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Organic reactions in water or biphasic aqueous systems under sonochemical conditions. A review on catalytic effects

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ABSTRACT

Catalysis in aqueous systems under sonochemical conditions has become an irreplaceable method in green synthetic chemistry after more than two decades of studies in this domain. The present review has the aim of describing the state-of-the-art with a comprehensive view of advantages and limitations as well as new potential applications. Catalytic procedures in water assisted by ultrasound and/or hydrodynamic cavitation are environmentally friendly with milder conditions, shorter reaction times and higher yields. Sonochemical processes can reduce the formation of hazardous by-products, the generation of waste and also produce energy savings. Cavitational implosion generates mechanical and chemical effects such as cleaning of catalyst surface and formation of free radicals by sonolysis of water. The present overview of sonochemical reactions in water (oxidation, bromination, aza-Michael, C–C couplings, MCR and aldol reactions) should provide useful models for furthering the progress of organic synthesis using harmless and greener sound energy.

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1. Introduction

Ultrasound (US) and hydrodynamic cavitation (HC) have proven themselves to be an important stepping stone towards process intensification in organic synthesis, placing sonochemistry among the elite of green chemical methods [1,2]. An acoustic pressure wave consists of alternate compressions and rarefactions in the transmitting medium along the wave propagation direction. When a large negative pressure is applied to a liquid, intermolecular van der Waals forces are not strong enough to maintain cohesion and small cavities or gas-filled microbubbles are formed. The rapid nucleation, growth and collapse of these micrometerscale bubbles constitute the phenomenon of cavitation. Sonochemical effects mainly arise from acoustic cavitation which generates enough kinetic energy to drive reactions to completion and releases short-lived, highenergy chemical species into solution after the implosive collapse of bubbles. It is now well-established that this process is capable of providing very high temperatures (4500–5000°K as typical figure) and very high pressures (\approx 1000 atm) in extremely short times (in the range of microseconds), thus rendering cavitation a quasi-adiabatic phenomenon [3]. US is especially efficient in activating hard metal surfaces as the well-known cleaning effect of ultrasonic waves provides a de-passivated layer where catalyst and reagent better interact with each other [4].

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http://dx.doi.org/10.1016/j.catcom.2014.12.014 1566-7367/© 2014 Elsevier B.V. All rights reserved. US promotes reagent diffusion from solution to the metal, electron transfer from the active surface to the reducible point of the organic substrate and finally, the extraction of ions from the surface to generate a soluble product [5]. Acoustic waves and cavitation strongly promote all these steps as observed in the formation of common organometallics under sonication [6,7]. Fig. 1 schematize the most common ultrasonic devices to work in batch with high-intensity US.

It is possible to empirically distinguish true chemical effects from mechanical ones, especially in heterogeneous reactions. In modern synthesis, so-called false sonochemistry is closely related to mechanochemistry and illustrates the advantages of using pressure waves in chemistry [8].

HC, a part of cavitational chemistry, also enables efficient catalysis under mild conditions by generating cavitation at low energy consumption. Easier scaling-up facilitates large-scale applications in several chemical processes, mainly in aqueous media such as oil hydrolysis, polymerization and depolymerization as well as oxidation reactions [9] and pollutant degradation [10]. HC use in organic synthesis and catalysis has not yet been explored as deeply as acoustic cavitation, but it is a powerful tool which has captured both academic and industrial interest [11].

Cavitation phenomena are able to dramatically enhance the reaction rates of several chemical conversions by means of mechanical effects in heterogeneous processes and chemical induction in homogeneous systems. Besides shortening reaction times and improving yields, cavitation may also induce higher selectivities while simplifying experimental

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Fig. 1. US probe transducers, A) Cup horn bath, B) Cup horn cavitating tube, C) Immersion horn.

procedure and workup. Synthetic protocols involving metal catalysis have long been a favorite and most rewarding topic in sonochemistry. The majority of such studies have focused on heterogeneous reactions performed in water or aqueous media [12], considered the solvent of choice in sonochemistry thanks to the excellent cavitation it facilitates from room temperature up to 50–60 °C. Besides being inexpensive, abundant, non-toxic and environmentally friendly, water can also be used as a dispersing medium under US. In addition to satisfying the above criteria, water also causes special effects in reactions that arise from intra- and inter-molecular non-covalent interactions and which lead to assembly processes.

As stated by Sheldon (1996), in green procedures "The best solvent is no solvent and if a solvent (diluent) is needed it should preferably be water" [13]. Sonochemical reactions in water often bring to the fore peculiar reactivities and selectivities that are not observed under anhydrous conditions [14]. In this respect, the development of water-tolerant catalysts and reagents has rapidly become an area of intense research.

One of the main limitations in the scale up of sonochemical equipment is the energy consumption. The flow and loop US reactors stand out above classic batch US reactors thanks to their greater efficiency and flexibility as well as lower energy consumption. Fig. 2 shows a multi-horn flow reactor in which the reacting mixture is pumped through the system.

2. Use of surfactants

Organic reactions in water are often difficult because most organic reactants, including catalysts, are insoluble in water. Surfactants, due to their dual hydrophobic and hydrophilic nature, can ride out this problem by forming micelles and promoting reactions in water. An example is p-dodecyl-benzenesulfonic acid (DBSA), a Brønsted acid-surfactant that combines catalytic action and the ability to form stable colloidal dispersions with water-insoluble substrates that facilitate reaction outcome. Proton acid catalyzed organic reactions can be carried out in the presence of water using DBSA [15]. It has been widely reported that US, when compared with conventional protocols, accelerates reactions via a more intimate mixing of reagents and enhances the activity of an insoluble catalyst by enlarging its surface area [16]. Li et al. reported two examples of improvements in organic syntheses in water via the use of DBSA under US. Firstly [17], they reported a green, efficient procedure for the preparation of bis(indolyl)methanes from indole and aromatic aldehyde in the present of DBSA in aqueous solution (Scheme 1).

The same group reported the DBSA catalyzed synthesis of amidinohydrazones under US in water. These versatile synthetic intermediates were obtained via the condensation of 1,5-diaryl-1,4-pentadiene-3ones with aminoguanidine hydrochloride [15] (Scheme 2).

The nucleophilic attack of the amino group to the carbonyl is followed by water elimination and DBSA catalysis is important in creating a good leaving group. The condensation of the solid–liquid mixture is strongly promoted by the emulsification generated by US in the presence of BDSA that increase the interfacial contact area of the reagents. The comparison between US and simple stirring reported in Table 1 evidenced the advantages of sonochemical catalysis, with shorter reaction times and higher yields.

Li et al. [18] reported a simple, efficient procedure for the deoximation of keto- and aldoximes to the corresponding carbonyl compounds using silica sulfuric acid/paraformaldehyde in water in the presence of sodium dodecylsulfonate (SDS) under US. The formation of ketones and aldehydes from oximes is useful because oxime serves as an efficient protective group for carbonyls, which are extensively used for the purification of carbonyl compounds. A typical deoximation protocol requires harsh conditions and reagents, sustained heating under reflux, a tedious work-up and may generate side products. Silica sulfuric acid is an excellent candidate for sulfuric acid or chlorosulfonic acid replacement in organic reactions and does not entail limitations such as the destruction of acid sensitive functional groups, the use of rather toxic solvents and expensive reagents (Scheme 3).

Sonochemical deoximation reactions were carried out on aldoximes in good yields using silica sulfuric acid in the presence of SDS. Experiments carried out under silent conditions gave comparable yields but in a much longer reaction times. The various substituents on the benzene ring affect product yield. When ketoximes that contain electrondonating groups on the benzene ring were used as substrates, ketones were obtained in good yields (92–97%), whereas ketoxime containing electron-withdrawing group gave the ketones in about an 80% yield. In addition, the catalyst can be reused three times without significant decrease in activity. It is worth noting that no Beckmann rearrangement products were formed.

3. Small catalyst molecules

Organic reactions catalyzed by small organic molecules have drawn a great deal of attention. Urea derivatives may coordinate carbonyl groups



Fig. 2. Multi-horn flow reactor (developed at the University of Turin in collaboration with Danacamerini sa.).

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Scheme 1. Sonochemical preparation of bis(indolyl)methanes.

and activate them via hydrogen bonding. Computational studies also indicated that hydrogen bond donors are able to provide two or more hydrogen atoms to bind the oxygen atoms in carbonyl groups. Thus, various carbonyl group urea catalyzed reactions have been developed. Li et al. [19] used urea in water to catalyze the synthesis of 2,2'-arylmethylene *bis*(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) derivatives from aromatic aldehydes and 5,5-dimethyl-1,3-cyclohexanedione under US (Scheme 4).

The main advantages of this procedure over some other reported methods are shorter reaction time, simpler work-up and lower environmental impact. Phase transfer catalysts have been used in previous reports of this reaction, however, they are more expensive and dangerous than urea as they are able to transfer chemicals from water into animal tissues.

The availability, cost effectiveness and non-toxic properties of glycine have prompted its use as a catalyst and organo-base in synthetic chemistry. Datta and Pasha [12] have reported a one-pot multicomponent synthesis of 2-amino-4*H*-chromenes from aryl-aldehydes, malononitrile and resorcinol at 28–30 °C in water under US, using glycine as an organo-catalyst (Scheme 5).

The use of a polar solvent was indispensable as the reaction yields the Knoevenagel condensation adduct as the major product when carried out in non-polar solvents, while only trace amounts of the desired product were obtained in solvent-free conditions. This clearly indicates that water is essential for shifting the reaction to the product side and probably stabilizes the transition state. In the presence of water, the reaction not only went efficiently to completion (9–45 min) but also gave excellent yields. By comparing sonochemical with silent conditions in similar reaction times, yield improved from a range of 25–47% up to 89–95%.

4. Multi-component reactions

Multi-component reactions (MCRs) have become a hot topic in organic synthesis in recent years on account of their atom economy, efficiency, rapidity and environmental friendliness. MCRs that lead to various heterocyclic scaffolds are particularly useful for the creation of chemical libraries of 'drug-like' molecules for biological screening, since the combination of three or more small molecular weight building blocks in a single operation leads to high combinatorial efficacy. The



Table 1

Reaction times and yields under US and under silent conditions.

		US		Simple stirring	
R ₁	R ₂	Time (h)	Isolated yield (%)	Time (h)	Isolated yield (%)
4-Cl	4-Cl	2	85	2 (4)	51 (58)
$4-CH_3$	$4-CH_3$	2	87	6	65
Н	4-0CH ₃	2	90	2	45
4-0CH ₃	4-0CH ₃	2	91	5	80
Н	4-Cl	2.5	94	2.5	67
Н	4-CH ₃	2.5	95	8	72

design of MCR in water is another attractive area as water is a cheap, safe and environmentally benign solvent. Banitaba et al. [20] have described a green and simple sonochemical protocol in water for assembling 2-amino-4,8-dihydropyrano[3,2-b]pyran-3-carbonitrile scaffolds via a three-component reaction with kojic acid, malononitrile and aromatic aldehydes (Scheme 6).

This is a green sonochemical method that furnishes a shorter reaction time, good yields, no need for a base, simple workup and excellent functional group tolerance. The Authors compared reactions carried out under sonochemical and silent conditions (high-speed stirring), at 30 °C yields were 78 vs 50%, and at 60 °C 88 vs 74% respectively.

Ziarati et al. [21] have combined the advantages of US and nanotechnology to design a new MCR method for the preparation of pyrazolone derivatives using CuI nanoparticles under US irradiation (Scheme 7).

A simple and green process for the preparation of nano-size copper iodide via sonication was also reported. These nanoparticles were used as an efficient catalyst for the synthesis of 2-aryl-5-methyl-2,3dihydro-1H-3-pyrazolones via the US-assisted four-component reaction of hydrazine, ethyl acetoacetate, aldehyde and β -naphthol in water. US can increase the surface area of the catalyst and supply additional activation through efficient mixing and enhanced mass transport. Acoustic cavitation is indeed a very effective means for the dispersion of solids and liquids emulsification by reducing the particle/droplet size, the total surface area of the phase boundary increases at the same time.

This MCR in water gave excellent yields in short reaction times and showed a wide range of applicability as it could be used with different substrates, including aromatic aldehydes and hydrazines to provide the corresponding pyrazolones in good yields.

Another example of the synergy between a nanosized catalyst and US was reported by Rostamizadeh et al. [22], which developed an efficient procedure for the synthesis of 1,8-dioxo-octahydroxanthene derivatives. In this method, several types of aromatic aldehyde, which contained both electron-withdrawing and electron-donating groups, were rapidly converted to the corresponding 1,8-dioxo-octahydro xanthenes in good to excellent yields. The reaction was carried out in water under US irradiation, using nanosized MCM-41-SO₃H, which is an ordered mesoporous material based nanocatalyst with covalently anchored sulphuric acid groups inside the mesochannels. The combined use of MCM-41-SO₃H and US is best explained in terms of the intercalation of guest molecules (reactant) into host nanoreactors. The intense localized pressure and temperature regions generated by US help the insertion of reactants into the nanocatalyst channels and the inherent Brönsted acidity of the -SO₃H groups, which are capable of bonding with the aldehyde carbonyl oxygens, assist in the generation of ionic intermediates via reactant activation. In other words, ionic intermediates are generated inside the



Scheme 2. Sonochemical preparation of amidinohydrazone derivatives.

Scheme 3. Sonochemical reaction of deoximation.

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Scheme 4. Urea-catalysed condensation of aromatic aldehydes and 1,3-cyclohexanedione.

nanoreactor by the abundant energy released during bubble collapse and the catalytic effect of the –SO₃H groups (Scheme 8).

This sonochemical procedure improved reaction rates and yields but failed in the presence of Lewis acids, such as ZrOCl₂, ZrOCl₂/K10, NaHSO₄ and NaHSO₄/SiO₂. Cavitation activated the catalyst while sonic waves favored the intercalation of guest molecules into the host nanoreactor. When similar reactions were carried out under silent reactions (simple stirring) much longer reaction times and higher temperature were required and poor yields were achieved (silent 60-90 °C vs US \rightarrow yields 0–50% vs 95%). The reaction worked well both when carried out with electron-withdrawing (NO₂, Cl, CN) and electrondonating groups (Me, MeO), and afforded various xanthene derivatives in 80-99% yields. This is a general method and can accommodate a variety of functional groups.

The synthesis of xanthenes and benzoxanthenes plays an important role in pharmaceutical chemistry because of their relevance as building blocks in drug design.

Mahdavinia et al. [23] have explored the use of US-assisted heterogeneous catalysis in the synthesis of various aryl-14H-dibenzo[a,j]xanthenes. They reported a general, efficient and eco-friendly method that gave excellent yields via the use of a recyclable silica supported ammonium dihydrogen phosphate (NH₄H₂PO₄/SiO₂) catalyst which provided several advantages such as low toxicity, low cost, ease of handling and high catalytic activity making it a potential new green catalyst. The experimental procedure for the efficient one-pot preparation of aryl-14Hdibenzo[a,j]xanthene is remarkably simple and requires no toxic organic solvents or inert atmosphere. The reactions were carried out at 40 °C with a 1:2 mol ratio aldehyde/ β -naphthol mixture in H₂O (US, 25 kHz) (Scheme 9).

A number of different benzoxanthenes were obtained in high yields while the mild reaction conditions respected sensitive functional groups, such as the methoxy group, which often undergoes cleavage in strongly acidic reaction media.

Indole and indoline fragments are important moieties found in a large number natural products and medicinal agents and some spiroannulated indoline with heterocycles in the 3-position have shown high biological activity. The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids. Therefore, a number of methods have been reported for the preparation of spirooxindole fused heterocycles. Bazgir et al. [24] have reported the synthesis of spiro [indoline-3,40-pyrazolo[3,4-b]pyridine]-2,60(10H)-dione via a threecomponent condensation reaction between 4-hydroxycumarin, isatines and 1H-pyrazol-5-amines in the presence of the inexpensive p-



Scheme 6. Sonochemical multi-component reaction with kojic acid, malononitrile and aromatic aldehydes.

toluenesulfonic acid (p-TSA) catalyst in water under US irradiation (Scheme 10).

The reaction was investigated with and without US irradiation at the same temperature (60 °C) and in various solvents in order to better understand the role of US and the solvent effect. It was found that the use of US leads to a higher yield in all reactions and that water was the solvent of choice. The method is simple, starts from readily accessible commercial starting materials and provides biologically interesting spirooxindole derivatives in good yields. Moreover, it is worth noting that two C-C and one C–O bonds are formed during the creation of a spirooxindole fused pyrazolopyridine in this one-pot, three-component process.

Although not MCRs, it is worth mentioning that Dandia et al. [25] have reported the novel aqueous mediated synthesis of other substituted spiro-compounds from the reaction of spiro [indole-3,20-oxiranes] with thioacetamide in the presence of an LiBr catalyst under sonication in water (Scheme 11).

They compared the use of a low-intensity ultrasonic (LIU) laboratory cleaning bath (which gives economic benefits) and a high-intensity US probe system (HIU). They also performed the reaction under microwave radiation (MW) and under conventional stirring and used solvents other than water, as reported in Table 2.

MW was not as efficient as US in the synthesis of spiro derivatives as there was no appreciable increase in yield, but was still better than the thermal method which gave a mixture of products. It appears that sonochemical activation is principally due to the mechanical effects of cavitation in this heterogeneous system.

Khorrami et al. [26] have developed a facile, one-pot and three component procedure for the preparation of oxindole derivatives from dimedone, 1H-pyrazol-5-amines and isatins in water under US and in the presence of a non-toxic and readily available InCl₃ catalyst (Scheme 12). For the sake of comparison the reaction was also carried out under silent conditions with high speed stirring. In all experiments vields were lower than 30%.

The use of water as the reaction medium provides remarkable benefits as it is highly polar and therefore immiscible with most organic compounds. Moreover, the water soluble catalyst resides and operates in the aqueous phase making the separation of the organic materials easy. This procedure, which was developed for oxindole synthesis, was applied to the reaction of 1,3-diphenyl-1H-pyrazol-5-amine and isatins to obtain 3,3-bis(5-amino-1H-pyrazol-4-yl)indolin-2-ones in good yields in 30-60 min (Scheme 13).



Scheme 5. Glycine-assisted sonochemical multi-component reaction of malononitrile, resorcinol and aromatic aldehydes.



Scheme 7. Sonochemical preparation of pyrazolones via MCR.

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Scheme 8. Sonochemical 1,8-dioxo-octahydroxanthenes preparation catalysed by MCM-41-SO₃H

5. Aza-Michael reactions

The conjugate addition of amines to conjugated alkenes (commonly known as the aza-Michael reaction) is a key step in the synthesis of various complex natural products, antibiotics, α -amino alcohols and chiral auxiliaries. Bandyopadhyay et al. [27] have developed a US-induced eco-friendly procedure for the aza-Michael reaction. No metallic, enzymatic or corrosive catalysts or solid supports are used in this method. The present procedure furnishes notable advantages that include a simple operational procedure, environmentally benign reaction conditions, short reaction times and high product yields (Scheme 14).

The procedure was tested on several amines and unsaturated ketones, a nitrile and an ester. The results can be considered nothing short of spectacular as all the US-assisted reactions in water were very rapid when compared to reactions in organic solvents under identical conditions, while no catalyst was necessary to complete the reaction. All reactions were completed within 10 min and gave the desired products in excellent yields (86-99%), high regio- and chemo-selectivity and no side products were formed. The presence of water most probably accelerated the reaction via the formation of hydrogen bonds with the carbonyl group which increased the electrophilic character at the β -carbon of the unsaturated compounds, resulting in significantly increased nucleophilic attack by the amine. On the other hand, hydrogen bond formation between the water oxygen atom and the amine hydrogen-atom increased the nucleophilic power of the amine N-atom. In addition, water has a high dielectric constant and a permanent dipole moment which allows the coupling between the oscillating electric field and molecular tumbling to occur, giving highly efficient heating. Under US, water therefore acts as a pseudo-organic solvent at the elevated temperature inside the hot spots.

6. Aldol reactions

Cravotto et al. [16] have used US in water as a means to re-consider the aldol reaction, one of the oldest organic reactions. It was found that this reaction takes place under US, furnishing good yields in aqueous heterogeneous systems, generally without requiring any catalyst. The aldol reaction of acetophenone and a number of non-enolizable aldehydes afforded the aldol in acceptable to good yields in aqueous NaOH under sonication (18 kHz, 280 W), with only two exceptions (Scheme 15).

Benzaldehyde reacted very quickly with acetone to afford the corresponding aldol (4-hydroxy-4-phenylbutan-2-one) in a good yield (72%), while the same reaction surprisingly only yielded cinnamaldehyde (79%) when carried out with acetaldehyde. The reaction between benzaldehyde and a number of 1,3-dicarbonyl compounds afforded, in all cases, the corresponding 2:1 adducts. This approach provides easy access to bis(benzylidene) derivatives. The aldol reaction between acetophenones



Scheme 9. Sonochemical preparation of benzoxanthenes.



Scheme 10. Sonochemical preparation of spirooxindole derivatives.

and excess formaldehyde offered ready access to libraries of new polyols (Scheme 16).

The above series of aldol reactions, when carried out in aqueous suspension under US irradiation, afforded a number of aldols that cannot usually be isolated in practical yields because they immediately undergo elimination. This efficient approach offers ready access to polyols and bis-benzylidene adducts.

7. Suzuki-Miyaura couplings

This reaction has gained considerable prominence as the biaryl motif is present in a wide variety of common organic compounds. Cravotto et al. [28] have reported the Pd-catalyzed Suzuki homocoupling of boronic acids which was successfully carried out in water under highintensity US using a Pd/C catalyst. Heterogeneous Pd/C catalysis facilitated work up and purification and was used without adding phosphine ligands. Compared to other expensive and air-sensitive Pd catalysts, Pd/ C can be more easily handled, recovered from the reaction mixture via simple filtration and reused (Scheme 17).

Reaction rates and yields were strongly influenced by the choice of oxidant and excellent results were obtained using either molecular oxygen or 3-bromo-4-hydroxycoumarin. The 3-arylation of the latter, carried out via the Suzuki procedure, failed and exclusively afforded the homocoupling products which were symmetric biaryls. Other oxidants (e.g., Cu(II) acetate and Cu(II) nitrate) were not effective.

The US-assisted reaction was much faster (reaction time reduced to a minimum of 90 min), gave higher isolated yields and even afforded homocoupling products that could not be obtained without resorting to US. The dioxane-water medium was replaced with pure water and



Scheme 11. Sonochemical reaction of spiroindole-oxiranes with thioacetamide catalysed by LiBr.

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Table 2

Reaction conditions and yield for the synthesis of spiro[indole-1,3-oxathiolane].

Entry	Solvent	Conditions	Time (min/h)	Yield (%)
1	H ₂ O	US bath (LIU)	50 min	80
2	H_2O	US (HIU)	7 min	84
3	H_2O	MW	20 min	76
4	DMF	MW	15 min	70
5	THF	Stirring	5 h	50
6	H ₂ O	Stirring	5 h	37

triphenylphosphine was omitted without any loss in efficiency. Furthermore, switching from KF to less expensive NaOAc did not affect the reaction adversely. Therefore, the use of US meant that the Pd/C-catalyzed Suzuki homocoupling of numerous arylboronic acids was carried out under more advantageous conditions (in pure water, in the absence of ligands and using oxygen as the oxidant) and afforded the corresponding biaryls in good yields. These features are great advantages for the large-scale preparation of these compounds.

Other groups have reported examples of the Suzuki reactions of phenylboronic acid and a series of arylhalides in water under sonication. Zhang et al. [29] investigated the use of cyclopalladated ferrocenylimine as a kind of phosphine-free compound that demonstrates almost all the properties of palladacycle catalysts. Their synthetic convenience and facile modification make them attractive while their air moisture stability makes these catalysts easy to handle. They reported examples of Suzuki cross-coupling reactions that were catalyzed by ligand-free cyclopalladated ferrocenylimines in water. It was possible to couple arylhalides, including electron-withdrawing aryl chlorides, with phenylboronic acid in moderate to good yields under both sonication and conventional heating. Compared with conventional heating, the reaction was strongly accelerated by US (Scheme 18).

8. Suzuki reaction in flow reactors

Flow reaction strategies have attracted huge amounts of interest from organic chemists in recent years, particularly from those interested







Scheme 13. Sonochemical preparation of indolin-2-one derivatives via MCR.

in process development and non conventional techniques [30]. Although many organic reactions with water soluble substrates/reagents are carried out smoothly in aqueous media, some reactions with rigorously heterogeneous substrate/reagent combinations proceed very poorly in sealed tubes or in continuous flow systems leading to incomplete conversion. A great deal of effort has been made to overcome the problem and the introduction of a co-solvent or the use of water soluble substrates and catalysts are particularly noteworthy. Homogeneous catalysts often create difficulties during product isolation. The application of easily separable and recyclable heterogeneous catalysts allows for cleaner work-up and avoids time-consuming and tedious catalyst purification. US irradiation, however, can offer an additional advantage in aqueous phase organic synthesis as it causes a greater number of molecular collisions under mild conditions. P. Shil et al. [31] have developed a fast, efficient and cost effective process for the synthesis of a solid supported palladium(0) nano/microparticle catalyst (SSPd) and investigated its applications. They reported a methanol/water mediated flow reaction technique for the Suzuki cross-coupling of aryl halides (Cl, Br and I) with phenyl boronic acid under sonication. The use of a mild base, the recyclability of the SS-Pd catalyst and the ambient temperature meet the essential precepts of a green chemical approach for a Suzuki reaction based biaryl synthesis (Scheme 19).

The SS–Pd catalyst was found to be very stable in aqueous media, easily separable and recyclable for up to five runs without significant loss in activity. The main disadvantage of large scale Suzuki reactions under thermal conditions is often the volatility of the haloarenes



R1, R2 = H, Alkyl X = CO_2Me , COMe, CN, COOEt

Scheme 14. Sonochemical Aza-Michael reaction.

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Scheme 15. Sonochemical aldol reaction of non-enolizable aldehydes with acetophenone.

which separate from the reaction mixture resulting in the incomplete conversion of the substrates, whereas by-product formation decreased in a flow system under temperature control, thus facilitating the large scale process. The up-scaling of biaryl synthesis to 5 g scale was successfully achieved and may be of industrial interest in the future. US enables to carry out the reaction in methanol–water by increasing the solubility of the solid base (K₂CO₃), which drove the reaction to the products with satisfactory yields.

9. Phase-transfer catalysis

A further method with which to perform reactions between mutually insoluble reactants is the use of phase-transfer catalysts under mild conditions which can provide high conversion and product selectivity. Phase-transfer catalysis reaction systems can be divided into several categories according to the phases present. The third-liquid phase transfer catalysis (TLPTC) is a reaction system where the catalyst is highly concentrated within a separate phase which is located between the aqueous phase and a low-polar or non-polar solvent phase meaning that the intrinsic reaction can be greatly promoted. TLPTC can be considered a green technology because of its high reaction rates, mild reaction conditions, easy product and catalyst separation, lack of halidecontaining solvent and easier catalyst recovery. The combined use of US and liquid-liquid phase-transfer catalysis has provided significant improvements in reaction rate. Yang and Chiu [32] investigated the green synthesis of 4-acetylphenyl benzoate via the reaction of sodium 4-acetylphenoxide in the aqueous phase and benzoyl chloride in the organic phase by combining US with a novel dual-site phase-transfer catalyst in TLPTC conditions and a batch reactor. Generally, benzoyl chloride can easily react with water in the liquid-liquid system interface to give benzoic acid. The hydrolysis side reaction of benzoyl chloride in synthesizing esters not only reduces product yield but also causes difficulty in the subsequent separations. This drawback can be solved by the TLPTC system. In the present US irradiation facilitated tri-liquid system, the formed third-liquid phase was employed to reduce the contact



Scheme 16. US-assisted polyols synthesis by aldol reaction of acetophenones and formaldehyde.



Scheme 17. US-assisted Suzuki homocoupling in the presence of O_2 or 3-bromo-4-hydroxycoumarin.

between water and benzoyl chloride and to enhance the overall reaction rate effectively. A novel dual-site phase-transfer catalyst, 1,4bis(tributylammoniomethyl) benzene dibromide, was prepared from the reaction of *p*-xylylene dibromide and tributylamine and used to conduct the benzoylation of sodium 4-acetylphenoxide via US-assisted third-liquid phase-transfer catalysis. The overall reaction rate was greatly enhanced by up to 6 times when using US irradiation (28 kHz at 300 W) as compared to silent conditions. A US-assisted solid-liquid phase-transfer catalysis (U-SLPTC) was used for the esterification of sodium 4-hydroxybenzoate with benzyl bromide [33]. The quasi-aqueous phase was generated by adding water and the prepared catalyst. US can effectively enhance the overall reaction rate and the liquid-jets generated by the US waves were able to remove the surface deposited side-product. The reaction mechanism of U-SLPTC was identified by analyzing the variation and distribution of the catalytic intermediate between phases and resulted in a greener esterification procedure.

10. Sonochemical reactions in aqueous biphasic systems

Reactions following a ionic mechanism in heterogeneous liquid–liquid biphasic systems, are strongly affected (rates and yields) by mechanical effects associated with sound waves to an extent depending on surface tension, density and temperature. Even bigger sonochemical activation occurs in electron-transfer mechanism paths [3]. These biphasic systems will also be sensitive to the mechanical component of shock waves in addition to chemical activation. Water is one of the most common solvent in sonochemistry, however, a little organic solvent can be beneficial in some cases or even crucial [34].

10.1. Oxidation of secondary alcohols

Mills and Holland [35] have studied the effect of US on the kinetics of the oxidation of octan-2-ol and other secondary alcohols using sodium bromate and mediated by ruthenium tetraoxide (RuO_4) which is generated in situ from RuO_2 in a biphasic system. RuO_4 is a common oxidant



Scheme 18. Sonochemical Suzuki reaction with palladacycle catalysts.

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Scheme 19. Sonochemical Suzuki reaction with SSPd catalysts.

in organic synthesis that has proven itself to be selective in the oxidation of primary alcohols to aldehydes, ethers to esters, amides to imides, alkenes to aldehydes and aldehydes to acids. Besides the excellent mixing that sonication provides, US generates a steady-state level with the formation of an emulsion of aqueous microdroplets with high interfacial surface area.

10.2. Bromination of aromatic compounds

Lévêque et al. [34] have reported the molybdate-catalyzed bromination of various aromatic compounds in the presence of KBr/H_2O_2 in an aqueous/chloroform biphasic system. This reaction occurred rapidly under US irradiation, whereas it did not take place at all under conventional mechanical stirring (1400 rpm) (see Table 2).

The bromination of phenol did not occur after 2 h of stirring, whereas bromophenol was obtained in good yields under US irradiation (71% and 81% at 36.6 and 480 kHz, respectively). Anisole and acetanilide were also efficiently brominated in 4 h under sonication. US was decisive in initiating the reaction over a large range of frequencies. Yields strongly decreased in the absence of H_2O_2 , although the sono-production of H_2O_2 was expected under prolonged sonication. US may accelerate the decomposition of the peroxomolybdate–hypobromite intermediate and thus accelerate the catalytic cycle. As the reaction takes place smoothly at pH values of below two, the activation mechanism of the Mo-catalyzed bromination by US can be attributed to the secondary indirect sonochemical effect, i.e., the lowering of pH via the sonolysis of CHCl₃–H₂O solvents. The strategic use of the secondary sonochemical effect, such as the in situ lowering of pH by sonolysis should be taken into account when applying US (Table 3).

11. Conclusions

Catalysis in aqueous systems under sonochemical conditions is well documented however, further diffusion and scaling up, should entail the development of more specific catalysts and a cost analysis. Besides the low environmental impact, chemists can take advantage from recent progress in US reactor engineering with new reliable flow-

Table 3

Reaction conditions and yields for the molybdate-catalyzed bromination of aromatic compounds.

Substrate ^a	Time (h)	Yield % ^b (o:p ratio)			
		Stirring (1400 rpm)	US (36.6 kHz)	US (480 kHz)	
он	2	0	71 (26:74)	81 (27:73)	
_/	2	-	17 (32:68) ^c	15 (33:67) ^c	
<>-<	4	0	96 (4:96)	75 (4:96)	
	4	0	92 (0:100)	100 (0:100)	

 $^a\,$ Substrate 0.1 mmol, H_2O_2 0.1 mmol, KBr 0.126 mmol, (NH_4)_6Mo_7O_{24} 0.005 mmol, solvent CHCl_3 1 mL + H_2 O5 mL, temp. 20 °C.

^b Determined by GC-MS (internal standard: dodecane).

^c Without H₂O₂.

systems well suited for application in practical protocols for catalysis in water.

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