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Environmentally friendlier organic transformations on mineral supports under non-traditional conditions†

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Synthetic organic reactions performed under non-traditional conditions are gaining popularity, primarily to circumvent growing environmental concerns. A solvent-free approach that involves microwave (MW) exposure of neat reactants (undiluted) catalyzed by the surfaces of less expensive and recyclable mineral supports, such as alumina, silica, clay, or 'doped' surfaces, is described which is applicable to a wide range of deprotection, condensation, cyclization, rearrangement, oxidation, and reduction reactions, including rapid one-pot assembly of heterocyclic compounds from *in situ*-generated reactive intermediates. The strategy is adaptable to multi-component reactions for rapid assembly of a library of compounds. The application of microwaves and ultrasound as successful alternative energy sources is described for the selective epoxidation of alkenes and α,β-unsaturated ketones over hydrotalcites as catalysts. The ability of "green" solvents such as supercritical (sc) CO_2 to dissolve many reactive gases like H_2 and O_2, and also a variety of organic compounds, can be exploited to facilitate many important industrial transformations in this medium, wherein the improved reactant solubility and minimized interphase mass-transfer limitations lead to enhanced reaction rates and unusual product selectivity. Consequently, the use of sc-CO_2 as an attractive medium for the selective hydrogenation of maleic anhydride and α,β-unsaturated aldehydes, such as cinnamaldehyde, over supported metallic catalysts (Pd/Al_2O_3) is illustrated. Furthermore, recent developments in the areas of microwave or ultrasound-expedited reactions, and the use of supercritical CO_2 in organic transformations are also reviewed. The salient eco-friendly features of these processes, namely the selectivity, the ease of experimental manipulation, and the enhanced reaction rates, are highlighted. Use of the above non-traditional methods promises to overcome many of the difficulties associated with conventional reactions and offers both process and environmental advantages in many cases.

Introduction

Industrial chemistry in the new millennium is widely adopting the concept of "green chemistry" to meet the fundamental scientific challenges of protecting human health and the environment while simultaneously achieving commercial profitability. The emerging area of green chemistry envisages minimum hazard as a performance criterion for the design of new chemical processes. One of the approaches for achieving this target is to explore alternative reaction conditions and reaction media to accomplish the desired chemical transformations with minimal by-products or waste, as well as eliminating the use of conventional organic solvents, if possible. Some of the important tools include the use of microwaves (MW) and ultrasound (US) as alternative energy sources, as well as the use of supercritical fluids (SCF) as an alternative and attractive reaction medium.

1 Microwave-expedited reactions

Microwave irradiation, an unconventional energy source, has been used for a variety of applications, including organic synthesis,[1–10] wherein chemical reactions are accelerated because of selective absorption of MW energy by polar molecules; non-polar molecules being inert to MW dielectric loss. Although this non-ionizing radiation is incapable of breaking bonds, coupling it with traditional heterogeneous reactions[11] could result in rate acceleration at ambient pressure.[1–5,9,10] Our recent results on this MW-expedited approach encompass the synthesis of a variety of industrially significant entities, namely imines, enamines, enones, nitroalkenes, oxidized sulfur species, and heterocycles. This methodology is exemplified by a concise synthesis of tetrahydroquinolones, flavones, 2-aroylbenzofurans, and thiazole derivatives, and demonstrates the exploitation of *in situ*-generated reactive intermediates in one-pot synthesis of heterocyclic compounds.[10] Furthermore, the protocols are adaptable to rapid and parallel synthesis in multi-component reactions, as has been demonstrated for the assembly of heterocycles *via* typical Ugi and Biginelli reactions.

Functional group transformations

Deprotection reactions are expedited by MW exposure of protected molecules on mineral oxides or benign 'doped' reagents, as has been shown in the regeneration of alcohols, acids, and carbonyl compounds.[12–15] Several reagents can also be used under these solvent-free conditions to expedite organic reactions, *e.g.* hydroxylamine on clay directly converts aldehydes to nitriles.[16] Several non-metallic hypervalent iodine oxidants on mineral oxide surfaces can be used under solventless conditions.[17] Interestingly, the crossed Cannizzaro reaction can be accomplished with paraformaldehyde on a barium hydroxide surface;[18] the sacrificial formaldehyde generated upon microwave exposure reacts as it is formed.

Pinacol rearrangement over montmorillonite and acetate alkylation using alkyl halides over silica and alumina have been achieved under solvent-free dry conditions using microwave heating.[19] Furthermore, high yields are reported in the microwave-assisted esterification of carboxylate ions intercalated in layered double hydroxides by reaction with alkyl halides in an intracrystalline alkylation reaction, where the reaction time could be significantly reduced.[20] A rapid

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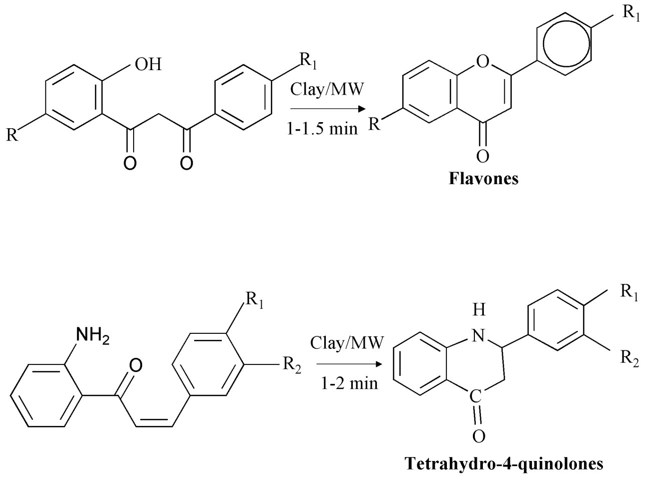
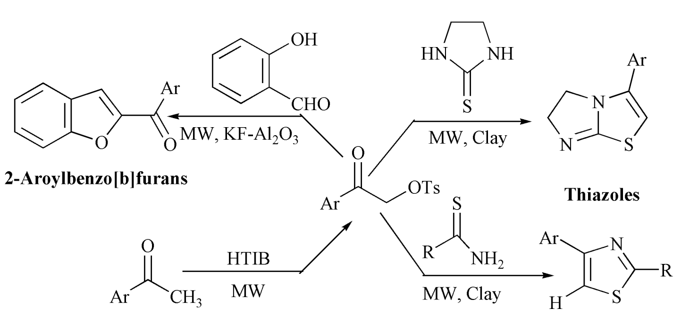
and efficient microwave-enhanced solventless preparation of herbicides based on 2,4-dichlorophenoxyacetic acid (2,4-D esters) has been accomplished under mild conditions over inorganic solid supports such as silica, clays, zeolites, and soil. The product remains adsorbed on the solid support, which can be directly applied in the field.[21]

Synthesis of heterocyclic compounds

Clays provide acidic surfaces for the rapid assembly of a variety of heterocyclic compounds, as demonstrated by the synthesis of flavonoids (Baker–Venkataraman rearrangement) and the related cyclization of 2′-aminochalcones to 2-aryl-1,2,3,4-tetrahydro-4-quinolones on clay (Scheme 1).[22a] The *in situ*-generated enamine derivatives can be reacted with *o*-hydroxyaldehydes, thus providing a concise one-pot route to isoflav-3-enes bearing basic amino substituents in the 2 position.[22b] This convergent strategy has been extended to the synthesis of naturally occurring and pharmacologically active 2-aroylbenzo[*b*]furans, which proceeds rapidly *via* the condensation of *in situ*-generated α-tosyloxyketones with a variety of salicylaldehydes on potassium fluoride-‘doped’ alumina (Scheme 2); this process avoids the use of lachrymatory starting materials.[23] Similarly, thiazoles can be readily obtained by the reaction of thioamides with α-tosyloxyketones in a clay-catalyzed reaction (Scheme 2). The versatility of the MW approach is apparent in the synthesis of bridgehead heterocycles when the reactants are cyclic thioureas.



Scheme 1



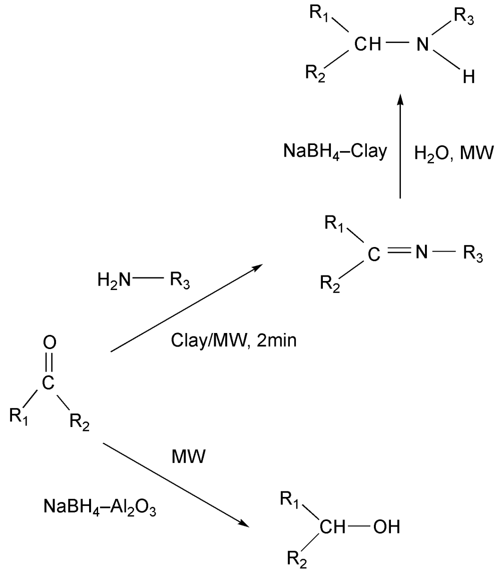
Scheme 2

Microwave-accelerated multi-component reactions

Combinatorial chemistry has gained significant importance as a tool for the synthesis of a wide variety of useful compounds, including pharmaceuticals. In this context, the multiple component condensation (MCC) approach is especially appealing in view of the fact that products are formed in a single step and diversity can be readily achieved simply by varying the reacting components. The generation of small-molecule libraries requires the development of efficient methodologies with special emphasis on the manipulative ease of the reaction. Such a facile protocol, which is amenable to the generation of a library of imidazo[1,2-*a*]pyridines, imidazo[1,2-*a*]pyrazines, and imidazo[1,2-*a*]pyrimidines under solvent-free conditions using MW irradiation, has been developed.[24] The conventional two-component synthesis, requiring lachrymatory α-haloketones and 2-amino heterocycles restricts the generation of a diverse library of these molecules. In view of the readily available precursors, a large collection of compounds can be potentially prepared, applying recently developed automated, high throughput robotic technologies for performing microwave-assisted combinatorial synthesis.[25]

Reduction reactions

The solid-state selective reduction of carbonyl compounds occurs readily on pre-moistened alumina-supported sodium borohydride ($NaBH_4$).[26] The alumina support can be reused repeatedly by simply washing off the product; a process that hydrates the alumina surface to facilitate subsequent reduction reactions. Our earlier optimized imine-forming (Schiff bases) reaction using a catalytic amount of clay[27] can be adapted for the borohydride reduction in the same pot, thus providing a simple route to secondary and tertiary amines.[28] Clay serves a dual purpose, functioning as a Lewis acid and also providing water from its interlayers, which enhances the reducing ability of $NaBH_4$ (Scheme 3). The air used for cooling the magnetron ventilates the microwave chamber, thus preventing build-up of any explosive concentrations of hydrogen.

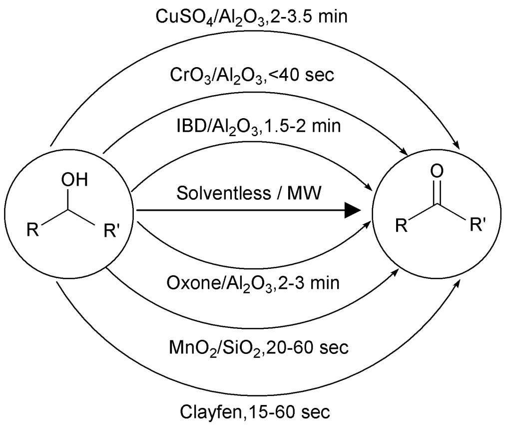


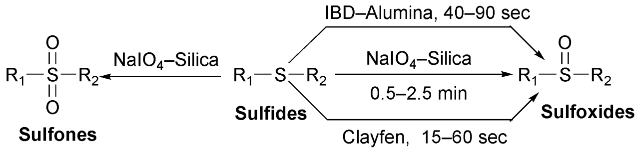
Scheme 3

Oxidation reactions

The introduction of metallic reagents onto solid supports has solved some of the associated toxicity problems and provides an attractive alternative to conventional oxidation reactions in view of the selectivity and ease of manipulation. Several MW-assisted oxidative protocols applicable to both alcohols and sulfides are available, using a wide variety of supported oxidants (Scheme 4).[29–32]

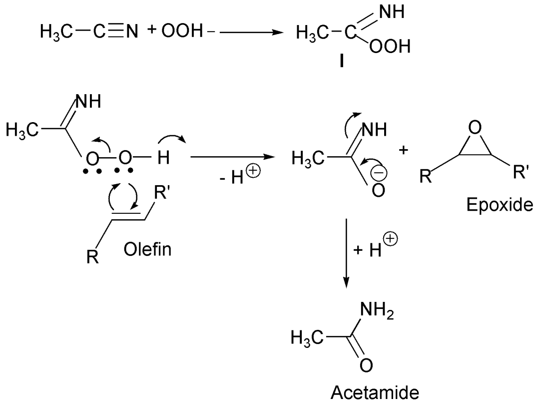
We have recently uncovered an expeditious and environmentally benign epoxidation protocol for olefins using hydrotalcite catalysts in the presence of MeCN and H_2O_2 under intermittent MW-irradiation conditions.[33] The detailed results of this investigation are summarized in Table 1. Under conventional heating conditions, these epoxidations are carried





Scheme 4

out in the presence of an organic solvent and also require a long reaction time (4–8 h) for a similar product yield. The mechanism of epoxidation involves the formation of perhydroxyl anion (OOH^-) by the reaction of H_2O_2 with a basic hydroxyl function on the hydrotalcite, nucleophilic attack of the anion on the nitrile generates a peroxycarboximidic acid intermediate (**I**, Scheme 5). The subsequent oxygen transfer from the intermediate to the olefin results in the formation of epoxide and an amide. The selective epoxidation of a variety of olefins occurs expeditiously upon MW irradiation, including substrates that are generally difficult to oxidize such as sterically hindered isophorone.[34–36] This rate acceleration is attributed to the selective absorption of microwave energy by the polar entities or reaction intermediates. The selectivity for epoxide formation is extremely good, with little or no formation of any undesired products. This approach significantly minimizes the longer reaction times required in conventional heating of olefins with H_2O_2 and avoids the use of the large excess of volatile organic solvent usually employed.



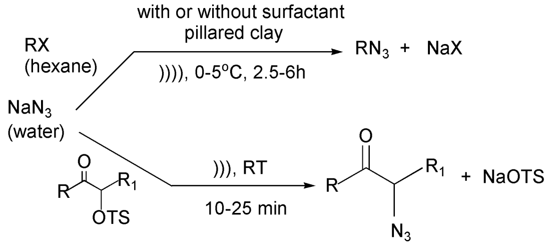
Scheme 5

2 Ultrasound-assisted organic transformations

The chemical effects of ultrasound are diverse and include significant improvements in both stoichiometric and catalytic reactions. In some cases, ultrasonic irradiation can increase reactivities by nearly a million-fold.[37] It does so through the process of acoustic cavitation: the formation, growth, and implosive collapse of bubbles in liquid. Cavitation within a liquid creates voids (bubbles), which are the seat of high-energy phenomena. Ultrasound *per se* has no direct action on chemical bonds. Nevertheless, it has found widespread application for initiation or enhancement of catalytic reactions, both homogeneous and heterogeneous systems.[38]

Nucleophilic substitution reactions on pillared clay

Azido compounds such as alkyl azides and α-azidoketones are highly reactive entities and are of immense synthetic utility.[39] A significant acceleration of reaction rate in the synthesis of azide derivatives from the corresponding alkyl halides and α-tosyloxyketones under ultrasound irradiation conditions has been demonstrated,[40] in contrast to the usual preparation involving complex procedures, long reaction times, low yields, and low purity. Furthermore, it has been pointed out that the sonochemical approach is a viable substitute for the phase-transfer catalyst usually employed in such reactions (Scheme 6).



Scheme 6

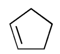
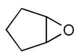
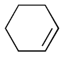
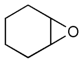
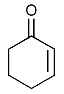
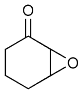
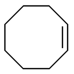
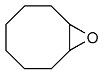
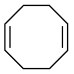
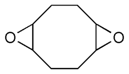
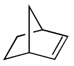
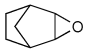
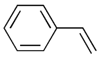
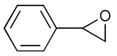
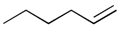
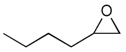
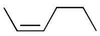
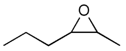
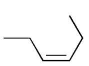
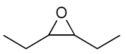
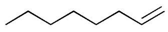
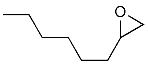
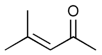
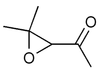
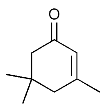
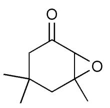
Epoxidation of olefins and α,β-unsaturated ketones

Catalytic epoxidation of carbon–carbon double bonds is a versatile transformation in synthetic organic chemistry due to the synthetic utility of the ensuing epoxides and their elaboration to useful products.[41] This is usually achieved in the presence of transition metal catalysts,[42] especially titanium-based catalysts, in relatively lengthy reactions involving volatile organic solvents. Increased environmental concerns and awareness has resulted in greater demand for eco-friendly protocols that use relatively benign oxidants, such as molecular oxygen and hydrogen peroxide, in combination with reusable and recyclable solid catalysts.[43]

A significant rate acceleration in the epoxidation of olefins using hydrotalcite catalysts in presence of MeCN and H_2O_2 under ultrasound irradiation conditions (Table 2) has been observed.[44] A variety of cyclic and linear olefins are oxidized to the corresponding epoxides in a relative shorter period with good to excellent yield. The salient advantages of the ultrasound method include significant reductions in the amount of catalyst required and the reaction time to achieve similar or improved product yield when compared to the conventional methods involving heating and stirring (Table 2). The ultrasound protocol is extendable for the selective epoxidation of a variety of α,β-unsaturated ketones, as evidenced by the results shown in Table 3.

The rate enhancement of epoxidation under ultrasound irradiation can be attributed to the enhanced molecular motion caused by acoustic streaming, which arises from non-linear coupling of the acoustic waves (due to the presence of obstacles in the acoustic field). In the vicinity of the surface, ultrasonic streaming produces strong convective currents which cause a reduction in the thickness of diffusion layers, thereby enhancing diffusion-controlled processes such as the catalyzed reactions described above. In addition, there are also other factors, such as enhancement of external transport phenomena and a local rise in temperature at the surface of the particle due to

Table 1 MW-assisted olefin epoxidation over hydrotalcite catalysts using H_2O_2[a]

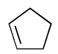
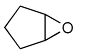
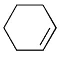
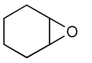
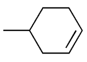
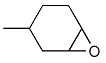
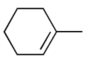
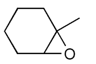
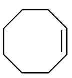
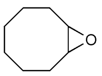
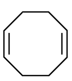
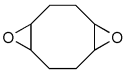
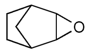
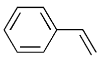
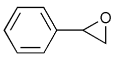
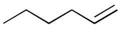
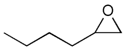
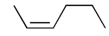
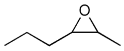
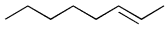
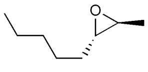
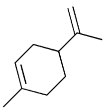
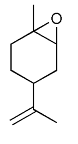
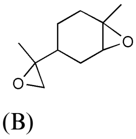
Olefin	MW Power/W	Reaction time/min	Product	Yield[b] (%)
	480	1		97
	480	1		100
	720	1		100
	720	6		88
	720	5		100
	480	3		92
	720	5		62
	480	3		100
	480	3		100
	480	3		100
	720	5		87
	720	8		66
	720	3		87

[a]Reaction conditions: 12.5 mmol substrate, 0.25 g hydrotalcite, 4 mL acetonitrile, 50 mmol H_2O_2 (30%). [b]GC yield. All the products are known compounds and were identified by GC-MS.

the cavitation of bubbles next to the external surface. Such "localized heating" could propagate inside the catalyst, producing higher reaction rates. This approach significantly reduces the amount of catalyst needed and the long reaction times required in conventional heating of olefins with H_2O_2, in addition to avoiding the use of the large excess of volatile organic solvent that is usually employed.

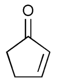
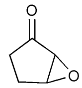
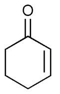
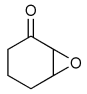
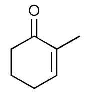
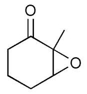
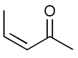
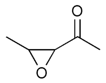
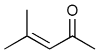
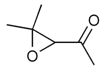
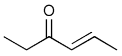
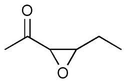
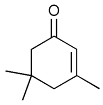
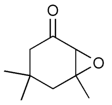
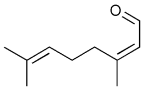
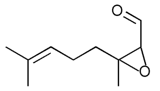
Many other ultrasound-enhanced reactions on mineral supports are also known. For example, Yadav *et al.* have found that ultrasound accelerates the three-component condensation in methanol of an aldehyde, a β-ketoester, and urea, in the presence of cerium ammonium nitrate, to yield the corresponding dihydropyrimidinones.[45] The reduction of aromatic nitro compounds to the corresponding amines and reductive coupling of aromatic ketones over samarium/ammonium chloride[46] or aluminum/ammonium chloride[47] have also been reported to be promoted by ultrasound irradiation. Ultrasound has been found to enhance the rates of formation of isoxazoles and 5-isoxazolones by condensation of 4-phenyl substituted β-enamino ketones and β-enamino esters with hydroxylamine hydrochloride using montmorillonite K-10 as catalyst.[48] The combination of K-10 and ultrasound is also reported to be useful in the preparation of disteryl ethers from unsaturated sterols[49] and for the

Table 2 Ultrasound-assisted olefin epoxidation over hydrotalcite catalysts using H_2O_2[a]

Olefin	Reaction time/h	Product	Yield[b] (%)
	1		>95
	1		>95
	3		>95
	3		90
	3		84
	1		75
	1		>95
	3		50
	4		67
	4		82
	3		>95
	1	 (A)	A: 24; B: 0
	3	 (B)	A: 32; B: 29

[a] Reaction conditions: 100 mmol substrate, 0.5 g hydrotalcite, 25 mL acetonitrile, 400 mmol H_2O_2 (30%). [b] GC yield. All the products are known compounds and were identified by GC-MS.

Table 3 Ultrasound-assisted epoxidation of α,β-unsaturated ketones over hydrotalcite catalysts using H_2O_2[a]

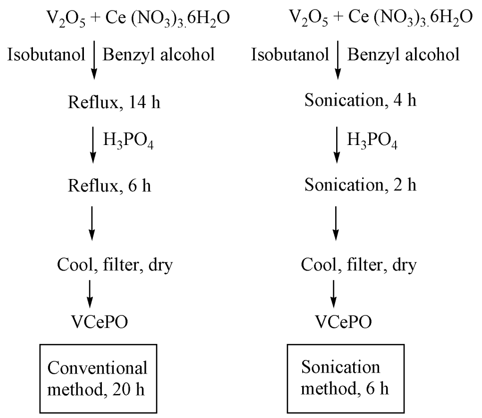
Olefin	Reaction time/h	Product	Yield[b] (%)
	0.5		86
	2		>95
	1 3		27 33
	2		>95
	3		60
	2		75
	2		30
	1		56

[a] Reaction conditions: 100 mmol substrate, 0.5 g hydrotalcite, 25 mL acetonitrile, 400 mmol H_2O_2 (30%). [b] GC yield. All the products are known compounds and were identified by GC-MS.

synthesis of pyrazoles and pyrazolinones.[50] A significant improvement in the benzylation rate of arenes has been reported under sonication over K-10-supported $ZnCl_2$ catalyst.[51] A facile and rapid ultrasound-assisted synthesis of pivalophenones by acylation of various aromatic and heterolytic compounds with pivaloyl chloride using $AlCl_3$ as catalyst has been reported.[52] Ultrasound also helps to modify the course of several photochemical bimolecular reactions, such as photopinacolization of benzophenone.[53] This is attributed to sonication-induced triplet-state quenching and the sonolytic decomposition of the light-absorbing transient species, thereby affording efficient photoconversion. Sonication is believed to be able to quench the long-lived excited states due to the intense streaming that favors easier collisional deactivation processes. More examples of the applications of ultrasound in organic synthesis can be found elsewhere.[54]

Ultrasound-assisted preparation of catalysts: cerium-promoted vanadium phosphorus oxide (VCePO)

Vanadium phosphorus mixed oxides (VPO) have been successfully used as catalysts for the commercial production of maleic anhydride by the oxidation of n-butane.[55] However, they are not very effective for the oxidation of other alkanes such as propane and cyclohexane. Several promoters have been explored for activating the VPO catalysts for the selective oxidation of propane to acrylic acid; the addition of Zr has been found to improve the acrylic acid selectivity.[56] Oxidation of cyclohexane to cyclohexanone is one of the primary targets of industrial chemistry, as cyclohexanone is an important intermediate for ε-caprolactam production, the raw material for nylon synthesis.[57] The classical oxidation process of cyclohexane operates at only a 4% conversion level and many attempts have been made to substitute this process with a



Scheme 7

variety of catalysts and biomimetic systems.[58] Molecular oxygen and hydrogen peroxide are the preferred oxidants in view of their environmentally benign and inexpensive nature. We have studied the oxidation of cyclohexane using VPO and promoted VPO catalysts and found that cerium promotion improves the oxidative catalytic activity of VPO catalysts. The preparation of VPO catalysts is usually a very time consuming process, as it involves the reduction of V_2O_5 in a mixture of isobutanol and benzyl alcohol under reflux for 12–14 h, followed by refluxing in phosphoric acid solution for an additional 6–8 h.[56] We have discovered that ultrasound irradiation of the mixture can significantly reduce the preparation time of Ce-promoted VPO catalysts (Scheme 7) to a total of around 6 h, as evidenced by a comparison of the XRD spectra of VCePO catalysts prepared by the conventional method (under reflux) and the ultrasound-expedited method (Fig. 1). This is further corroborated by their similar activity and selectivity for liquid-phase cyclohexane oxidation using hydrogen peroxide as the oxidant (Fig. 2).

Ultrasound has also been applied as a successful tool for the synthesis of other catalysts and catalytic materials, such as mesoporous MCM-41 silicates,[58] mesoporous silica–alumina,[59] mesoporous yttrium–zirconium oxides[60] with controlled pore size distribution, mesoporous TiO_2 with high photocatalytic activity,[61] and polycrystalline MoO_3.[62]

3 Supercritical carbon dioxide as an alternative reaction medium

In the past decade, supercritical carbon dioxide (sc-CO_2) has been increasingly used as an environmentally friendly reaction medium. Carbon dioxide is one of the most naturally abundant and the least expensive solvents. The use of green solvents, such as carbon dioxide, would eliminate or reduce several uncertainties regarding the chemical life-cycle of solvents. sc-CO_2 is a non-toxic, non-flammable, low cost (less than \$80 per ton) solvent that leaves no residual byproducts. It is one of the few solvents that is not regulated as a VOC by the US Environmental Protection Agency. Supercritical fluid technology facilitates better use of the vast amounts of CO_2 gas emitted by industry. The ability of sc-CO_2 to dissolve many reactive gases, such as H_2 and O_2, and also a variety of organic compounds, facilitates oxidation and hydrogenation reactions in this medium, thereby eliminating interphase mass-transfer limitations and enhancing reaction rates.[63] The fact that slight variations in temperature and pressure near the critical point can significantly change the activity and selectivity provides remarkable potential for its use as a reaction medium. sc-CO_2 has been used as a replacement solvent for many existing processes, for example, innovative uses of sc-CO_2 in extraction and separation processes in the food and pharmaceutical industries, in the design of new materials with specific characteristics (foams, aerogels, powders, fibers, microcapsules, liposomes), and in organic transformations where the unique properties of sc-CO_2 can be capitalized upon. Use of sc-CO_2 as alternative medium promises to overcome many of the difficulties associated with conventional reactions and offers both process and environmental advantages.

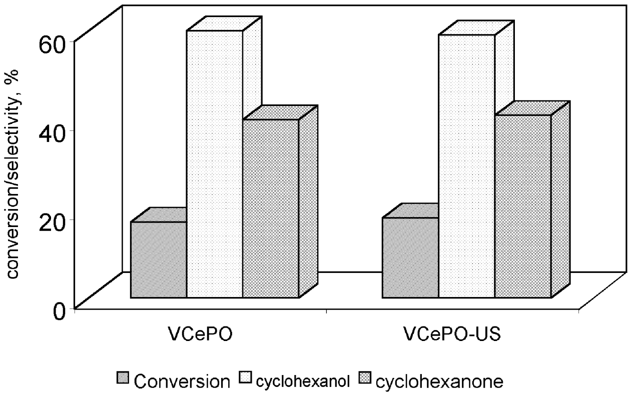


Fig. 2 Cyclohexane conversion and product selectivity over Ce-promoted VPO catalysts prepared by the conventional method (VCePO) and by ultrasound irradiation (VCePO-US).

Selective hydrogenation in supercritical CO_2

Several recent publications have demonstrated the potential of sc-CO_2 as an alternative reaction medium for a variety of synthetic transformations.[63–66] Recently, we have demonstrated,

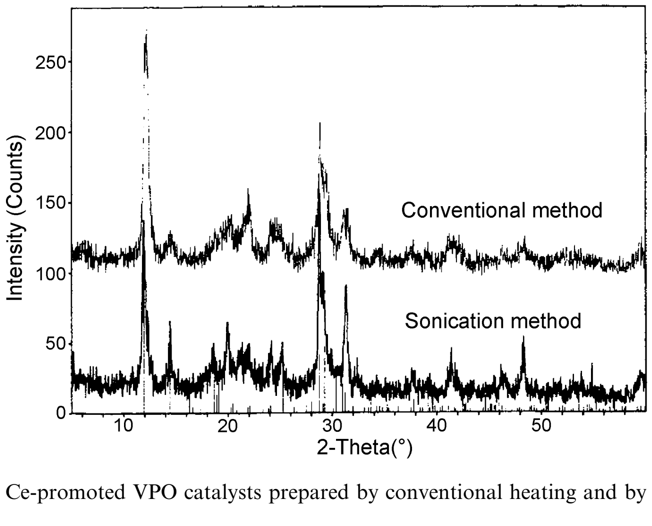
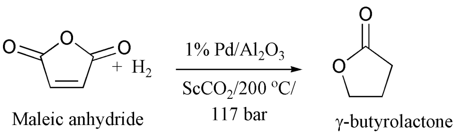


Fig. 1 XRD spectra of Ce-promoted VPO catalysts prepared by conventional heating and by ultrasound irradiation.



Scheme 8

for the first time, an organic solvent-free selective hydrogenation of a low vapor pressure compound, *viz.* maleic anhydride over an alumina-supported palladium catalyst (1% Pd/Al_2O_3) under supercritical conditions.[67] Supported Pd catalysts are highly efficient hydrogenation catalysts widely employed in many complete hydrogenations. They are, however, not generally effective as partial/selective hydrogenation catalysts, such as Pt or Rh.[68] Nevertheless, a different selectivity profile has emerged in the supercritical CO_2 medium that contrasts with the selectivity observed under normal liquid-phase hydrogenations in organic solvents (Scheme 8). A nearly quantitative maleic anhydride conversion occurs, providing ~80% yield of γ-butyrolactone (GBL) at 200 °C and at a pressure of 21 bar H_2 and 117 bar CO_2 (Table 4). Conventional hydrogenation reaction in the presence of organic solvents affords predominantly the double bond hydrogenated product, succinic anhydride (SAH). Furthermore, there is an additional requirement to remove the high boiling point solvents (polyethylene glycol, ethylene glycol dimethyl ether) from the reaction mixture in typical liquid-phase reactions. The unusual γ-butyrolactone selectivity obtained over Pd/Al_2O_3 may be due to the enhanced reactant–product solubility, as well as different reaction energetics in sc-CO_2. Miscibility studies of maleic anhydride in sc-CO_2 indicate a single phase under the reaction conditions.

The advantage of sc-CO_2 as a reaction medium in hydrogenations is further exemplified by the hydrogenation of cinnamaldehyde over Pd/Al_2O_3 catalyst. Table 5 compares the results of cinnamaldehyde hydrogenation over Pd/Al_2O_3 catalysts in the presence of methanol and sc-CO_2 as solvents, as well as with the reaction under N_2 pressure. Reaction under sc-CO_2 shows a higher conversion when compared to the reactions in methanol and under N_2 pressure. This may again be attributed to the improved reactant (cinnamaldehyde and hydrogen) solubility and enhanced mass-transport rate in sc-CO_2. Product selectivity also varies depending on the reaction medium. Cinnamaldehyde hydrogenation over Pd/Al_2O_3 under sc-CO_2 and N_2 forms mainly the C=C double bond hydrogenated product, 3-phenylpropionaldehyde, whereas cinnamaldehyde dimethyl acetal is the major product formed in methanol.

There are a few other studies on hydrogenation reactions in supercritical fluid media.[69–75] Poliakoff and co-workers have reported hydrogenations of a variety of liquid compounds in sc-CO_2 over Deloxan aminopolysiloxane-supported noble metal (Pd, Ru, Pt) catalysts.[74] Recently, Balasubramaniam *et al.* have reported fixed-bed hydrogenation of cyclohexene to cyclohexane in sc-CO_2 over Pd/C catalyst.[75] Arai and co-workers have very recently studied the selective hydrogenation of α,β-unsaturated aldehyde over unpromoted Pt/SiO_2[76a] and Pt/Al_2O_3[76b] catalysts under supercritical CO_2, wherein high selectivity to α,β-unsaturated alcohols is reported, in contrast to the poor selectivities obtained in organic solvents with monometallic catalysts.

Selective oxidation in supercritical CO_2

The selective oxidation of different organic substrates, such as alkenes, alkanes, and alcohols, over Pt/Al_2O_3, Pd/Al_2O_3, and iron complex {*cis*-$[Fe\text{-}(dmp)_2(H_2O)_2](CF_3SO_3)_2$ (dmp = 2,9-dimethyl-1,10-phenanthroline)} catalysts in supercritical carbon dioxide using clean oxidants, *viz.* molecular oxygen at around 200 bar pressure and at 60–100 °C, has been investigated (Table 6).[77] The conversion to oxygenated products is found to be dependent more on the oxygen pressure than the temperature and duration of the reaction. Oxidation of cyclohexene over Pt and Pd/Al_2O_3 results in a mixture of oxygenated and dehydrogenation products.[77]

Partial oxidation of propane to oxygenates has been studied in supercritical CO_2 over Al_2O_3-, SiO_2-, and ZrO_2-supported Cu, Co, Mn, and Pd catalysts at 150–300 °C and 8–100 bar pressure in a stirred batch reactor.[78] The study indicates that a decrease in CO_2 density results in an increase in the selectivity of oxygenates. Total oxidation of toluene and tetrahydronaphthalene to CO_2 and water in supercritical CO_2 has been reported over a 0.5% Pt/Al_2O_3 catalyst at moderate temperatures of 300–390 °C and pressures of 86–117 bar.[79] Supercritical CO_2 has also proved to be useful in the oxidation of secondary alcohols using a 0.5% Pd/Al_2O_3 catalyst, where no significant catalyst deactivation is observed and the rate of the reaction is 2–4 times higher than that in nitrogen.[80] Wacker oxidation of 1-octene to the corresponding carbonyl product

Table 4 Comparison of maleic anhydride hydrogenation over 1% Pd/Al_2O_3 under supercritical CO_2 and in organic solvents[a]

Reaction temperature/°C	CO_2 pressure/bar	Organic solvent	Conversion (%)	Yield[b] (%)	
				GBL	SAH + SA
200	117	No solvent	100	~80[c]	ND[d]
200	—	PEG[e] 10 mL	100	2	78
200	—	EGDME[f] 10 mL	100	7	80
200	—	Acetone 10 mL	100	2	96

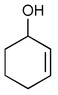
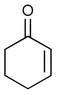
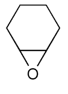
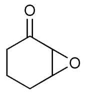
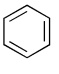
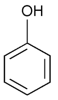
[a] Reaction conditions: 25 mmol MA, 0.5 g catalyst, 21 bar H_2, 350 rpm stirrer, 2 h. [b] GC yield. [c] Exact values could not be ascertained above 80% as the GC-MS signals for SAH and SA at these concentrations were close to their method detection limits. [d] ND = below the method detection limit of GC-MS. [e] PEG = polyethylene glycol. [f] EDGME = ethylene glycol dimethyl ether.

Table 5 Comparison of cinnamaldehyde hydrogenation over 1% Pd/Al_2O_3 under supercritical CO_2, N_2, and in methanol[a]

CO_2 pressure/bar	Solvent (volume)	Conversion (%)	Selectivity (%)		
			3-Phenylpropionaldehyde	3-Phenylpropanol	Cinnamaldehyde dimethyl acetal
—	MeOH (10 mL)	23	39	—	61
90	—	37	83	17	—
90 (N_2)	—	21	81	19	—

[a] Reaction conditions: 25 mmol cinnamaldehyde, 0.25 g catalyst, 7 bar H_2, shaker, 2 h.

Table 6 Cyclohexene oxidation using O_2 over various catalysts in supercritical CO_2[a]

Catalyst	O_2 pressure/bar	Conversion (%)	Selectivity (%)					
								
0.5%Pd/Al_2O_3	4.8	0.43	5.2	15.1	2.5	—	39.5	37.6
0.5%Pt/Al_2O_3	4.8	0.17	16.4	19.6	3.5	—	55.2	5.21
Fe complex[b]	5.5	4.0	34.7	58.4	5.4	1.4	—	—

[a]Reaction conditions: 100 °C, 6 h, total pressure 200 bar. [b]*cis*-[Fe-(dmp)$_2$(H_2O)$_2$](CF_3SO_3)$_2$ (dmp = 2,9-dimethyl-1,10-phenanthroline).

has also been studied in supercritical CO_2 over $PdCl_2/CuCl_2$ catalysts, revealing that supercritical CO_2 as the reaction medium greatly enhances the selectivity of the reaction and reduced the isomerization of 1-octene.[81]

Supercritical CO_2 has also been employed as a solvent for the synthesis of nanoporous silica, titania and platinum, where the precursors are dissolved in supercritical CO_2 and attached to an activated carbon template.[82] The results suggests that supercritical fluids offer a definite advantage in nanoscale casting which may be useful in the synthesis of nanoporous materials whose structures can be controlled through a judicious choice of the template. In addition, supercritical CO_2 can also be used as an antisolvent in the preparation of catalysts such as amorphous vanadium phosphates (VPO), which have been shown to be more active than crystalline VPO catalysts.[83] This antisolvent precipitation procedure eliminates the need for extensive pretreatment or activation procedures and helps to maintain the amorphous nature of the catalysts throughout the catalyst test period.

Conclusions

In conclusion, solvent-free microwave and ultrasound approaches, as well as reactions in alternative media, such as supercritical carbon dioxide, open up numerous possibilities for conducting rapid organic synthesis, functional group transformations, and materials synthesis in an efficient and eco-friendly manner. Additionally, these protocols confer distinct advantages, since they allow the amount of volatile organic solvents used in the reactions to be greatly reduced, or in some cases eliminated, thereby preventing pollution in organic synthesis ‘at source’. The chemo-, regio-, or stereo-selective synthesis[84] of high value chemical entities and parallel synthesis to generate a library of small molecules[85] will add to the growth of such reactions in the near future.

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