3.2 TOOLS OF GREEN CHEMISTRY

Alternative Synthesis

The difficult task for chemists and others is to create new products, processes and services that achieve the societal, cheap and environmental boons that are now required in organic synthesis. This requires a new approach which sets out to minimize the materials and energy requirement of chemical processes and products, minimize or eliminate the dispersion of hazardous chemicals in the environment, to make as large as possible the use of renewable resources and extend the durability and recyclability of products. Challenges of organic chemists include the discovery and development of new synthetic pathways using green chemistry tools such as, green solvents, green catalysis in organic synthesis, dry media synthesis, and catalyst free reactions in organic synthesis, energy efficient synthesis.

Green solvents have been distinguished for their low toxicity, low miscibility in water, easily biodegradability under environmental conditions, large boiling point, not easily evaporating, low offensive smell, health problems to workers and easy to recycle after use. Some of the green solvents used by the chemist are water, ionic liquids, supercritical fluids and polyethylene glycols. By using these green solvents, outstanding progresses towards the development of green reaction have been achieved.

Green catalysis in organic synthesis is one of the key parts of green chemistry, the design and use of new catalysts and catalytic systems are simultaneously meets the dual objectives of environmental protection and economic benefit. Catalysis offers numerous green chemistry advantages including lower energy necessities, catalytic against stoichiometric quantity of materials, enhanced selectivity, and decreased use of processing and separation agents, and permit for the use of less hazardous materials. Catalysis is principally divided in two branches: homogenous catalysis, when the catalyst is in the same phase as the reaction mixture (typically in liquid phase), and heterogeneous catalysis, when the catalyst is in a different phase (typically solid/liquid, solid /gas/liquid/gas). One of the main advantages of homogenous molecular catalysts, when they work under ideal conditions, is that their active sites are spatially well separated from one another, just like as they are in enzymes catalysis. Heterogeneous catalysis, in particular, addresses the goals of Green Chemistry is to provide the ease of phase separation of product and catalyst, bi-functional phenomena involving reactant activation over between support and active phases, thereby eliminating the need for separation through distillation or extraction. Environmentally useful catalysts such as clays and zeolites, may replace more hazardous catalysts currently in use.

A dry media reaction or solid-state reaction or solvent less reaction is a chemical reaction system in the absence of a solvent. A solvent-free or solid state reaction could be carried out using either the reactants alone or incorporating them in clays, zeolites, silica, alumina or other catalytic substances. Thermal process or irradiation with UV, microwave or ultrasound (sonochemical method) can be used to bring about the reaction. Solvent-free reactions obviously reduce pollution and economic due to simplification of experimental procedure, work up skill and saving in time. These would be especially significant in industrial production. Often, the products of solid state reactions turn out to be different from those incurred in solution phase reactions. This is due to specific spatial orientation or packing of the reacting molecules in the crystalline phase. This is true not only of the crystals of single compounds, but also of co-crystallized solids of two or even more reactant molecules. Avoiding the use of catalyst and dangerous solvents in organic reactions is a highly challenging task. Catalyst free synthesis of various organic compounds is a best greener alternative for chemist.

In addition to the thermal process, irradiation with UV, microwave (refer unit II) or ultrasound (sonochemical method) are considered as green and alternative technique in organic synthesis. Microwave mediated organic synthesis is described in unit II. A brief account on sonochemical approach is given below.

Sonochemistry as a Green and Alternative Technique in Organic Synthesis

Sonochemistry is considered as a useful methodology to carryout organic reactions without solvents. High yields, low energy requirements, low waste, no use of solvents are some of the fundamental advantages of these sonochemical techniques. The use of ultrasound in chemical reactions in solution provides specific activation based on a physical phenomenon: acoustic cavitation (Figure 1). Cavitation is a process in which mechanical activation destroys the attractive forces of molecules in the liquid phase. Applying ultrasound, compression of the liquid is followed by rarefaction (expansion), in which a sudden pressure drop forms small, oscillating bubbles of gaseous substances. These bubbles expand with each cycle of the applied ultrasonic energy until they reach an unstable size; they can then collide and/or violently collapse.

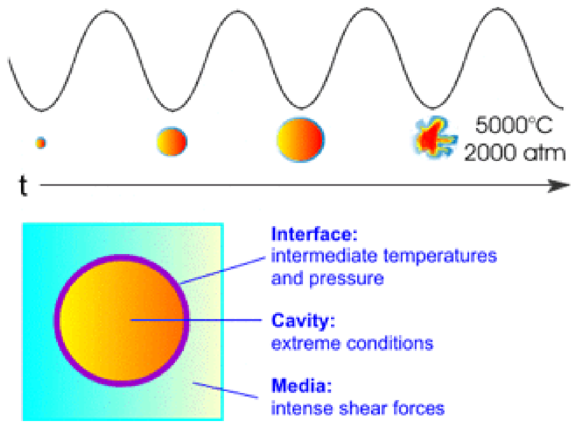


Figure 1 Formation of cavitation in a sonochemical reaction

For example, sonolysis of $Fe(CO)_5$ in decane under argon produces amorphous iron upon decarbonylation instead of crystalline iron, which shows that both very high temperatures and also rapid cooling rates (~ 10^6 K s^{-1}) are involved, the more volatile pentane yields $Fe_3(CO)_{12}$, indicating a somewhat slower collapse. It has been estimated and calculated that the pressure within a bubble in water can rise to more than one thousand atmospheres, and the temperature can reach several thousand degrees during a collapse, as heat conduction cannot keep up with the resulting adiabatic heating. As these bubbles are small and rapidly collapse, they can be seen as microreactors that offer the opportunity of speeding up certain reactions and also allow mechanistically novel reactions to take place in an absolutely safe manner.

Many reactions can be conducted even in a simple ultrasonic cleaning bath, although the amount of energy that reaches the reaction is only between 1 and 5 W cm^{-2}, and temperature control is normally poor. Large-scale reactions can be better conducted using immersible ultrasonic probes that circumvent the transfer of the energy through water and the reaction vessel. The applied energies in this case can be several hundred times higher. Laboratory equipment uses frequencies between 20 kHz and 40 kHz, but cavitation can be generated well above these frequencies and recent research uses a much broader range.

Ultrasound in synthetic organic chemistry

There are two types of effects mediated by ultrasound: chemical and physical. When the quantity of bubbles is low - using standard laboratory equipment it is mainly physical rate acceleration that plays a role (Figure 2). For example, a specific effect is the asymmetric collapse near a solid surface, which forms microjets. This effect is the reason why ultrasound is very effective in cleaning, and is also responsible for rate acceleration in multiphasic reactions, since surface cleaning and erosion lead to improved mass transport.

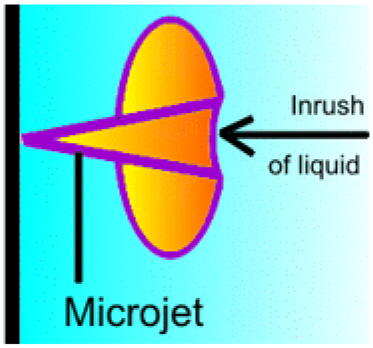
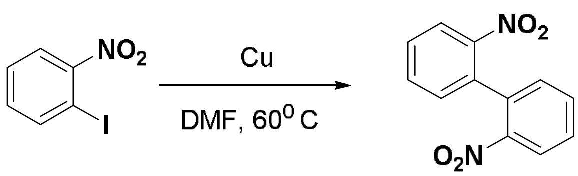


Figure 2 Asymmetric collapse of a sonowave near a solid surface.

For example, when ultrasound is applied to an Ullmann reaction of 1-iodo-2-nitrobenzene that normally requires a 10-fold excess of copper and 48 h of reaction time, this can be reduced to a 4-fold excess of copper and a reaction time of 10 h (Scheme 1).

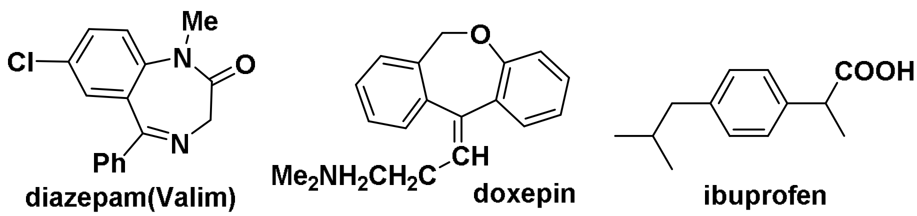


Scheme 1 Ullmann reaction of 1-iodo-2-nitrobenzene

The particle size of the copper shrinks from 87 to 25 μm, but the increase in the surface area cannot fully explain the increase in reactivity. It was suggested that sonication also assists in the breakdown of intermediates and desorption of the products from the surface.

A Photochemical Alternative to Friedel-craft Reaction

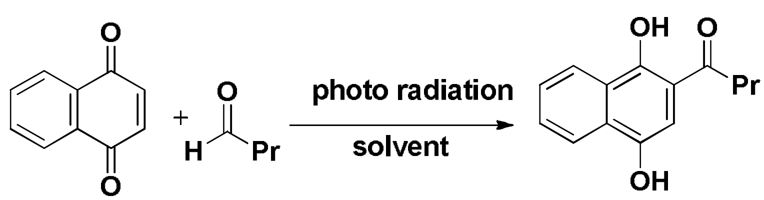
The Friedel–Crafts (FC) reactions are a set of reactions developed by Charles Friedel and James Crafts in 1877 to attach substituents to an aromatic ring. Electrophilic aromatic alkylation and acylation could be carried out via Friedel–Crafts reactions. Shown below are three pharmaceutically-important drugs, each currently produced annually in ton quantities through Friedel-Crafts reaction.



The FC reaction, a widely used reaction in both industrial and academic laboratories, produces several by-products which must be handled as pollutants. It involves corrosive and air sensitive acid chlorides, Lewis acids such as $AlCl_3$, stannic chloride or titanium tetrachloride and solvents such as nitrobenzene, carbon disulfide, carbon tetrachloride or methylene chloride. Methods for minimization of amount of Lewis acid needed for the FC reaction has been reported. However, it requires elevated temperatures. FC reactions conducted with acidic resins have also been reported. This research appears promising but is in the early stages. Obviously, an attractive alternative to the traditional FC reaction would have an impact on pollution prevention.

From the point of view of pollution prevention, there are a number of reasons why alternatives must be considered. Electricity or light are some of the alternative form of energy/reagent which could be used in FC reactions. Visible light is already a reagent of choice which finds wide application in organic photochemistry and also available abundantly.

An extremely useful photochemical alternative was firstly reported by Heinrich Klinger in 1891. The photoproducts, acylated quinones and their derivatives are important natural compounds (*e.g.* alkanninor shikonin), and serve as useful key intermediates in the synthesis of pharmaceuticals (*e.g.* Nanoamycin A or Frenolicin B).



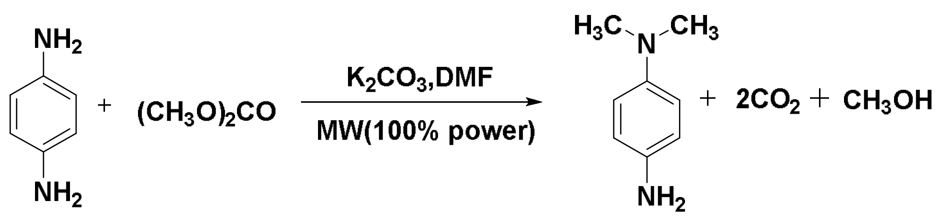
Scheme 2 Acylation of 1,4-napthoquinone to form acylated hydroquinone

The photoreaction of 1,4-naphthoquinone with butyraldehyde was chosen as a model system using an artificial light source. Prolonged photolysis for 5 days in benzene and on a multi-gram scale, the corresponding acylated hydroquinone (Scheme 2) was produced in good yield of 78%. Thus alternate method developed for the FC acylation reaction especially using photochemical condition was found to be highly advantageous.

Dimethyl Carbonate as a Methylating Agent

Dimethyl carbonate (DMC) is an organic compound with the formula $OC(OCH_3)_2$. It is a colourless, flammable liquid. It is classified as a carbonate ester. This compound has found use as a methylating agent and more recently as a solvent that is exempt from the restrictions placed on most volatile organic compounds (VOCs) in the US. DMC is a nontoxic, environmentally safe reagent that can be used as a "green substitute" for toxic reagent used in conventional methylation reaction.

A new method for N-methylation of aromatic diamines using environmentally safe and less toxic methylation reagent dimethyl carbonate (DMC) has been developed (Scheme 3). The effect of various functional groups on the aromatic ring has been investigated. This method provides the desired product in high yields with high purity under microwave irradiation.



Scheme 3 N-Methylation of *p*-phenylenediamineusing DMC

Synthesis of N-dimethyl aniline from aniline using DMC as a green reagent and onium salt has been demonstrated. The application of microwave irradiation (MWI) has been under taken as it is an established methodology for eco-friendly procedure, takes short reaction time as compared to conventional heating, ease of work-up after reaction and the reduction in usual thermal degradation and better selectivity.

Green oxidants

Oxidation reactions are one of the most useful industrial processes and, at the same time, the most hazardous and polluting ones. They often occur with high E-factor, defined by Sheldon as the mass of waste, corresponding to all compounds used which are not incorporated in the product, per mass unit of product. Indeed, oxidation reactions often deliver considerable amounts of toxic waste, e.g., metal salts in oxidations carried out with stoichiometric Cr(VI) or Mn(VII) derivatives, or nitrogen oxides from reactions with HNO_3. In a green chemistry context, it is of paramount importance to develop alternative oxidation methods making use of cleaner oxidants, which minimize the waste, producing only benign waste. Green oxidant is the one which produces the no waste product and works under mild reaction conditions. Some of the common oxidants in the order active content, used in the organic reactions, are listed below.

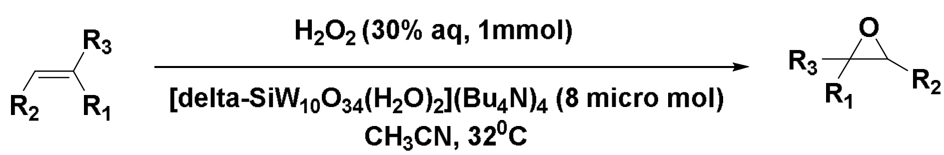
Table 1 Common oxidants ordered by active content.

Oxidant	Active oxygen content (wt. %)	Waste product
O_2	100.00	Nothing or H_2O
O_2/redactor	50.0	H_2O
H_2O_2	47.0	H_2O
N_2O	36.4	N_2
O_3	33.3	O_2
$KMnO_4$	30.4	Mn(II) salt
HNO_3	25.0	NO_X
CrO_3	24.0	Cr(III) salts
NaOCl	21.6	NaCl
CH_3COOH	21.1	CH_3COOH
t-BuOOH	17.8	t-BuOH
$C_5H_{11}NO_2$(NMO)	13.7	$C_5H_{11}NO$(NMM)
$KHSO_3$	10.5	$KHSO_4$
$MClC_6H_4COOOH$	9.3	$MClC_6H_4COOH$
$Me_3SiOOSiMe_3$	9.0	$Me_3SiOOSiMe_3$
$NaIO_4$	7.5	$NaIO_3$
PHIO	7.3	PhI

Oxidation chemistry plays a central role in many important industrial processes. Much effort has been put into the research for ideal conditions for its use in oxidation reactions. Examples include the bleaching of wood pulp to make white paper, remediation of waste-water streams, dye bleaching in the textiles industry, and drinking water purification.1,2 In most of these examples chlorine-based oxidants such as Cl_2, HOCl, or ClO_2 are used because these rapidly oxidise organic compounds under ambient conditions. However, a very undesirable by-product of reactions with these oxidants is the formation of organo-chlorines which are often highly toxic and prone to bioaccumulation when released into the environment.

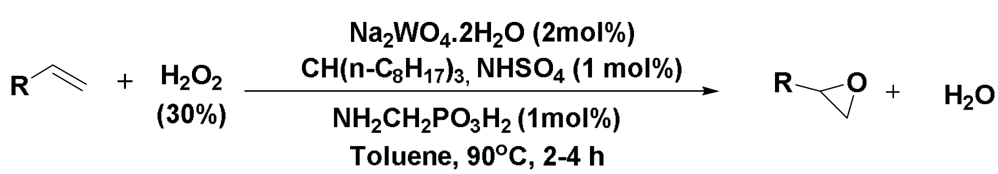
Among the different oxidants known, hydrogen peroxide constitutes a potentially green and environmentally-friendly oxidant because it releases only water as by-product. Although hydrogen peroxide is a cost-effective and powerful oxidant, its uptake by industry has been limited because it suffers from the problem of being very slow to react with most organic compounds under ambient conditions due to high activation barriers. The development of efficient green catalysts that can lower these activation barriers would open the way for hydrogen peroxide to be used as an effective replacement for chlorine-based oxidants in industry. This in turn would completely eliminate the release of organo-chlorines to the environment from these sources. Thus utilization of efficient green catalysts for oxidations of organic compounds with hydrogen peroxide is an important step in development of green oxidation method.

Mizuno et al found that silicadecatungstate catalyst displays exceptional efficiency in the epoxidation of alkenes with 30% aqueous H_2O_2 (Scheme 4), either in terms of catalyst activity, selectivity, and efficiency in use of H_2O_2. Moreover, the catalyst could be recovered and recycled up to 5 times with no loss of activity.



Scheme 4 Mizuno's epoxidation of alkenes promoted by silicadecatungstate and aqueous H_2O_2

Excellent yields in the epoxidation of alkenes, including terminal ones, have also been obtained by Noyori and co-workers by using $Na_2WO_4.2H_2O$ as the catalyst precursor under solvent-free (or in toluene) and halide free conditions (Scheme 5).



Scheme 5 Noyori's epoxidation of alkenes promoted by tungstate anions and aqueous H_2O_2

The efficiency of the reaction is dependent on the use of aminomethylphosphonic acid and trioctylmethyl ammonium hydrogensulfate as additives in 1 mol% amount, which are the best performing conditions.

Super critical carbon dioxide for synthetic chemistry

It is a fluid state of carbon dioxide where it is held at or above its critical temperature and critical pressure. Carbon dioxide usually behaves as a gas in air at standard temperature and pressure (STP), or as a solid called dry ice when frozen. If the temperature and pressure are both increased from STP to be at or above the critical point for carbon dioxide, it can adopt properties midway between a gas and a liquid. More specifically, it behaves as a supercritical fluid above its critical temperature (304.25 K, 31.10 °C, 87.98 °F) and critical pressure (72.9 atm, 7.39 MPa, 1,071 psi), expanding to fill its container like a gas but with a density like that of a liquid. Supercritical $CO_2$is becoming an important commercial and industrial solvent due to its role in chemical extraction in addition to its low toxicity and environmental impact. The relatively low temperature of the process and the stability of CO allows most compounds to be extracted with little damage or denaturing. In addition, the solubility of many extracted compounds in CO_2 varies with pressure, permitting selective extractions.

As a reaction medium the attractive physical and toxicological inertness properties of supercritical carbon dioxide ($scCO_2$) have made it superior to conventional organic solvents. First, $scCO_2$ has liquid like density and gas-like viscosity and consequently leads to high solubility and rapid mass transfer velocity. Secondly, a slight change of pressure, especially near the critical point of CO_2 enable the solvent properties such as density, viscosity, diffusivity and polarity to change constantly from approximate gaseous to similar liquid state. Thirdly, separating CO_2 from the reaction mixture is energy-efficient and a product can be obtained by simple treatment. More importantly, CO_2 is inexpensive, nonflammable, nontoxic, environmentally friendly and one of the reaction media, which is favored for Green chemistry research. At present, $scCO_2$ has been used as a medium in the following chemical reactions: enzyme-catalyzed reactions, polymerization, radical reactions, cyclo-addition reactions, transition metal catalyzed reactions and so on. Palladium-catalyzed reactions performed are the Heck and Stille reaction.

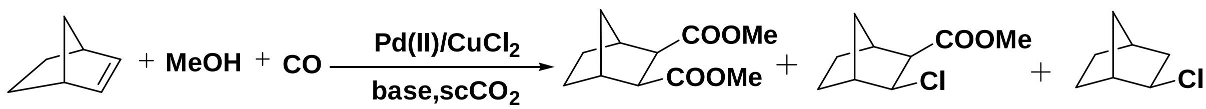
Application of super critical carbon dioxide in synthesis

Efficiency of fictionalization of organic compounds in $scCO_2$ increases by few tens of times, with high atom efficiency, and there are many examples of clean processes in this area.

This allows the development of concentrated, environmentally friendly reactions and technical processes.

Carbonylation of Alkenes

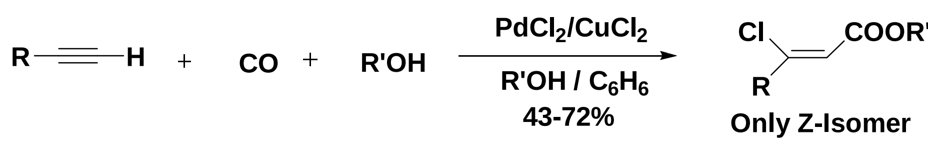
The functionalisation of alkenes is one of the most important areas of chemistry. Conversion and regioselectivity is always an important question for Pd-catalyzed carbonylation. Among many means to raise the reactant conversion and product regioselectivity, the choice of a suitable solvent is one of the most important. When norbornene was carbonylated in the presence of MeOH in $scCO_2$, three products, *cis*-*exo*-diester, *cis*-*exo*-β-chloride ester and *exo*-chloronorbornane were obtained(Scheme 6).



Scheme-6 Conversion and regioselectivity for Pd-catalyzed carbonylation

Carbonylation of Alkynes

Examination of Pd-catalyzed carbonylation of alkynes (Scheme-6) in $scCO_2$ reveals that there is a competition between carbonylation and dimerziation(Scheme 7).

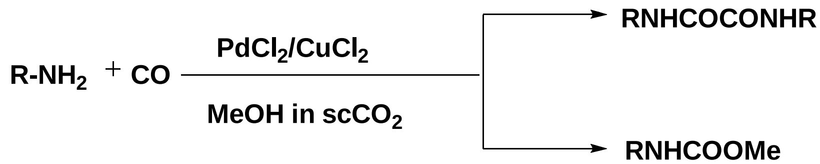


Scheme7 Pd-catalyzed carbonylation of alkynes

Adding alcohol is beneficial to carbonylation up to a certain limit, beyond which both carbonylation and dimerization have lower rates of reaction. The result is that media affect the stereoselectivity of reactions as well as controlling the chemoselectivity of reactions. This provides the biggest distinction between the common organic solvent and $scCO_2$.

Amines

Carbamate compounds, which have wide and general bioactivity, have been applied as pesticide, germicide, animal-anesthetic and so on. Carbonylation amide is one of the prospective methods for synthesizing carbamates compounds (Scheme 8). The chemoselectivity of amine carbonylation in $scCO_2$ and in common organic solvents are not alike. When amine was added during carbonylation of alkenes, formation of carbamate was detected.

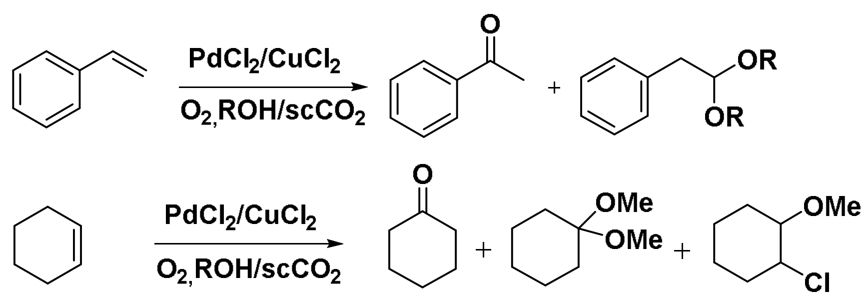


Scheme 8 Carbamate formation using $scCO_2$

In MeOH, only carbamate was obtained in the presence of O_2 while in MeOH/$scCO_2$, methyl *N*-n-butylcarbamate and oxalbutyline were obtained and the ratio of methyl *N*-n-butylcarbamate to oxalbutyline could be regulated with the amount of MeOH. In the absence of O_2 oxalbutyline was obtained primarily.

Waker Oxidation reaction in $scCO_2$

$scCO_2$ is expected to affect the regioselectivity of olefinic oxidation, and reaction rules could be obtained for alkenes with different electronegativity (Scheme 9).



Scheme 9 Olefin oxidation of styrene and cyclohexene

Wacker oxidation of styrene and cyclohexene proceeded very smoothly to provide expected products acetophenone and cyclohexanone in regular organic solvents. However the same reaction in $scCO_2$ lead to the formation of a considerable amount of acetal. To some extent it revealed some specific characteristics of, it also revealed the influence of electronegativity or substituting group to oxidation region-selectivity.

Similar to the above mentioned reaction several other reactions such as dimerization and trimerization of alkynes in the presence of palladium chloride catalyzed cyclotrimerization of alkynes in the presence of $CuCl_2$, Co-polymerization of acrylic acid in the presence of per fluorinated compounds, radical addition reactions, were also successfully studied in supercritical carbon dioxide as a reaction medium.