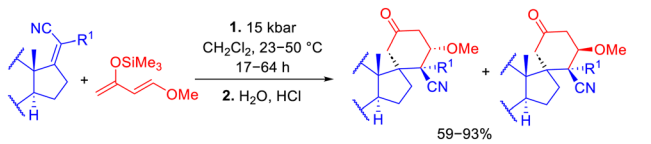
The same research group, Rutjes and co-workers, applied another Diels–Alder cycloaddition for the synthesis of an intermediate for the preparation of a privileged steroid scaffold (Scheme 5).[66]

In addition, hetero-Diels–Alder reactions were also investigated by Chmielewski and Jurczak under high pressure conditions. In a series of reactions to generate unsaturated δ-lactones, high pressure was required for the Diels–Alder cyclization between 1-methoxybuta-1,3-diene with aldehydes that do not normally perform well at ambient pressure. High pressure allowed a new series of δ-lactone rings to be produced under mild reaction conditions with yield of up to 80% with some aldehydes (Scheme 6).[67]

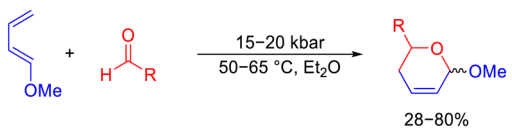
3.3.2.2. [2 + 2] Cycloadditions. [2 + 2] Cycloadditions provide excellent opportunities for the synthesis of strained products containing 4-membered rings, such as cyclobutanes. High pressure has been applied in derivatizing steroid structures to unlock new functionality. To obtain the end product, the carbonyl group at C-17 of dehydroepiandrosterone (DHEA) must undergo a Knoevenagel condensation, which product was subjected to a high pressure-initiated [2 + 2] cycloaddition (Scheme 7). DHEA had reduced reactivity to both reaction types due to steric hindrance. To overcome the obstacle, 15 kbar of pressure was applied to the reaction and quantitative yields were obtained by the Rutjes group.[66]

3.3.2.3. [3 + 2] Cycloadditions. Similarly to the above cyclizations [3 + 2] cycloadditions are another branch of concerted reactions. The [3 + 2]-cycloaddition of thiocarbonyl ylides with alkenes and alkynes is another application of high-pressure chemistry for the synthesis of complex molecules, such as tetracyclic meroterpenoids.[68] The reaction was described by Magauer's group[69] in a comprehensive study (Scheme 8). In the control experiments under thermal conditions the reaction yielded only minute amounts of the cycloadduct.[70] In contrast, high pressure appeared to be effective in initiating this pericyclic reaction, likely due to the negative activation and reaction volumes. The authors compared the reaction under thermal and high-pressure conditions. Thermal conditions resulted in up to 40% yield, while high pressure was much more effective giving up to 86% yield. When testing the effect of pressure, a significant improvement (16%–85%) in yield was observed with the increase in pressure (1 bar–5 kbar), while in higher pressure range (up to 14 kbar), only negligible increase in yield (1%) was found.

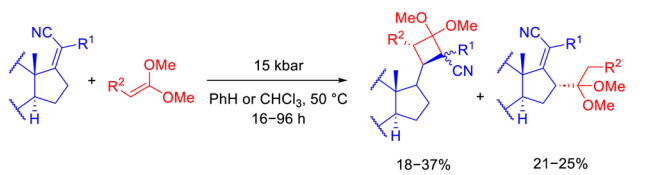
3.3.3. Nitro–aldol reaction. One of the major challenges in organic chemistry is modulating the stereochemical outcome of C–C bond forming reactions. The Henry reaction (a.k.a. nitro–aldol reaction) is one of the best performing methods from this point of view. An earlier report by Matsumoto, already pointed out that the Henry reaction generally responds well to high pressure showing significant rate enhancement.[71] Later, the Matsumoto group[72] developed a highly selective high pressure-initiated reaction system for the Henry reaction (Scheme 9). The reaction of *N*,*N*-dibenzyl α-amino aldehydes with 3-amino-2-hydroxy acids in acetonitrile at 8 kbar pressure provided the diastereoselective nitro–aldol products in a 12 h long reaction. The obtained yields were moderate to good (66–83%), however, the ee values were excellent (90–99% ee). The use of high pressure added a significant green advantage,



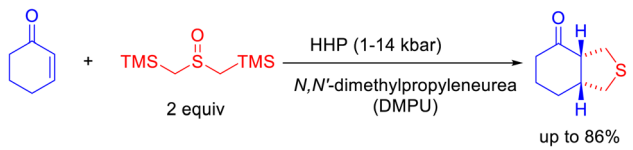
Scheme 5 High-pressure-promoted selective Diels–Alder reaction for the synthesis of a privileged steroid scaffold.



Scheme 6 High-pressure-promoted hetero-Diels–Alder reaction for the synthesis of δ-lactone rings.



Scheme 7 High-pressure-promoted [2 + 2] cycloaddition for the synthesis of a privileged steroid scaffold.



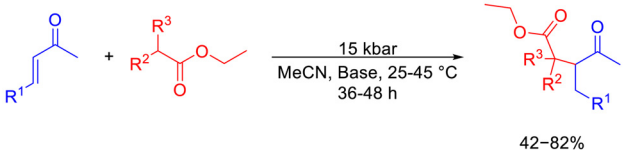
Scheme 8 Representative scheme of [3 + 2] cycloaddition of thiocarbonyl ylides under high-pressure conditions.

Scheme 9 Diastereoselective nitro–aldol reaction of α-amino aldehydes with nitroalkanes under high pressure.

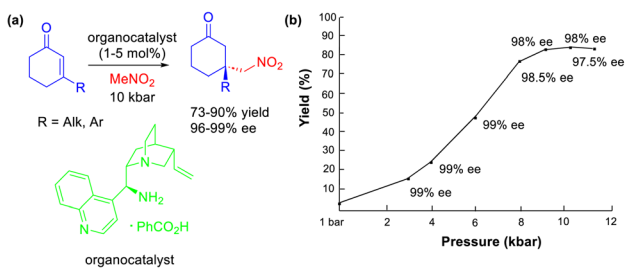
such as the elimination of the toxic and expensive catalysts from the reaction system.

3.3.4. Michael and Aza-Michael additions. In an effort to expand the list of reagents that can participate in Michael reactions, high pressure was used as a way of overcoming steric hindrance. Often a barrier to chemical reactions, steric hindrance prevents more substituted enone acceptors from participating in Michael reactions. Dauben and Gerdes reported that with high hydrostatic pressure of 15 kbar in acetonitrile, and using either triethylamine or 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) as a base catalyst, the reaction between β-ketoesters or 1,3-cyclic diones with enones have been observed with good yield (Scheme 10). When compared with control reactions, no yield or very small yield was observed. It was also noted that when under the mild conditions, no further cyclization or rearrangements occurred unlike in the alternate base catalyzed control reactions. High pressure here is also used as a way of controlling the products formed.[73]

In a similar organocatalytic addition of nitromethane to α,β-unsaturated substrates high hydrostatic pressure was used to improve the outcome of the reaction by Kwiatkowski *et al.* HHP appeared to add significant benefits to this otherwise difficult process that is mainly due to the sterically congested enones.[74] The high pressure protocol ensured the preparation of γ-nitroketones in good yields (73–90%), and excellent enantioselectivity (96–99% ee). The authors selected the addition of nitromethane to 3-methylcyclohexenone (Scheme 11(a)) as a test reaction to determine the pressure dependence of the reaction rate as well as the enantiomeric excess. Scheme 11(b) demonstrates that up to 8 kbar, increasing pressure significantly improved the yield of the product.



Scheme 10 Michael addition of activated acyclic donors with di-substituted enone acceptors under high pressure.



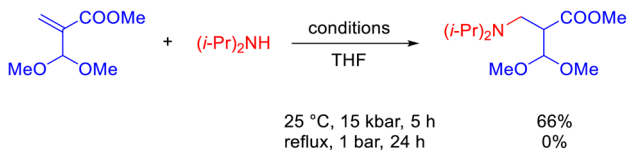
Scheme 11 Highly enantioselective synthesis of γ-nitroketones with quaternary stereogenic centers under high pressure (a), and the effect of pressure on yield and ee for the addition of nitromethane to 3-methylcyclohexenone as the model reaction (b).

Above 8 kbar, however, pressure increase only provided limited enhancement, the yield essentially plateauing at 9 kbar. Interestingly, the ee appeared to be the highest (99% ee) at lower pressures (3–6 kbar) and showed some decline, although minimal, at higher pressures (97.5–98% ee). A similar Michael addition of α-substituted cyclic ketones with acrylates was also carried out under high pressure by Kotsuki's group using a chiral 1-methylbenzyl amine organocatalysis providing good yields and enantioselection, although in quite long reaction times (48 h).[75]

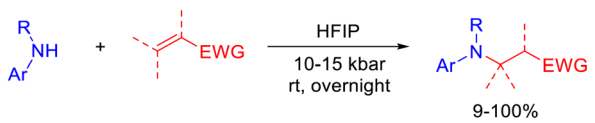
High pressure has been instrumental to improve aza-Michael additions. The addition of amines to α-dialkoxymethyl α,β-unsaturated ester was successfully carried out by Rulev, Kotsuki, and Maddaluno to produce the expected aza-Michael adducts. The reaction conditions were mild using 15 kbar pressure at ambient temperature, yielding 66% product.[76] While it is only a moderate yield, it must be noted, that the same reaction did not produce any product under atmospheric pressure despite the 24 h long reflux (Scheme 12). It appears that the high pressure activation is an effective method to carry out the conjugate addition of nitrogen nucleophiles to alkenes.

A similar, direct aza-Michael addition of anilines to activated alkenes was carried out by Fedotova *et al.* with the aid of hexafluoroisopropanol (HFIP),[77] which was applied as a catalyst and a solvent as well. The effects of HFIP and HHP were found to be synergistic in activating the Michael acceptor. This dual enhancement ensured the efficient 1,4-addition of anilines of poor nucleophilicity onto Michael acceptors for the first time. The protocol resulted in up to 100% yield for the corresponding products (Scheme 13).

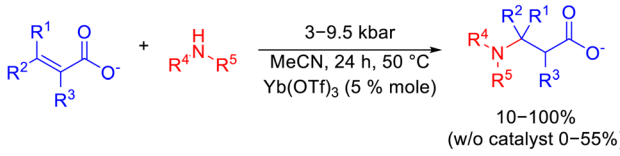
The synthesis of β-lactams often starts with a β-aminoester intermediate. β-Lactams are a common structure in antibiotics. Diversity of them and, therefore, their intermediates are important in creating new antibiotics. Previously, the creation of β-aminoesters was limited by steric hindrance; only the simplest un-substituted reagents were shown to react. Scheme 14 reports a high pressure application by Jenner that



Scheme 12 Comparison of the aza-Michael addition of amines onto α-dialkoxymethyl α,β-unsaturated ester under high pressure (15 kbar) and ambient pressure (1 bar).



Scheme 13 HFIP-promoted aza-Michael addition of anilines under high pressure.

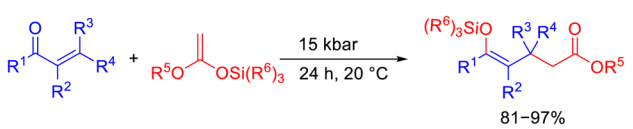


Scheme 14 $YB(OTf)_3$-catalyzed aza-Michael addition of amines to α,β-unsaturated acids under high pressure.

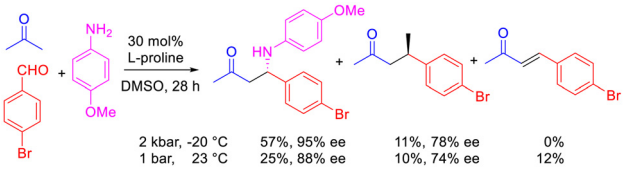
shows not only how a new lanthanide triflate catalyst can encourage the reaction, but also, when combined with high pressure, such reaction yields a whole new array of compounds at excellent yields using mild reaction conditions. While neither catalyst alone, nor pressure alone resulted in any extraordinary outcomes, when both were applied together, the yields were up to 100%, and created products that under other circumstances would not be attained through this scheme.[78]

3.3.5. Conjugate additions. Another example of high hydrostatic pressure effect on organic synthesis was demonstrated with addition of *O*-silylated ketene acetals to α,β-unsaturated carbonyl systems. The same reaction was carried out by Heathcock's group, either under high pressure in acetonitrile at room temperature *versus* high temperature with a Lewis acid catalyst at atmospheric pressure. The results were in favor of the high pressure as a better activator of the conjugate addition reaction. While several reactions produced the same yields, the more sterically hindered the enones became, the better the positive effect of high pressure could be observed. Not only was high pressure able to overcome the barrier of steric hindrance, but it also eliminated the need for high temperatures and catalysts (Scheme 15).[79]

3.3.6. Mannich reaction. The Mannich reaction is a three-component reaction that is highly useful in synthetic chemistry. To circumvent the need for special apparatus, Hayashi *et al.*[80] developed a novel method to generate high pressure which was induced by water freezing. Although the pressure is at the low end of the HHP range, the generated approximately, 2 kbar pressure is achieved by freezing water to −20 °C in a sealed vessel, its simplicity make it easy to use.[81] This method was used in the List–Barbas–Mannich reaction and significant improvements were observed under high pressure conditions. The test reaction using acetone, *p*-bromobenzaldehyde, and *p*-anisidine as starting materials was conducted under 2 kbar pressure induced by water-freezing. The authors reported that the Mannich product was obtained in 57% yield with 95% ee, while the aldol adducts formed in 11% yield with 78% ee (Scheme 16). The control reactions were significantly slower



Scheme 15 Conjugate addition of *O*-silylated ketene acetals to α,β-unsaturated carbonyl systems under high pressure.

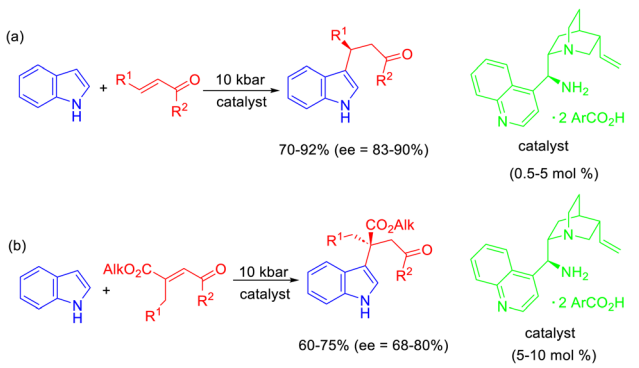


Scheme 16 The Mannich reaction of *p*-bromobenzaldehyde, *p*-anisidine, and acetone under ambient pressure and high pressure induced by water freezing.

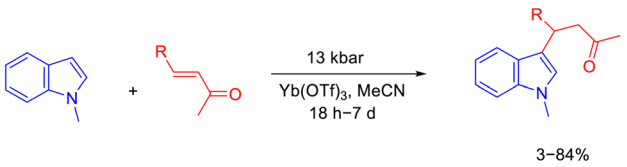
and less enantioselective under 1 bar pressure, providing the Mannich product in 25% yield and 88% ee, and the aldol products in 10% yield and 74% ee. 4-(*p*-Bromophenyl)-3-butene-2-one, the aldol condensation product, also formed in 12% yield. Based on these observations, HHP conditions clearly improved the yield, chemo- and enantioselectivity.

3.3.7. Friedel–Crafts reaction. The Friedel–Crafts reactions are one of the most useful C–C bond forming reactions at the laboratory scale as well as in the fine chemicals industry.[82] These reactions occur by the electrophilic aromatic substitution (S_EAr) mechanism, which is also applicable to several other reactions beyond alkylation and acylation, such as nitration, halogenation or sulfonation.[83] Lyzwa *et al.* reported that the application of HHP was found to be beneficial for several organocatalytic Friedel–Crafts alkylation of indoles. The catalysts were cinchona-alkaloid-based amines activating the processes *via* an iminium ion formation.[84] The pressure served as an efficient initiator for the alkylation reactions at 10 kbar pressure applying only 0.5–5 mol% of organocatalysts. The products were obtained in good yields (up to 92%) and enantiomeric excess (up to 90%) (Scheme 17(a)). Prochiral sterically hindered β,β-disubstituted enones could also be applied as substrates under HHP conditions, producing substituted indoles with carbon-only stereogenic centers with good yields (up to 75%) and enantiomeric excess (up to 80%) (Scheme 17(b)).

Harrington and Kerr found high pressure conditions to be effective at overcoming steric hindrance in additional similar applications as well. Scheme 18 is another example of coming



Scheme 17 High-pressure accelerated asymmetric organocatalytic Friedel–Crafts alkylation of indoles with enones (a) and enone-carboxylic acid esters (b).



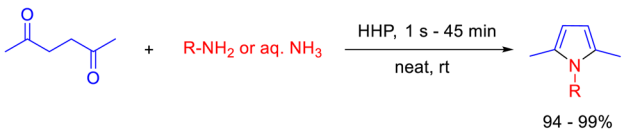
Scheme 18 High-pressure-initiated $Yb(OTf)_3$-catalyzed Friedel–Crafts alkylation of indoles with α,β-unsaturated ketones.

across the obstacle of steric hindrance despite having an effective catalyst in this conjugate addition of indole to olefins. As complexity of reagents rose, a decrease in yield was observed. 13 kbar of pressure was applied to increase yields to quantitative amounts that couldn't be observed at ambient pressures.[85]

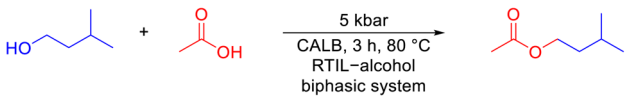
3.3.8. Paal–Knorr reaction. Another cyclization, the Paal–Knorr reaction was also found to significantly benefit from the application of high hydrostatic pressure. Traditionally this reaction entailed the use of an acid catalyst; however, it has been reported to occur under catalyst- and solvent-free conditions as well, although requiring long reactions (24 h or longer) to achieve good yields.[86] To address the rate issues, the Török group tested the reaction under high pressure conditions while maintaining the catalyst- and solvent-free environment. The reactions of ammonium hydroxide, and primary alkyl- and aryl amines with 2,5-hexanedione were evaluated (Scheme 19).[87] It was observed that the HHP reaction provided the appropriate products in nearly quantitative yields in very short (often 10 s) reactions. Since the reactions occurred without any additional reagent, solvent or catalyst, the catalyst separation, recycling or disposal were completely eliminated, and the quantitative yields ensured that products were isolated after a short air drying without any purification.

The calculation of the ΔV values by the Joback fragmentation method[88] for the reaction steps revealed reasonably negative values for the cyclization providing a theoretical explanation of the obtained results.

3.3.9. Esterification, transesterification. Although esterification is a common reaction catalyzed by acids, there is always a need for greener and more rapid alternatives. The reaction displayed in Scheme 20 is an enzyme-catalyzed process carried out in a biphasic system. Eisenmenger and Reyes-De-Corcuera synthesized isoamyl acetate by using isoamyl alcohol and acetic acid using *Candida antarctica* lipase B (CALB) as a catalyst. Testing the effect of high pressure on the system showed an increase of enzyme productivity up to 15-fold *versus*



Scheme 19 HHP-assisted catalyst- and solvent-free Paal–Knorr reactions for the green synthesis of pyrrole derivatives.

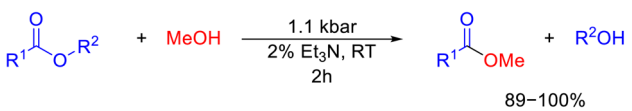


Scheme 20 HHP-assisted enzyme-catalyzed esterification of isoamyl alcohol.

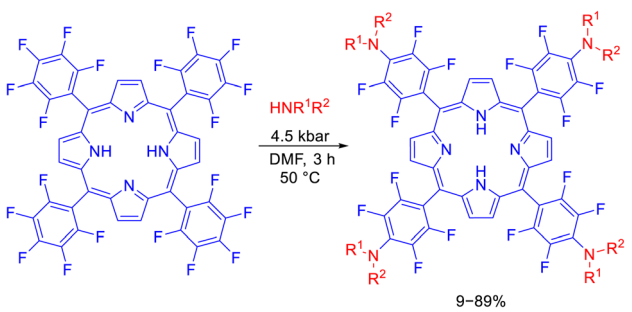
ambient pressure. Additional tests carried out in a monophasic system showed reduced activity as acetic acid is an inhibitor of CALB. A biphasic system was required for the maximum isoamyl acetate concentration, but high pressure was also a required component to ensure that the biphasic system worked properly by having a portion of the layers combine to react.[89]

High pressure was used in basic *trans*-esterification reactions by the Sałański group to show its efficacy in producing increasing yields of well-known reactions. Alkyl acetates and benzoates were reacted at 1.1 kbar for 2 h with methanol using triethyl amine catalysis to afford the *trans*-esterification products seen in Scheme 21 at high yields.[90]

3.3.10. Miscellaneous reactions. Porphyrins are commonly modified as they are valuable molecules in a multitude of areas. A common reaction is $H_2(TF_5PP)$ or $M(TF_5PP)$ with a variety of nucleophiles as the only product produced is a substitution at the *para* position. It is a different story when using amines as a nucleophile, however. They require high temperatures and result in a mixture of derivatives that require purification. Gomes *et al*. used high pressure to negate the need for higher temperatures and yield only a single product as well as obtain yield on derivatives not seen before because of their low reactivity. 4.5 kbar of pressure applied to the system allowed for amines to be added to $H_2(TF_5PP)$ or $M(TF_5PP)$ in low to good yields (Scheme 22).[91]



Scheme 21 HHP-assisted triethyl amine-catalyzed transesterification of alkyl acetates with methanol.

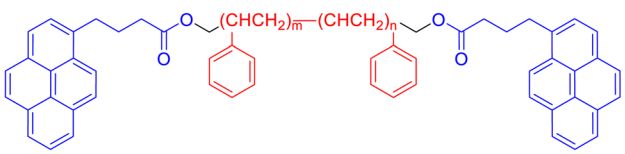


Scheme 22 HHP-assisted synthesis of 5,10,15,20-tetrakis[4-(substituted amino)-2,3,5,6-tetrafluorophenyl]porphyrins.

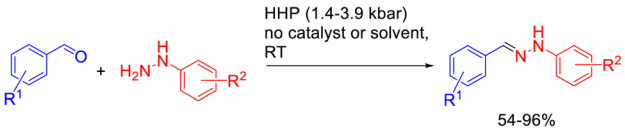
Three factors have been noted for their influence on conformational changes and dynamics of polymers: temperature, solvent, and high hydrostatic pressure. Martinho *et al.* reported the effect of high pressure on polystyrene chains with pyrene derivative end labels by following the rate of excimer formation (Scheme 23). In experiments employing several solvents and temperature levels to study pressure effects in a multitude of conditions, higher pressure was found to reduce the excimer formation. High pressure was found to increase solvent viscosity, leading to a decreased likelihood of cyclization.[92]

Hydrazones are valuable compounds in biomedical applications, for example, as multifunctional anti-Alzheimer disease agents,[93] or antioxidants applied in mitochondrial antioxidant therapy in preeclampsia.[94] Thus, their synthesis, and especially the green alternatives of synthetic protocols, attracted significant attention. A new, catalyst- and solvent-free synthesis was described by Costa *et al.* *via* the condensation of benzaldehydes and phenylhydrazones, which was initiated by HHP, providing moderate to excellent yields (Scheme 24).[95] The authors also carried out control experiments at ambient pressure, and it was found that the pressurized reactions usually provided 10–30% increase in product yields. During the syntheses the so-called pressure cycling was used, when compression–decompression cycles were applied in a predetermined sequence (Fig. 1b). Under the current conditions cycling improved the yields by about 20% compared to the static system.

3.3.11. Scaling up HHP reactions. Availability of large size high pressure reactors designed for large scale processing in the food industry is one of the factors that make scaling up synthetic reactions promising. In an effort to make this promise a reality, the Paal–Knorr reactions, that showed exceptional reaction rates and overall yields in the 1 mmol scale were scaled up to the several gram level in the same apparatus using 3.8 kbar pressure (Scheme 19)[87] by the Török group.



Scheme 23 HHP-assisted catalyst- and solvent-free synthesis of polystyrene–pyrene co-polymers.



Scheme 24 HHP-assisted catalyst- and solvent-free synthesis of diaryl hydrazones by the condensation of benzaldehydes and phenylhydrazines.

Later the same group further scaled up this HHP protocol to a preparative, approximately 300 g level using a high pressure instrument of appropriate size and design.[96] The HHP reactor was a 5 L volume pilot apparatus, equipped with a compressed air-driven intensifier with water as a pressure medium (Pressure BioSciences Inc.) (Fig. 11) that used the same pressure generating approach as the Barocycler 2320EXT described earlier. The only major difference was the considerably larger reaction chamber (5 L *vs.* 20 mL). While commercially available Telfon reaction vessels exist for the small chamber instrument; none is available for the 5 L size. The authors had adapted conventional low-density poly(ethylene) (LDPE) liquid storage bottles for this purpose. LDPE is an adequately flexible material that can accommodate the minor deformation necessary to account for the volume changes due to fluid compression, while maintaining the integrity of the vessel and the cap seal at high pressures. Safe and secure containment of the reactants is extremely important, especially at larger scales, to avoid the leakage of the reaction material into the high-pressure chamber. Thus, rigid plastics such as polypropylene, polystyrene, polycarbonate, or poly(methyl metacrylate, *etc.*) are not recommended for experiments involving high pressure. Another advantage of LDPE is that it is fairly resistant to chemicals *e.g.* acids/bases, or polar organic solvents such as alcohols, and reasonably resistant to many organic materials, *e.g.* ketones aldehydes, acids. Due to its interaction with hydrocarbons (solvents, mineral oil) only limited use is recommended. The use of LDPE vessels, however, is not recommended when halohydrocarbons (chloroform, dichloromethane, *etc.*) are considered, although the use of these solvents is unequivocally undesirable from the Green Chemistry point of view.

The scale-up reactions yielded excellent results, as shown in Scheme 25. Based on the data obtained in the pilot experiment, it appears that the reaction scale can be readily increased. The successful completion of reactions with up to 2100-fold increase in the mass of the starting materials demonstrated that the application of the reaction parameters from the mg scale reactions to the several hundred-gram level did not negatively affect the outcome of the reactions. Reaction

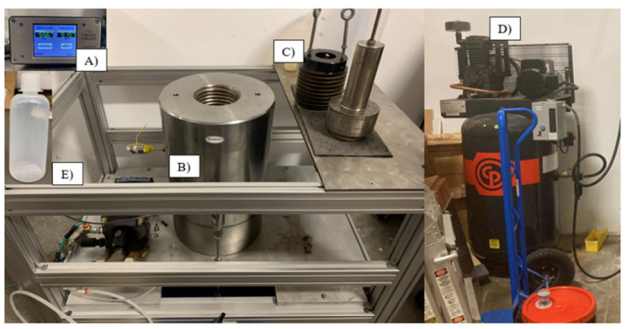
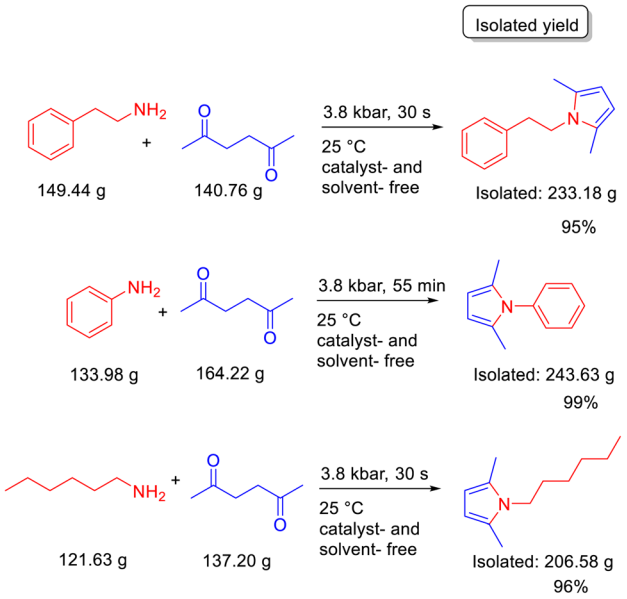


Fig. 11 Pressure BioSciences Inc. pilot scale high pressure reactor indicating (A) pressure indicator, (B) 5 L chamber, (C) screw cap, (D) air compressor, (E) 1000 mL LDPE reaction bottle.



Scheme 25 Examples of scaled up high pressure-initiated Paal–Knorr reactions. Yields (and amounts) shown are all isolated yields.

times and yields remained essentially the same providing quantitative yields without any by-product formation, thus purification was not necessary, further improving the green advantages of the methodology.

4. Potential disadvantages and limitations of barochemistry

Similarly to any methodology, barochemistry also has its disadvantages and limitations. These aspects originate from multiple issues such as the instruments and technical aspects, and the reactions themselves.

4.1. Instrument and other technical issues

(i) The first such issue is the generation of the pressure. Pneumatic intensifiers are less expensive; they require an air compressor or a gas tank as pressure input. However, they are difficult to scale up due to the limits of power that can be delivered by highly compressible gas, as well as due to the safety concerns arising from large compressible volume of gas being used.

(ii) The pressure vessels of the smaller instruments are commonly made from a single metal block. A disadvantage of the single block pressure vessels is an inability to predict when the material fatigue will cause a failure. Most of the stress occurs initially on the inner surface of the pressure vessel, initiating hairline cracks that will eventually propagate outward. Therefore a high quality surface finish on the inner surface is critical to eliminate any possible stress concentrators. Periodic inspection of the vessel ID surface by a dye penetrant technique[42] can reveal small hairline cracks that would eventually propagate to the outside of the vessel.

(iii) Although the scale up of barochemical syntheses at static pressure appears to be relatively straightforward,[96] it must be mentioned that scaling up is significantly more difficult when doing pressure cycles rather than static pressure. It is much easier to hold pressure at the large scale for a given time, rather than constantly pressurize and decompress with relatively short holding times.

(iv) The reaction vessel, that holds the reaction mixture and is immersed into the pressure vessel, could also represent a challenge. It must be chemically inert, and flexible. Although the compressibility of water, used as a pressure transmitting fluid, is low, no liquid is completely noncompressible. Thus, a rigid reaction vessel can easily break under high pressure condition, losing the reaction mixture and contaminating the pressure vessel. This limitation excludes all crystalline polymeric reaction vessels. In addition, some reaction vessels might not be compatible with the solvent use. Some solvents swell, and sometimes even dissolve certain polymers.

4.2. Potential issues derived from the reactions

(i) Since the beneficial effects of high pressure organic synthesis (different from the diamond-anvil-cells used in solid phase materials applications) are mainly derived from the low compressibility of liquids, the reaction mixture must be in the liquid state. That certainly results in some limitations. For example, if solvent-free reactions are attempted, at least one of the components must be liquid, and it should dissolve the other components. If all starting materials are solids, then either a solvent must be used, leading to another limitation, or one can shift to solid state synthesis using diamon anvil cells.

(ii) The solvent compatibility is important considering the flexible nature of the reaction vessels, that are made of one form of plastic. The solvent must not react with or swell the reaction vessel, otherwise leaks could occur compromising the outcome of the reaction. One must consult with the literature to make sure that an appropriate solvent is selected. Commonly, Teflon vessels are resistant to solvents, but other common materials such as polyethylene might present challenges when the solvent selection is in question.

(iii) As we pointed out above, the effect of pressure on a process is dependent upon the $\Delta V^{\ddagger}$ and ΔV values of the reaction. When both are negative, the reaction benefits from pressure, when both are positive, then pressure works against the reaction. Any other combination is an individual case. When the sum of the changes amount to zero, then the reaction will occur similarly to the non-pressurized reaction. In short, not all reactions improve under pressure, and one should calculate the potential volume changes to predict the direction of the pressure effect or consult the literature for similar examples.

5. Relevant green chemistry metrics[97]

(i) Mass-related descriptors are either dependent upon the reaction itself, or the conditions applied. The atom economy

(AE) as a theoretical descriptor is independent from the conditions and only related to the reaction itself. More practical mass-related metrics, such as the *E*-factor, environmental quotient (EQ), mass efficiency (ME), reaction mass efficiency (RME), and process mass intensity (PMI), however, are significantly dependent on the reaction conditions. These metrics are strongly dependent on practical factors such as chemical yield, selectivity (chemo-, regio, or stereo), since these descriptors determine the amount of waste, the use of solvent and auxiliary materials, the potentially required purification method and the likes. When a barochemical synthesis occurs with excellent yields and selectivity under potentially catalyst- and solvent-free conditions then the process will produce highly desirable mass-related metrics. However, every reaction is unique, and the benefits of high pressure must be evaluated on a case-by-case basis.

(ii) Solvents also play an important role in any process, especially in barochemistry, where the reaction mixture must be in the liquid phase. The compatibility of the solvent with the reaction vessel is an obvious issue, as was discussed above. Another parameter is the compressibility of the solvent. When it is high, the use of pressure is less than ideal due to large volume changes or higher adiabatic thermal effect. The third issue is the solvent intensity, *i.e.* how much solvent a process requires. Not considering purification (that is independent of the use of pressure during the reaction) the solvent intensity of the actual reaction will be dependent on the solubility of the reactants in each solvent. Once a process/reaction vessel is selected the applicable solvents must be evaluated based on these parameters, and their overall greenness.

(iii) Energy efficiency. The amount of energy used in a reaction is also crucial in determining the overall greenness of a process. Different forms of energy (convective heating *vs.* non-traditional activation methods) will result in different efficiency in each system. However, just like in the case of different other descriptors, there is no ultimate best. The polarity, viscosity, chemical nature, boiling point, compressibility *etc*. all contribute to the energy efficiency of a reaction. In addition, various reactions respond quite differently to the type of activation. In a recent study the effect of different activation methods was investigated on the catalyst- and solvent-free Paal–Knorr reaction.[98] It was observed, that the barochemical synthesis was the most energy efficient, due to the extremely short reaction times. Even conventional heating appeared to be more energy efficient than microwave irradiation. However, the opposite was observed, namely microwave activation was superior, when the reaction was catalyzed by a solid acid, K-10 montmorillonite.[99] However, in this case the solid acid acted as a strong microwave absorber providing internal heating for the reaction, while in the catalyst-free approach, the starting materials appeared to be poor microwave absorbers, *i.e.* most of the energy input was wasted. This example shows, how complex the appropriate selection of the activation method could be, to ensure the most energy efficient conditions.

6. Conclusions and outlook

In this tutorial review the fundamental characteristics of high hydrostatic pressure-induced organic synthesis have been described. After a brief introduction about history and theory, the application side has been highlighted, from equipment to applicable reactions. We believe that the broader applications of HHP or barochemistry would bring extensive benefits to the green synthesis of APIs, building blocks, and fine chemicals at the laboratory and likely at the industrial scale. Based on the major findings, the key benefits of barochemistry can be summarized in the following main points: (i) many reactions (cyclizations in particular) occur in a catalyst- and solvent-free environment, eliminating catalyst separation/recycling and reagent disposal steps; (ii) the reactions produce higher yields and often improved selectivities; in the ideal cases quantitative yields and exclusive selectivity were obtained, thus no product purification is required; (iii) the majority of reactions occur at room temperature or moderate temperatures, which is convenient, safe and energy efficient (iv) the commercially available HHP instruments allow safe protocols with tuneable characteristics, such as pressure, temperature, reaction time, or pressure cycles, if needed, (v) the instruments use water as a pressure transmitting fluid, that is non-flammable, non-toxic, inexpensive, widely available, and also has the lowest compressibility of most liquids, in short, ideal from both engineering and green chemistry point of views.

Despite the above summarized advantages, efforts were also made to address the drawbacks and limitations of barochemistry. There are still multiple gaps in our understanding of the effect of HHP on chemical reactions. Although the mechanistic understanding of pericyclic reactions appears more advanced than that of some other types, one must not forget, that those reaction proceed in one step. In contrast, many catalytic reactions, including multicomponent reactions proceed in many steps, thus the pressure effect should be investigated on each of those elementary steps to explain the final experimental outcome. However, as more advances are made in high pressure synthesis, more data will be available to corroborate experimental findings with the theoretical fundamentals. This progress will help overcome the existing gaps and will undoubtedly help apply HHP to a wide range of reactions.

The high-pressure methodology is a promising activation strategy that is applicable to many reaction types. Based on the examples listed in this work, it might enable other reactions as well, such as multicomponent cyclizations that produce important heterocycles, Pd-catalyzed cross-coupling reactions, or alkene metathesis among other possibilities.

Data availability

The data supporting this article have been included in the References.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Research reported in this publication was supported by the National Institute of General Medical Sciences of the National Institutes of Health under award number R15GM157702 (BT). Support of our work by the University of Massachusetts Boston is also gratefully acknowledged.

References

1 *Green Chemistry: An Inclusive Approach*, ed. B. Török and T. Dransfield, Elsevier, Oxford-Cambridge, MA, 2018.
2 P. Anastas and J. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, Oxford, UK, 1998.
3 *Contemporary Chemical Approaches for Green and Sustainable Drugs*, ed. M. Török, Elsevier, Amsterdam, Oxford, Cambridge, MA, 2022.
4 (*a*) S. Datta, A. Sood and M. Török, *Curr. Org. Synth.*, 2011, **8**, 262–280; (*b*) M. Mishra and B. Török, Sustainable large-scale synthesis of fine chemicals, active pharmaceutical ingredients and biologically active compounds by non-traditional activation methods and biocatalysis, in *Mechanochemistry and Emerging Technologies for Sustainable Chemical Manufacturing*, ed. E. Colacino, D. Crawford and F. Garcia, CRC Press/Taylor & Frances, Boca Raton, FL, 2023.
5 *Handbook of Green Chemistry – Green Solvents*, ed. W. Leitner, P. G. Jessop, C. J. Li, P. Wasserscheid and A. Stark, Wiley-VCH, Weinhheim, 2010.
6 *Encyclopedia of Sustainable Science and Technology*, ed. R. A. Meyers, Springer-Nature, 2018. DOI: **10.1007/978-1-4939-2493-6_1008-1**.
7 B. Török, C. Schäfer and A. Kokel, *Heterogeneous Catalysis in Sustainable Synthesis*, Elsevier, Cambridge, Oxford, 2021.
8 *Non-traditional Activation Methods in Green and Sustainable Applications: Microwaves, Ultrasounds, Photo, Electro and Mechanochemistry and High Hydrostatic Pressure*, ed. B. Török and C. Schäfer, Elsevier, Cambridge, Oxford, 2021.
9 R. B. Vlocskó, G. Xie and B. Török, *Molecules*, 2023, **28**, 4153.
10 W. C. Röntgen, *Annu. Rev. Phys. Chem.*, 1892, **281**, 98–107.
11 B. H. Hite, *Bull. - W. Va. Univ., Agric. Exp. Stn.*, 1899, **58**, 15–35.
12 P. W. Bridgman, *J. Biol. Chem.*, 1914, **19**, 511–512.
13 R. J. Hemley, *High Pressure Res.*, 2010, **30**, 581–619.
14 T. Grauwet, I. Van der Plancken, L. Vervoort, M. Hendrickx and A. Van Loey, High-pressure processing uniformity, in *High Pressure Processing of Foods*, ed. V. M. Balasubramaniam, G. V. Barbosa-Cánovas and H. L. M. Lelieved, Springer, New York, 2016, pp. 253–268.
15 K. Yamamoto, High hydrostatic pressure in food industry applications, in *Non-traditional Activation Methods in Green and Sustainable Applications: Microwaves, Ultrasounds, Photo, Electro and Mechanochemistry and High Hydrostatic Pressure*, ed. B. Török and C. Schäfer, Elsevier, Cambridge, Oxford, 2021, pp. 559–574.
16 W. G. Dauben and H. O. Krabbenhoft, *J. Am. Chem. Soc.*, 1976, **98**, 1992–1993.
17 A. Y. Rulev and F. I. Zubkov, *Org. Biomol. Chem.*, 2022, **20**, 2320–2355.
18 D. Margetic, *High Pressure Organic Synthesis*, De Gruyter, Berlin, Boston, 2019. DOI: **10.1515/9783110556841**.
19 C. L. Hugelshofer and T. Magauer, *Synthesis*, 2014, 1279–1296.
20 W. Holzapfel and N. Isaacs, *High Pressure Techniques in Chemistry and Physics. A Practical Approach*, Oxford University Press, 1997, p. 400.
21 (*a*) T. Asano and W. J. Le Noble, *Chem. Rev.*, 1978, **78**, 407–489; (*b*) R. Van Eldik, T. Asano and W. J. Le Noble, *Chem. Rev.*, 1989, **89**, 549–688; (*c*) A. Drljaca, C. D. Hubbard, R. Van Eldik, T. Asano, M. V. Basilevsky and W. J. Le Noble, *Chem. Rev.*, 1998, **98**, 2167–2290.
22 M. Miao, Y. Sun, E. Zurek and H. Lin, *Nat. Rev. Chem.*, 2020, **4**, 508–527.
23 V. Schettino and R. Bini, *Chem. Soc. Rev.*, 2007, **36**, 869–880.
24 P. F. McMillan, *Chem. Soc. Rev.*, 2006, **35**, 855.
25 G. Xie, A. Lazarev and B. Török, Organic Synthesis With High Hydrostatic Pressure, in *Encyclopedia of Green Chemistry*, Elsevier, 2024. DOI: **10.1016/B978-0-443-15742-4.00113-7**.
26 I. Chataigner and J. Maddaluno, High-Pressure Synthesis: An Eco-friendly Chemistry, in *Activation Methods: Sonochemistry and High Pressure*, ed. J.-P. Goddard, M. Malacria and C. Ollivier, ISTE Ltd and John Wiley & Sons, Inc., 1st edn, 2019, pp. 95–149.
27 B. Chen, R. Hoffmann and R. Cammi, *Angew. Chem., Int. Ed.*, 2017, **56**, 11126–11142.
28 The Engineering ToolBox **https://www.engineeringtoolbox.com/water-thermal-properties-d_162.html** (accessed: 02/25/2025).
29 K. Knoerzer, R. Buckow and C. Versteeg, *J. Food Eng.*, 2010, **98**, 110–119 and the references cited therein.
30 T. Grauwet, C. Rauh, I. Van der Plancken, L. Vervoort, M. Hendrickx, A. Delgado and A. Van Loey, *Trends Food Sci. Technol.*, 2012, **23**, 97–110.
31 Objectives_template. **https://archive.nptel.ac.in/content/storage2/courses/112104118/lecture-2/2-4-compressibility.htm** (accessed 02/25/2025).
32 D. F. Farkas, A Short History and Development Efforts leading to eth Commercialization of High-Pressure Processing of Food, in *High Pressure Processing of Food, Technology and Applications*, ed. V. M. Balasubramaniam, G. V. Barbosa-Canovas and H. L. M. Lelleveld, Springer, 2016, pp. 19–36.
33 **https://www.hiperbaric.com/en/** (accessed 02/25/2025).

34 https://www.jbtc.com/foodtech/products-and-solutions/brands/avure-technologies/ (accessed 02/25/2025).
35 https://www.thyssenkrupp-uhde.com/ (accessed: 02/25/2025).
36 https://www.kobelco.co.jp/english/ (accessed: 02/25/2025).
37 https://btkf-hpp.com/ (accessed: 02/25/2025).
38 https://www.pressurebiosciences.com/ (accessed: 02/25/2025).
39 https://www.highpressure.com/ (accessed: 02/25/2025).
40 https://www.parker.com/us/en/home.html (accessed: 02/25/2025).
41 https://highpressuretech.com/ (accessed: 02/25/2025).
42 ASME Boiler and Pressure Vessel Code, Section V, Art. 24 Standard Test Method for Liquid Penetrant Examination SE-165.
43 T. Johannisson and K. Zander, Wire Wound High Pressure Vessels for Industrial Applications, in *High-Pressure Science and Technology*, ed. K. D. and Timmerhaus, M. S. Barber, Springer, Boston, MA, 1979.
44 H. Herberhold, S. Marchal, R. Lange, C. H. Scheyhing, R. F. Vogel and R. Winter, *J. Mol. Biol.*, 2003, **330**, 1153–1164.
45 A. C. Bourges, A. Lazarev, N. Declerck, K. L. Rogers and C. A. Royer, *Biophys. J.*, 2020, **118**, 2670–2679.
46 J. Koehler, M. B. Erlach, E. Crusca Jr., W. Kremer, C. E. Munte and H. R. Kalbitzer, *Materials*, 2012, **5**, 1774–1786.
47 M. T. Lerch, Z. Yang, C. Altenbach and W. L. Hubbell, *Methods Enzymol.*, 2015, **564**, 29–57.
48 D. R. Davydov, Z. Yang, N. Davydova, J. R. Halpert and W. L. Hubbell, *Biophys. J.*, 2016, **110**, 1485–1498.
49 Y. O. Kamatari, R. Kitahara, H. Yamada, S. Yokoyama and K. Akasaka, *Methods*, 2004, **34**, 133–143.
50 D. K. Rai, R. E. Gillilan, Q. Huang, R. Miller, E. Ting, A. Lazarev, M. W. Tate and S. M. Gruner, *J. Appl. Crystallogr.*, 2021, **54**, 111–122.
51 E. Y. Ting, A. Lazarev, J. Ma, *US Pat.*, 11156295B2, 2021.
52 B. J. Deschner, D. E. Doronkin, T. L. Sheppard, G. Rabsch, J. D. Grunwaldt and R. Dittmeyer, *Rev. Sci. Instrum.*, 2021, **92**, 124101.
53 https://www.hiperbaric.com/en/hpp-technology/equipment/hpp-in-bulk/ (accessed 02/22/2025).
54 G. Smejkal, E. Ting, V. Gross, N. Cutri and A. Lazarev, *High, Pressure Optical Spectroscopy (HiPOS) and Real-Time Analysis of Enzyme Kinetics at Elevated Hydrostatic Pressure*, South Easton, 2021.
55 H. Vass, S. L. Black, E. M. Herzig, F. B. Ward, P. S. Clegg and R. J. Allen, *A Multipurpose Modular System for High-Resolution Microscopy at High Hydrostatic Pressure*, American Institute of Pysics, 2010, p. 81.
56 HUB High Pressure Generators and Accessories – Pressure BioSciences, Inc. https://products.pressurebiosciences.com/collections/hub-high-pressure-generators-and-accessories (accessed 02/25/2025).
57 B. Török, C. Schäfer and A. Kokel, Hydrogenation, in *Heterogeneous Catalysis in Sustainable Synthesis*, Elsevier, Cambridge, Oxford, 2021, ch. 3.1.
58 A. Kulkarni and B. Török, Heterogeneous Catalytic Hydrogenation as an Environmentally Benign Tool for Organic Synthesis, *Curr. Org. Synth.*, 2011, **8**, 187–207.
59 A. Tomin, A. Lazarev, M. P. Bere, H. Redjeb and B. Török, Selective Reduction of Ketones Using Water as a Hydrogen Source under High Hydrostatic Pressure, *Org. Biomol. Chem.*, 2012, **10**, 7321–7326.
60 H. Cho, C. Schäfer and B. Török, Hydrogenations and Deuterium Labeling with Aluminum-based Metal Alloys under Aqueous Conditions, *Curr. Org. Synth.*, 2016, **13**, 255–277.
61 O. Diels, *Ber. Dtsch. Chem. Ges. A, B*, 1936, **69**, 11.
62 (*a*) K. Kumamoto, I. Fukada and H. Kotsuki, *Angew. Chem., Int. Ed.*, 2004, **43**, 2015–2017; (*b*) D. Loco, R. Spezia, F. Cartier, I. Chataigner and J.-P. Piquemal, *Chem. Commun.*, 2020, **56**, 6632–6635.
63 *Thiophene and Its Derivatives, Part 1*, ed. S. Gronowitz, Wiley, New York, 1985, pp. 697–705.
64 S. G. Stewart, J. H. Gwion, K. J. McRae, Y. Teng, L.-J. Yu, B. Chen, R. Cammi, M. L. Coote, M. G. Banwell and A. C. Willis, *J. Org. Chem.*, 2020, **85**, 13080–13095.
65 D. C. J. Waalboer, M. C. Schaapman, F. L. Van Delft and F. P. J. T. Rutjes, *Angew. Chem., Int. Ed.*, 2008, **47**(35), 6576–6578.
66 D. Blanco-Ania, R. W. M. Aben, L. W. A. Van Berkom, H. W. Scheeren and F. P. J. T. Rutjes, *Eur. J. Org. Chem.*, 2014, 1438–1444.
67 M. Chmielewski and J. Jurczak, *J. Org. Chem.*, 1981, **46**, 2230–2233.
68 R. Wildermuth, K. Speck, F.-L. Haut, P. Mayer, B. Karge, M. Brönstrup and T. Magauer, *Nat. Commun.*, 2017, **8**, 2083.
69 F.-L. Haut, C. Habiger, K. Speck, K. Wurst, P. Mayer, J. N. Korber, T. Müller and T. Magauer, *J. Am. Chem. Soc.*, 2019, **141**, 13352–13357.
70 K. Speck and T. Magauer, *Chem. – Eur. J.*, 2017, **23**, 1157–1165.
71 K. Matsumoto, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 617–618.
72 Y. Misumi and K. Matsumoto, *Angew. Chem., Int. Ed.*, 2002, **41**, 1031–1033.
73 W. G. Dauben and J. M. Gerdes, *Tetrahedron Lett.*, 1983, **24**, 3841–3844.
74 P. Kwiatkowski, K. Dudzinski and D. Lyzwa, *Org. Lett.*, 2011, **13**, 3624–3627.
75 R. Horinouchi, K. Kamei, R. Watanabe, N. Hieda, N. Tatsumi, K. Nakano, Y. Ichikawa and H. Kotsuki, *Eur. J. Org. Chem.*, 2015, 4457–4463.
76 A. Y. Rulev, H. Kotsuki and J. Maddaluno, *Green Chem.*, 2012, **14**, 503–508.
77 A. Fedotova, B. Crousse, I. Chataigner, J. Maddaluno, A. Y. Rulev and J. Legros, *J. Org. Chem.*, 2015, **80**, 10375–10379.
78 G. Jenner, *Tetrahedron Lett.*, 1995, **36**, 233–236.
79 R. A. Bunce, M. F. Schlecht, W. G. Dauben and C. H. Heathcock, *Tetrahedron Lett.*, 1983, **24**, 4943–4946.

80 (*a*) Y. Hayashi, W. Tsuboi, M. Shoji and N. Suzuki, *J. Am. Chem. Soc.*, 2003, **125**, 11208–11209; (*b*) Y. Hayashi, *J. Synth. Org. Chem.*, 2014, **72**, 1228–1238.
81 (*a*) Y. Hayashi and K. Nishimura, *Chem. Lett.*, 2002, 296–297; (*b*) Y. Hayashi, K. Okado, I. Ashimine and M. Shoji, *Tetrahedron Lett.*, 2002, **43**, 8683–8686.
82 D. Lewis, *Synform*, 2018, **4**, A49–A52.
83 B. Török, C. Schäfer and A. Kokel, Friedel-Crafts and related reactions catalyzed by solid acids, in *Heterogeneous Catalysis in Sustainable Synthesis*, Elsevier, Cambridge, Oxford, 2021, ch. 3.5.
84 D. Łyżwa, K. Dudzinski and P. Kwiatkowski, *Org. Lett.*, 2012, **14**, 1540–1543.
85 P. Harrington and M. A. Kerr, *Can. J. Chem.*, 1998, **76**, 1256–1265.
86 H. Cho, R. Madden, B. Nisanci and B. Török, *Green Chem.*, 2015, **17**, 1088–1099.
87 G. Xie, A. Lazarev and B. Török, *Green Chem.*, 2023, **25**, 1582–1587.
88 K. G. Joback and R. C. Reid, *Chem. Eng. Commun.*, 1987, **57**, 233–243.
89 M. J. Eisenmenger and J. I. Reyes-De-Corcuera, *J. Mol. Catal. B: Enzym.*, 2010, **67**, 36–40.
90 J. Jurczak, D. T. Gryko, P. Lipkowski and P. Salanski, *Rev. High Pressure Sci. Technol.*, 1998, **7**, 1236–1240.
91 A. T. P. C. Gomes, P. C. Freire, C. R. M. Domingos, M. G. P. M. S. Neves, J. A. S. Cavaleiro, F. A. Almeida Paz, J. A. Saraiva and A. C. Tomé, *J. Porphyrins Phthalocyanines*, 2016, **20**, 1377–1389.
92 J. M. G. Martinho, E. M. S. Castanheira, A. T. Reis e Sousa, S. Saghbini, J. C. André and M. A. Winnik, *Macromolecules*, 1995, **28**, 1167–1171.
93 B. Török, A. Sood, S. Bag, R. Tulsan, S. Ghosh, D. Borkin, A. R. Kennedy, M. Melanson, R. Madden, W. Zhou, H. LeVine III and M. Török, *Biochemistry*, 2013, **52**, 1137–1148.
94 M. Mastyugin, R. B. Vlocskó, Z. K. Zsengellér, B. Török and M. Török, *J. Med. Chem.*, 2025, DOI: **10.1021/acs.jmedchem.5c00010**.
95 M. Costa, F. Adhamidhi, M. Mastyugin, A. R. Fusco, A. Lazarev, Z. K. Zsengeller, M. Török and B. Török, *Molecules*, 2024, **29**, 5287.
96 V. Wright, G. Xie, M. Costa, A. Lazarev and B. Török, High Hydrostatic Pressure-assisted reactions at a large scale: Scale-up of HHP-initiated solvent-free and catalyst-free Paal-Knorr reactions from milligram to kilogram scale. *ACS Spring 2024 National Meeting - Many Flavors of Chemistry, Division of Organic Chemistry, New Orleans, LA, March 17–21, 2024*, Paper ID: 3981077.
97 D. Daggett, Y. Shi and B. Török, Characterizing the Environmentally Benign Nature of Chemical Processes: Green Chemistry Metrics, in *Contemporary Chemical Approaches for Green and Sustainable Drugs*, ed. M. Török, Elsevier, Amsterdam, Oxford, Cambridge, MA, 2022.
98 M. Costa, S. Baoengan, A. Lazarev, B. Török and M. Török, Energy Efficiency of Paal-Knorr Reactions using Traditional and Non-traditional Activation Methods: Ultrasonication, Microwave-Assisted Heating, and High Hydrostatic Pressure, *ACS Spring 2025 National Meeting, Division of Organic Chemistry, San Diego, CA, March 22–27, 2025,* Paper ID: 4192162.
99 H. Cho, F. Török and B. Török, *Green Chem.*, 2014, **16**, 3623–3634.