

Sonochemistry Part 2—Synthetic Applications

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1 Introduction

A large number of articles have been published over the past few years which describe the various applications of ultrasound to chemical synthesis. These have encompassed organic, organometallic, inorganic, and polymer chemistry together with some aspects of catalysis. As a result of this the majority of chemists will be aware of the developing science of sonochemistry, to the extent that some have already been tempted to experiment with ultrasound in their own laboratories. This, the second part of the review, is designed to provide an overview of the synthetic aspects of sonochemistry for chemists in both academic and industrial laboratories.

Sonochemistry is not a new subject—it was under active investigation over 50 years ago! There are literature references to applications in polymer and chemical processes in the 1940s.^{1,2} The renaissance of the subject which has occurred over the past few years is undoubtedly due to the more general availability of commercial ultrasonic equipment. In the 1960s the ultrasonic cleaning bath began to make its appearance in metallurgy and chemical laboratories. Having seen the way in which these baths cleaned soiled glassware and dispersed immiscible organic solvents in aqueous detergent it was not surprising that chemists began to consider using them to enhance chemical reactivity—as indeed we ourselves did in the early 70s. It was not long before some remarkable syntheses were achieved in this manner, one of the first being that reported by Fry in 1978 involving the use of ultrasonically dispersed mercury in acetic acid for the reduction of α,α' -dibromoketones to a mixture of α -acetoxyketones.³ The reaction was performed by dissolving the dibromoketone in acetic acid and dispersing a small amount of mercury in the medium by means of an ultrasonic laboratory cleaning bath, for 1–4 days. After this publication, and others of similar type, interest in the application of ultrasound to chemical synthesis started growing. In the 1970s ultrasonic cell disruptors began to be used on a regular basis in biology and biochemistry laboratories. Such instruments offered the chance of introducing greatly increased ultrasonic power into chemical reactions at a modest cost. A number of reviews on the chemical applications of ultrasound have been published over the past few years.^{4–11}

¹ A. Weissler, *J. Chem. Educ.*, 1948, 28.

² H. Mark, *J. Acoust. Soc. Am.*, 1945, 16, 183.

³ A. J. Fry and D. Herr, *Tetrahedron Lett.*, 1978, 19, 1721.

⁴ J.-L. Luche, *L'actualité chimique*, 1982, 21.

⁵ P. Boudjouk, *Nachr. Chem. Tech. Lab.*, 1983, 31, 78.

⁶ T. J. Mason, *Lab. Pract.*, 1984, 13.

In part 1* the types of ultrasound which are used in chemistry were broadly divided into *power ultrasound*, between 20 and 100 kHz, which is used for cleaning, plastic welding, and to affect chemical reactivity and *high frequency ultrasound*, in the 2—10 MHz range, which is used in medical scanning, chemical analysis, and the study of relaxation phenomena.

For the majority of synthetic chemists interest in sonochemistry will be in power ultrasound because this provides a form of energy for the modification of chemical reactivity which is different from that normally used *i.e.* heat, light, and pressure. Power ultrasound produces its effects *via* cavitation bubbles. These bubbles are generated during the rarefaction cycle of the wave when the liquid structure is literally torn apart to form microbubbles which collapse in the compression cycle. It has been calculated that pressures of hundreds of atmospheres and temperatures of thousands of degrees are generated on collapse of these bubbles.¹² The synthetic chemist will be mainly concerned with reactions in solution, and the effects of ultrasound in such cases are best summarized in terms of four different reaction types.

A. Reactions involving Metal Surfaces.—There are two types of reaction involving metals: (i) those in which the metal is a reagent and is consumed in the process and (ii) those in which the metal functions as a catalyst. It is tempting to explain that the ultrasonically induced enhancements in chemical reactivity which are observed in such heterogeneous reactions are due simply to the well-known cleaning action of ultrasound. It is certainly true that sonication will clean the surface of a metal and that dirty surfaces can inhibit a chemical reaction. It is because of surface contamination that many of the metals used in chemical reactions are cleaned before use *e.g.* copper is washed with EDTA to remove surface salts and iodine is commonly used in the preparation of a Grignard reagent to remove oxide film and promote magnesium reactivity. In some respects sonication serves a similar purpose to these chemical techniques—it exposes clean or reactive surface to the reagents involved. Examination of irradiated surfaces by electron microscopy reveals 'pitting' of the surface of the metal which acts both to expose new surface to the reagents and to increase the effective surface area available for reaction. The pitting is thought to be caused by two possible processes: (i) the implosion of cavitation bubbles formed from seed nuclei on the surface and (ii) microstreaming of a jet of solvent onto the surface when a cavitation bubble collapses in the solvent close to it.

In many cases, however, it has been shown that the cleaning effect alone is not

* 'Sonochemistry. Part 1 The Physical Aspects' by John P. Lorimer and Timothy J. Mason, *Chem. Soc. Rev.*, 1987, 16, 239.

⁷ T. J. Mason, *Ultrasonics*, 1986, 24, 245.

⁸ K. S. Suslick, *Modern Synthetic Methods*, 1986, 4, 1.

⁹ K. S. Suslick, *Adv. Organomet. Chem.*, 1986, 25, 73.

¹⁰ D. Bremner, *Chem. Br.*, 1986, 22, 633.

¹¹ RSC Sonochemistry Symposium, University of Warwick, 1986, *Ultrasonics*, 1986, 25, January.

¹² M. A. Margulis, *Russ. J. Phys. Chem.*, 1976, 50, 1.

sufficient to explain the extent of the sonochemically enhanced reactivity. In such cases it is thought that sonication serves to sweep reactive intermediates, or products, clear of the metal surface, thus presenting renewed clean surface for reaction. This sweeping effect would not be so effective under normal mechanical agitation.

B. Reactions involving Powders or other Particulate Matter.—In heterogeneous reactions involving solids dispersed in liquids the overall reactivity, just as with the metal surface reactions described above, will depend upon the available reactive surface area. In the case of powders (metallic or non-metallic) ultrasonic 'pitting' will lead to fragmentation and consequent particle size reduction. The significant feature of such reductions is that there appears to be an optimum size for the reduction beyond which ultrasound has no further effect.

One important benefit of particle size reduction and simultaneous surface activation is the possibility of using sonication in place of a phase-transfer catalyst (PTC) as a means of assisting heterogeneous solid-liquid reactions.

C. Emulsion Reactions.—Ultrasound is known to generate extremely fine emulsions from mixtures of immiscible liquids. In such emulsions there is a dramatic increase in the interfacial contact area between the liquids *i.e.* an increase in the region over which any reaction between species dissolved in the liquids can take place. As with the powder reactions this allows the use of ultrasound in place of a PTC. In some cases, however, it has been found that a combination of sonication and PTC has a better overall effect than either of the two techniques alone.

D. Homogeneous Reactions.—Thus far we have attributed ultrasonically enhanced chemical reactivity to the mechanical results of cavitation bubble collapse. That this cannot be the whole reason for the effect of ultrasound on reactivity is clear when we turn our attention to homogeneous reactions. In Part 1, for example, we discovered that light can be emitted from sonicated water (sonoluminescence) and that ultrasound can fragment liquid alkanes or accelerate the solvolysis of 2-chloro-2-methylpropane in aqueous alcoholic solvents.

The answer lies in the actual process of cavitation bubble collapse. The microbubble does not enclose a vacuum—it contains vapour from the solvent and any volatile reagents so that, on collapse, these vapours are subjected to the enormous increases in both temperature and pressure referred to above. Under such extremes the solvent and/or reagent suffers fragmentation to generate reactive species of the radical- or carbene-type, some of which are high enough in energy to fluoresce. In addition the shock wave produced by bubble collapse, or even by the propagating ultrasonic wave itself, could act to disrupt solvent structure and could in this way influence reactivity by altering solvation of the reactive species present.

The practising chemist might thus expect to use ultrasound for a range of applications and perhaps achieve one or more of a number of beneficial effects:

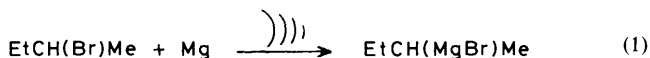
- (1) to accelerate a reaction or permit use of less forcing conditions

- (2) to reduce the number of steps which are required using normal methodology
- (3) to make use of cruder reagents
- (4) to initiate reaction, often without the need for additives
- (5) to reduce any induction period involved
- (6) to drive a reaction through an alternative pathway.

In the succeeding sections of this article a number of these exciting synthetic prospects will be examined.

2 Synthetic Applications of Ultrasound

A. Organometallic Compounds.—The use of ultrasound in the synthesis of organometallic compounds, especially of the soft metals, has seen intense activity in recent years. The first report was published in 1950 by Renaud,¹³ who obtained improved yields in the direct metallation of alkyl halides with Li, Mg, and Al in undried diethyl ether using ultrasound (960 kHz, 2 Wcm⁻²). This method was unsuccessful with Zn, Hg, Ca, and Be. Surprisingly, this work was not followed up for thirty years until Luche and Damanio published the sonochemical preparation of Grignard and organo-lithium reagents, a paper which signalled the renaissance of organometallic sonochemistry.¹⁴ In their studies the ultrasonic equipment used was neither a purpose-built ultrasonic generator nor a piece of equipment 'borrowed' from other disciplines but a common laboratory cleaning bath (50 kHz). In the case of Grignard reagents initiation occurs instantaneously without the aid of activators and in commercial undried ether. n-Propyl, n-butyl, and phenyl lithium were prepared in >90% yield by reaction of the appropriate bromide with Li wire (or Li-2% Na sand); in these cases the reaction commenced immediately, although with secondary and tertiary alkyl bromides longer periods of sonication were required.



Today one of the most common chemical applications of ultrasound is the initiation of a reluctant Grignard reaction by immersion of the reaction vessel in an ultrasonic cleaning bath. This technique has been put on a more quantitative basis with some studies of the induction times for formation of Grignard reagents with various grades of ether (equation 1) (Table 1).¹⁵

In order to induce reaction after the extended periods required under normal conditions, it was necessary to activate the magnesium by crushing pieces of the metal. In no case, however, with or without sonication, was there any significant difference in the yield of organometal, the figures being 65, 55, and 55%. This work was performed in an ultrasonic bath and it is significant that prior sonication of the

¹³ P. Renaud, *Bull. Soc. Chim. Fr., Ser. 5*, 1950, 17, 1044.

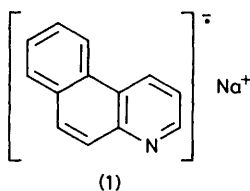
¹⁴ J.-L. Luche and J. C. Damanio, *J. Am. Chem. Soc.*, 1980, **102**, 7926.

¹⁵ J. D. Sprich and G. S. Lewandos, *Inorg. Chim. Acta*, 1982, **76**, 1241.

Table 1 Preparation of butan-2-yl magnesium bromide in ether (50 kHz bath at 50 °C)

Diethyl ether	Method	Induction time
pure, dried (0.01% water)	non-u/s	6—7 min
(0.01% ethanol)	u/s	< 10 s
reagent grade (0.5% water)	non-u/s	2—3 h (<i>crushed</i>)
(2.0% ethanol)	u/s	3—4 min
50% saturated (0.01% ethanol)	non-u/s	1—3 h (<i>crushed</i>)
	u/s	6—8 min

metal in ether had no effect on the induction time. This clearly eliminates simple surface cleaning as the source of the effect and suggests that sonication removes adsorbed water from the metal surface.



Ultrasound facilitates the production of arene radical anion salts of the alkali metals.^{16–18} In a comparative study of several methods for the synthesis of sodium isobenzoquinoline (1) the method using an ultrasonic probe (25 kHz) was found to be superior to the others; the reaction was complete in 45 min compared with 48 h for the non-ultrasonic control.

Similarly, rate enhancements were reported for the formation of sodium naphthalene in commercial undried THF using a 36 kHz cleaning bath.¹⁸

Improvements in yields and reaction times have been reported for the preparation of the alkyl aluminium halides.¹⁹ The yields of isobutenyl aluminium sesquichloride [(2) R = CH₂=CMeCH₂, X = Cl] from the reaction of Al and isobutenyl chloride were found to be higher in dioxane than in diethyl ether but were unaffected by changes in ultrasound frequency in the range 32—36 kHz. It would appear that the better cavitation which is possible in the higher boiling dioxane is important. In another study²⁰ a comparison of methods using ultrasonic agitation

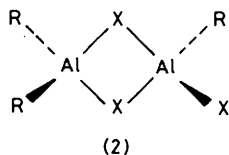
¹⁶ W. Slough and A. R. Ubbelohde, *J. Chem. Soc.*, 1957, 918.

¹⁷ M. W. T. Pratt and R. Helsby, *Nature*, 1959, **184**, 1694.

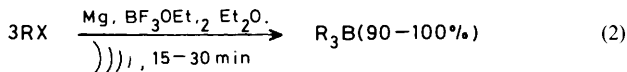
¹⁸ T. Azuma, S. Yanagida, H. Sakurai, S. Sasa, and K. Yoshino, *Synth. Commun.*, 1982, **12**, 137.

¹⁹ A. V. Kurchin, R. A. Nurushev, and G. A. Tolstikov, *Z. Obshch. Khim.*, 1983, **53**, 2519.

²⁰ K. F. Liou, P. H. Yang, and Y. T. Lin, *J. Organomet. Chem.*, 1985, **294**, 145.



with those using mechanical stirring showed that the reaction of bromoethane with Al in THF to give ethyl aluminium sesquibromide [(2), R = Et, X = Br] was complete in 19 min with ultrasound at room temperature, while no reaction at all occurred in the mechanically stirred control reaction.

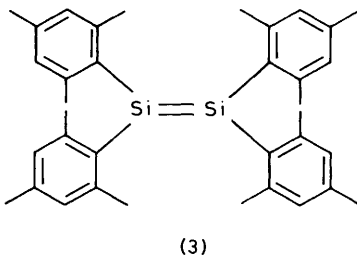


Sonication using a 20 kHz probe gives significant improvements in the synthesis of organoboranes *via in situ* generated Grignard reagents (equation 2).²¹

Symmetrical trialkyl boranes such as Pr³B are obtained with this method giving purities >99%, compared with only 93% purity using the usual hydroboration route. The ultrasonic method also has distinct advantages in the synthesis of hindered boranes, thus (1-naphthyl)₃B is obtained in 93% yield in 15 min compared with 91% yield in 24 h in the absence of ultrasound.

The formation of disilanes and distannanes from the reaction of trialkylchlorosilanes or stannanes with lithium in THF is facilitated by low intensity ultrasound (cleaning bath, 50 kHz).²² The method has been used to prepare the novel tetramesitylsilene (3) in 90% yield. The fact that other workers were able to obtain only cyclic trisilanes²³ while trying to repeat this work underlines the importance of specifying all sonochemical parameters (equipment, power, apparatus) when reporting sonication results.

The use of low intensity ultrasound (cleaning bath) also leads to increased yields and a reduction in reaction time from 48 to 6 h in the preparation of tris(phenyldimethylsilyl)methane.²⁴



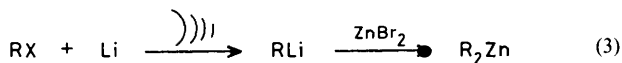
²¹ H. C. Brown and U. S. Racherla, *Tetrahedron Lett.*, 1985, **26**, 4311.

²² P. Boudjouk, B. H. Han, and K. R. Anderson, *J. Am. Chem. Soc.*, 1982, **104**, 4992.

²³ S. Masamune, S. Murakami, and H. Tobita, *Organometallics*, 1983, **2**, 1464.

²⁴ C. Eaborn, P. B. Hitchcock, and P. D. Lickiss, *J. Organomet. Chem.*, 1984, **269**, 235.

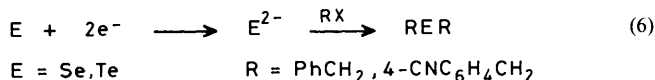
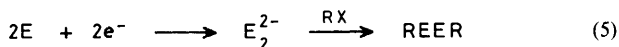
There have been numerous reports of the use of ultrasound to generate organozinc reagents.²⁵⁻²⁹ In many cases the organozinc is formed directly from the metal and organic halide and then reacted *in situ* with electrophiles. This important simplification in technique for organic synthesis will be described later. A more reliable route to organozinc compounds involves the *trans*-metallation of zinc halides with organolithium reagents (equation 3).^{29,30}



Although quite good yields of diarylzinc can be obtained by a one-pot procedure using aryl halide, zinc bromide, and lithium wire in THF in a cleaning bath (50 kHz),²⁹ more consistent results are obtained for dialkyl zincs by using a sonic horn (see Equipment section below).³⁰ Toluene containing a little THF was also found to be a better solvent in this reaction, which again suggests that the more powerful cavitation in the higher boiling toluene is beneficial. Using this system quantitative yields of dialkylzinc are obtained in 20–30 min compared with only 75% yield in 2 h without ultrasound.



Ultrasound also facilitates the formation of organocopper compounds by transmetallation of copper(I) iodide (equation 4) with *in situ* generated alkyl- or aryl-lithium in 1:1 diethyl ether/THF in a cleaning bath (50 kHz, 90W).³¹



Scheme 1

A novel route to organoselenium and organotellurium compounds involves the

²⁵ P. Knochel and J. F. Normant, *Tetrahedron Lett.*, 1984, **25**, 1475.

²⁶ B. H. Han and P. Boudjouk, *J. Org. Chem.*, 1982, **47**, 751.

²⁷ T. Kitazume and N. Ishikawa, *J. Am. Chem. Soc.*, 1985, **107**, 5186.

²⁸ T. Kitazume and N. Ishikawa, *Chem. Lett.*, 1982, 137.

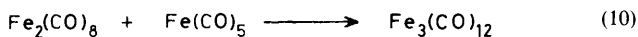
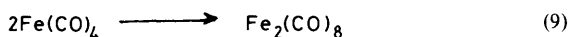
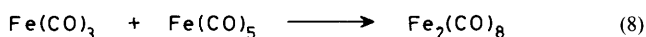
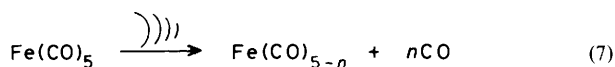
²⁹ J.-L. Luche, C. Petrier, J. P. Lansard, and A. E. Greene, *J. Org. Chem.*, 1983, **48**, 3837.

³⁰ C. Petrier, J. C. de S. Barbosa, C. Dupuy, and J.-L. Luche, *J. Org. Chem.*, 1985, **50**, 5761.

³¹ J.-L. Luche, C. Petrier, A. L. Gemal, and N. Zirka, *J. Org. Chem.*, 1982, **47**, 3805.

ultrasonic acceleration of the electroreduction of Se or Te to their anions followed by reaction with electrophiles, RX, (Scheme 1).³²

B. Ligand Displacement Reactions.—Substitution in metal complexes proceeds mainly by dissociation processes. In systems which are coordinatively saturated and kinetically inert ligand dissociation is generally induced either thermally or photochemically. The local high temperatures and pressures which are produced during cavitation bubble collapse have also been shown to be an effective means of promoting these reactions. In a study of the sonolysis of $\text{Fe}(\text{CO})_5$ in hydrocarbon solvents Suslick and co-workers^{33,34} have obtained results which are different from both the thermal and photochemical methods. The thermolysis of $\text{Fe}(\text{CO})_5$ above 100°C produces mainly finely divided iron, ultraviolet photolysis gives $\text{Fe}_2(\text{CO})_9$ via reaction of the intermediate $\text{Fe}(\text{CO})_4$ with $\text{Fe}(\text{CO})_5$, whereas sonolysis yields $\text{Fe}_3(\text{CO})_{12}$ and finely divided iron in a ratio which is dependent on solvent vapour pressure. The clusterification to $\text{Fe}_3(\text{CO})_{12}$ is favoured in high vapour pressure solvents such as heptane in which $>82\%$ yield is obtained, whereas in low vapour pressure solvents such as decalin only a 4.7% yield is obtained. These results are clearly related to the energetics of cavitation bubble collapse which is inversely proportional to solvent vapour pressure. The clusterification, being the process of lower activation energy, is the favoured process in the lower boiling point solvents which produce weaker cavitation. The formation of $\text{Fe}_3(\text{CO})_{12}$ during sonolysis is considered to arise mainly from the multiple coordinatively unsaturated species $\text{Fe}(\text{CO})_3$. The principal reactions are shown in Scheme 2.



Scheme 2

In the presence of added ligands such as phosphines and phosphites substitution occurs to give $\text{LFe}(\text{CO})_4$, $\text{L}_2\text{Fe}(\text{CO})_3$, small amounts of $\text{L}_3\text{Fe}(\text{CO})_2$ and, only in low vapour pressure solvents, finely divided iron. The ratio of $\text{LFe}(\text{CO})_4$ to

³² B. Gautheron, G. Tainturier, and C. Degrand, *J. Am. Chem. Soc.*, 1985, **107**, 5579.

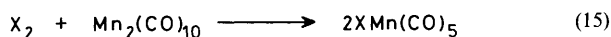
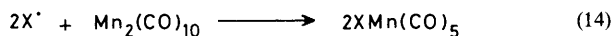
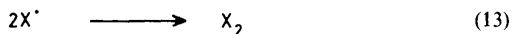
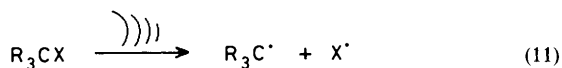
³³ K. S. Suslick, P. F. Schubert, and J. W. Goodale, *J. Am. Chem. Soc.*, 1981, **103**, 7324.

³⁴ K. S. Suslick, J. W. Goodale, P. F. Schubert, and H. H. Wang, *J. Am. Chem. Soc.*, 1983, **105**, 5781.

$L_2Fe(CO)_3$ remains constant on prolonged sonolysis which suggests that $LFe(CO)_4$ is inert to further sonochemical substitution.

Sonochemical substitution of other metal carbonyl systems such as $Mn_2(CO)_{10}$, $Re_2(CO)_{10}$, $Cr(CO)_6$, $Mo(CO)_6$, $W(CO)_6$, and $Ru(CO)_5$ illustrates the generality of the technique.^{35,36} The sonochemical substitution of the dimeric $Mn_2(CO)_{10}$ and $Re_2(CO)_{10}$ proceeds without rupture of the metal-metal bond which is more akin to thermal rather than photochemical substitution.

Sonolysis of $Mn_2(CO)_{10}$ and $Re_2(CO)_{10}$ in halogenocarbon solvents give rise to halogenopentacarbonyl metal complexes due to a secondary reaction with solvent-derived radicals (Scheme 3).



Scheme 3

Sonolysis using a cleaning bath (80 W, 50 kHz) at room temperature of $Fe_2(CO)_9$ in benzene in the presence of alkenyl epoxides gives good yields of η^3 -allylironcarbonyl lactone complexes, which are easily oxidized to lactams and lactones (Scheme 4).³⁷

In a similar way sonolysis of $Fe_2(CO)_9$ in the presence of dienes gives good yields of the (η^4 -diene) $Fe(CO)_3$ complexes.³⁸

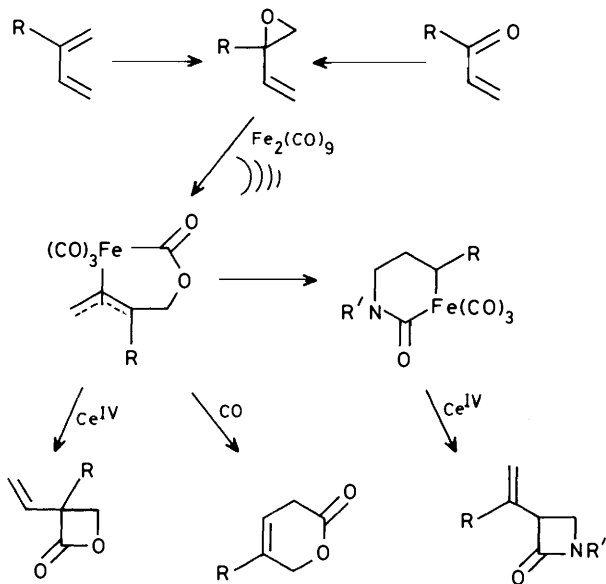
C. Reactive Metal Powders and Catalysts.—Reduction of metal salts in the presence of ultrasonic fields has been a major area of study. In general the ultrasonic field produces fine dispersions and cavitation phenomena give rise to clean surfaces containing an increased number of dislocations, which are widely considered to be the active sites in catalysis.

³⁵ K. S. Suslick and P. F. Schubert, *J. Am. Chem. Soc.*, 1983, **105**, 6042.

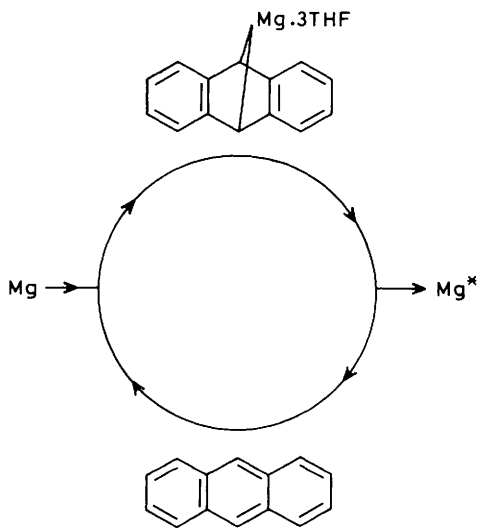
³⁶ G. Wilkinson, *Chem. Br.*, 1983, 986.

³⁷ A. M. Horton, D. M. Hollinshead, and S. V. Ley, *Tetrahedron*, 1984, **40**, 1737.

³⁸ S. V. Ley, C. M. R. Low, and A. D. White, *J. Organomet. Chem.*, 1986, **302**, C13.



Scheme 4

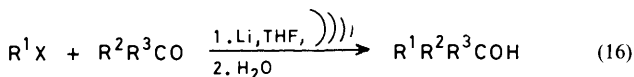


Scheme 5

Reduction of metal halides with lithium in THF at room temperature in the presence of low intensity ultrasound (cleaning bath, 50 kHz) gives rise to metal powders which have reactivities comparable to those of the so-called Rieke powders prepared by reduction of metal halide with potassium in refluxing THF.^{39,40} Thus powders of Zn, Mg, Cr, Cu, Ni, Pd, Co, and Pb were obtained in <40 min by this ultrasonic method compared with reaction times of 8 h using the experimentally more difficult Rieke method. Reductions with lithium in THF which were mechanically stirred took up to 26 h. In cases where the metal halides are insoluble in THF the addition of naphthalene as an electron-transfer agent is recommended. These powders show enhanced reactivity in organic syntheses involving metals *e.g.* the Reformatsky and Ullmann coupling reactions.

A highly active form of magnesium is formed when magnesium powder in THF is subjected to low intensity ultrasound (cleaning bath) in the presence of anthracene.⁴¹ The anthracene forms an electron-transfer complex with magnesium and this effectively acts as a phase-transfer agent (Scheme 5).

The magnesium produced in this way is an excellent reducing agent for metal salts and when the reduction is carried out in the presence of Lewis base ligands it is a useful route to organo-transition metal complexes, for example η^5 -cyclopentadienyl complexes Cp_2M ($M = V, Fe, Co$), η^3 -allyl complexes ($M = Co, Ni$), alkene complexes ($M = Ni, Pd, Pt, Mo$), and phosphine complexes ($M = Pd, Pt$). The magnesium-anthracene complex is also a convenient route to allyl Grignard reagents at temperatures as low as $-35^\circ C$. This eliminates the coupling of allyl magnesium halides with the starting alkyl halide which is a common side-reaction with conventional methods (equation 16).⁴²



$R^1 = 1^\circ, 2^\circ, 3^\circ$ — alkyl, alkyl, vinyl

yield 76–100%
15–40 min

Reduction of transition metal halides with sodium sand in the presence of CO at low pressure (1–5 atm) at $10^\circ C$ under prolonged sonication (20 kHz probe, 100 W cm^{-2}) in THF gives reasonable yields of metal carbonyl anions $[W_2(CO)_{10}]^{2-}$ 47%, $[Mo_2(CO)_{10}]^{2-}$ 54%, $[Nb(CO)_6]^-$ 51%, $[V(CO)_6]^-$ 35%.⁴³ Metal halides of low solubility in THF give reduced yields. These results are quite remarkable as such compounds are usually obtained by reduction of metal halides at high temperatures (100–300 $^\circ C$) and high CO pressures (100–300 atm) in an autoclave. It is postulated that these reactions proceed by a mechanism in which CO traps partially reduced metal species at the sodium surface. It is also

³⁹ P. Boudjouk, D. P. Thompson, W. H. Ohrbom, and B. H. Han, *Organometallics*, 1986, 5, 1257.

⁴⁰ R. D. Rieke, *Acc. Chem. Res.*, 1977, 10, 301.

⁴¹ H. Bonnermann, B. Bogdanovic, R. Brinkman, D. W. He, and B. Spliethoff, *Angew. Chem., Int. Ed. Engl.*, 1983, 22, 728.

⁴² W. Opolzer and P. Schneider, *Tetrahedron Lett.*, 1984, 25, 3305.

⁴³ K. S. Suslick and R. E. Johnson, *J. Am. Chem. Soc.*, 1984, 106, 6856.

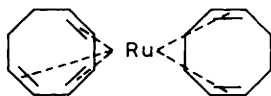
conceivable that the reactions proceed *via* excited CO molecules which are produced during the cavitation process.

Sonication (35 kHz cleaning bath) is a simple and convenient method for preparing colloidal alkali metals.⁴⁴ Thus the typical blue colour of colloidal potassium is produced in a few minutes in toluene or xylene. However, sodium is dispersed in xylene but not in toluene. This is another example of the more powerful cavitation in the higher boiling solvent being an important factor in determining reaction products. These colloidal systems are particularly useful in condensations of the Dieckmann type and in the generation of ylide intermediates in Wittig reactions. Such potassium dispersions are also effective in the desulphurization of sulphones.⁴⁵

Highly dispersed mercury emulsions in acetic acid are conveniently generated by sonication (cleaning bath).³ Such emulsions are efficient in promoting the reductive substitution of α, α' -dibromoketones.

Sonication of commercial copper-bronze in DMF at 60 °C using a 20 kHz probe reduces the average particle size of the copper to a finite limit of 20 μm and is also an efficient means of cleaning the copper surface by the removal of metal salts.⁴⁶ Copper treated in this way gives improvements in Ullmann coupling reactions.

Reduction of ruthenium chloride with zinc dust in methanol containing 1,5-cyclooctadiene in a 50 kHz cleaning bath gives a 93% yield of $(\eta^6\text{-}1,3,5\text{-cyclooctatriene})(\eta^2\text{-}1,5\text{-cyclooctadiene})\text{ruthenium}$ (4) compared with less than 35% yield using a two-stage non-ultrasonic method.⁴⁷



(4)

Reduction of metal salts in the presence of ultrasound has been widely used in the preparation of heterogeneous catalysts.⁴⁸ Palladium and platinum blacks prepared by reduction of aqueous solutions of metal salts with formaldehyde in ultrasonic fields of intensities between 0.4 and 14.6 Wcm^{-2} had up to 30% increase in surface area, increased paramagnetism, and higher background intensity of XRD patterns which indicates a higher concentration of atomic phase. These blacks gave increased activity in the decomposition of H_2O_2 , in the hydrogenation of hex-1-ene, and in the oxidation of ethanol. Interestingly the catalytic activity of the platinum blacks increased with increasing frequency (20 kHz, 548 kHz, 3 MHz)

⁴⁴ J.-L. Luche, C. Petrier, and C. Dupuy, *Tetrahedron Lett.*, 1984, **25**, 753.

⁴⁵ T. S. Chou and M. L. You, *Tetrahedron Lett.*, 1985, **26**, 4495.

⁴⁶ J. Lindley, J. P. Lorimer, and T. J. Mason, *Ultrasonics*, 1986, **24**, 292.

⁴⁷ K. Itoh, H. Nagashima, T. Ohshima, N. Ohshima, and N. Nishiyama, *J. Organomet. Chem.*, 1984, **272**, 179.

⁴⁸ A. N. Mal'tser, *Russ. J. Phys. Chem.*, 1976, 995.

of the ultrasound used in their production, whereas the palladium blacks showed the opposite trend; there is no obvious explanation for this.

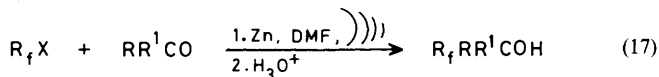
Increased surface area of metals deposited on alumina and silica gels can be obtained using ultrasonic techniques. Thus the reduction of solutions of platinum complexes in the presence of suspended silica gel subjected to ultrasound (440 kHz, 5 Wcm^{-2}) gave an 80% larger platinum surface on the gel compared with a control sample.⁴⁹

Alkene hydrogenation catalysts are usually noble metals (Pt, Pd) or specially activated metal powders. High intensity ultrasound has been used to activate nickel powders even at room temperature and pressure. Ultrasound also has a marked accelerating effect on the formation of intercalation compounds of a range of layered solids (e.g. ZrS_2 , V_2O_5 , TaS_2 , and MoO_3).⁵⁰

D. Ultrasound in Organic Synthesis.—(i) *Reactions at Carbonyl Functions.* Luche and Damiano¹⁴ have observed significant improvements both in yields and simplification of experimental techniques over conventional methodology in the Barbier reaction (equation 16)⁵¹ when the reactions are carried out in a simple ultrasonic cleaning bath (50 kHz).

Significant advantages of this method are that the reactions can be carried out in commercial undried THF and are largely free from side reactions such as reduction and enolization, which are common in conventional methodology. Even benzyl halides give yields in excess of 95% and very little Wurtz coupling, which often predominates with non-ultrasonic methods, has been observed.

For perfluorohalides the use of *in situ* sonochemically generated perfluorozinc is preferred to Li or Mg, which are normally used in the Barbier reaction, as perfluoroalkyl derivatives of these metals are prone to β -elimination to give alkenes (equation 17).^{27,52,53} Here it is necessary to use a higher boiling solvent such as DMF, which allows the more powerful cavitation needed to activate the zinc.



An elegant application of this method has enabled chiral perfluoroalcohols with 30–66% optical induction to be obtained from the reaction sequence shown in Scheme 6.⁵⁴

An alternative route to perfluoroalkyl alcohols is *via* the Barbier reaction of perfluoroaldehydes with *in situ* sonically generated alkyl or allyl Grignard reagents (equation 18).⁵⁵

⁴⁹ V. I. Shekhobalova and L. V. Voronova, *Vestn. Mosk. Univ., Ser. 2: Khim.*, 1986, **27**, 327.

⁵⁰ K. S. Suslick, D. J. Casadonte, M. L. H. Green, and M. E. Thompson, *Ultrasonics*, 1987, **25**, 56.

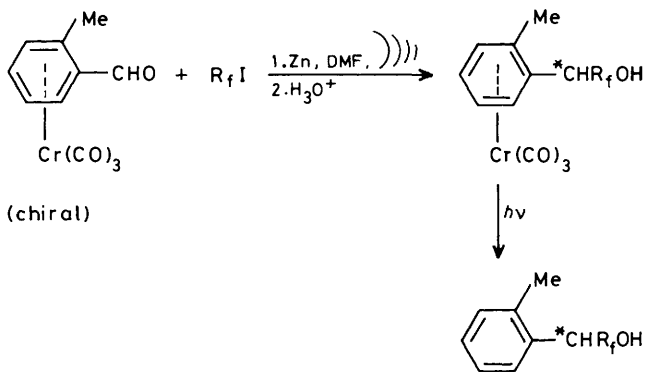
⁵¹ C. Blomberg and F. A. Hartog, *Synthesis*, 1977, 18.

⁵² N. Ishikawa and T. Kitazume, European Patent 0 082 252 Al, 1982.

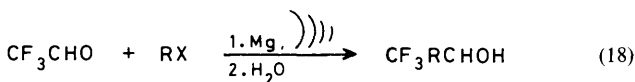
⁵³ T. Kitazume and N. Ishikawa, *Chem. Lett.*, 1981, 1679.

⁵⁴ A. Solladie-Cavallo, D. Farkharic, S. Fritz, T. Lazrak, and J. Suffert, *Tetrahedron Lett.*, 1984, **25**, 4117.

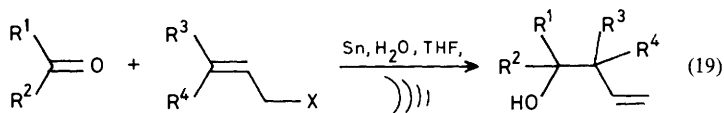
⁵⁵ N. Ishikawa, M. G. Koh, T. Kitazume, and S. K. Choi, *J. Fluorine Chem.*, 1984, **24**, 419.



Scheme 6

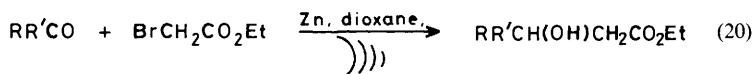


Allyl halides readily react under sonication with aldehydes and ketones in the presence of tin in aqueous THF (5:1) to give high yields of homoallylic alcohols (equation 19).⁵⁶



This reaction can also be performed non-ultrasonically with Zn but yields are consistently lower. Aldehydes react more quickly than ketones to the extent that in competition reactions and in molecules containing both functionalities reaction occurs almost exclusively at the aldehyde group.

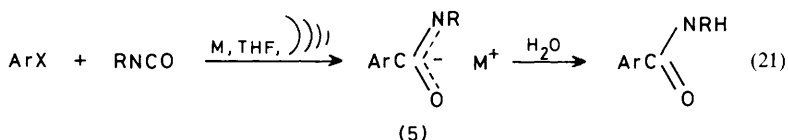
Low intensity ultrasound also facilitates the Reformatsky reaction of β -halogenoesters with aldehydes and ketones (equation 20).⁵⁷ Thus the ultrasonic method gave ethyl 2-hydroxyphenylacetate 98% in 5 min for $\text{R} = \text{C}_6\text{H}_5$ and $\text{R}' = \text{H}$ compared with 98% obtained in 1 h using activated zinc powders, 95% in 5 h using the $(\text{MeO})_3\text{B}/\text{THF}$ solvent system, and only 61% after 12 h using the conventional methodology. The ultrasonic Reformatsky reaction also gives good yields with perfluoroalkyl aldehydes.⁵⁵



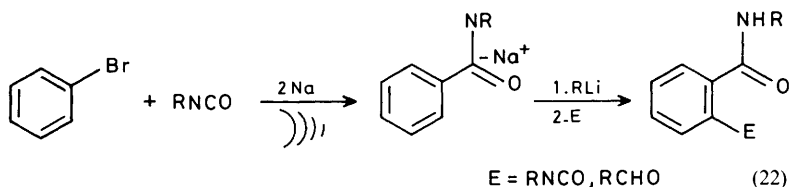
⁵⁶ C. Petrier, J. Einhorn, and J. L. Luche, *Tetrahedron Lett.*, 1985, **26**, 1449.

⁵⁷ B. H. Han and P. Boudjouk, *J. Org. Chem.*, 1982, **47**, 5030.

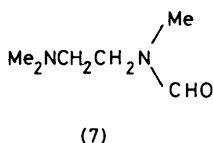
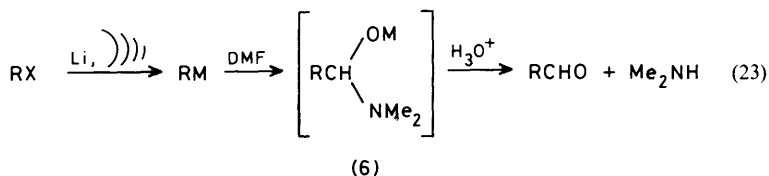
Alkali metals and magnesium react with aryl halides and alkyl isocyanates under the sonochemical Barbier conditions to give secondary aryl amides (equation 21).⁵⁸



Good yields of the intermediate (5) are obtained when $\text{M} = \text{Mg}$, and low yields with Li . The reaction with Na is slow but is greatly accelerated by the addition of 1 equiv. of HMPA. The intermediate (5) can be readily *ortho*-lithiated when $\text{M} = \text{Na}$ but complications occur with $\text{M} = \text{Mg}$ due to Mg-Li exchange. These *ortho*-lithiated intermediates readily react with a wide range of electrophiles to give *ortho*-substituted aryl amides (equation 22).



The low intensity ultrasonic generation of organolithium reagents and their application in the Bouveault reaction has resulted in higher yields of product aldehydes than in traditional methods (equation 23).⁵⁹

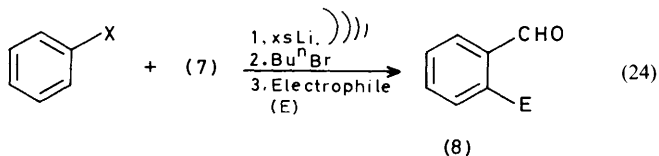


Non-ultrasonic Bouveault reactions suffer from numerous side reactions, although the method is improved when DMF is replaced by more elaborate (and

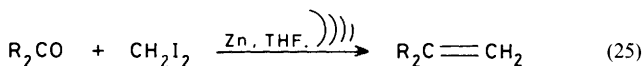
⁵⁸ J. Einhorn and J.-L. Luche, *Tetrahedron Lett.*, 1986, **27**, 501.

⁵⁹ C. Petrier, A. L. Gemal, and J.-L. Luche, *Tetrahedron Lett.*, 1982, **23**, 3361.

expensive) formamides such as (7). There is no advantage to be gained, however, by using an extra chelating group such as (7) in the sonochemical route since in this case the reaction with DMF is clean. Interestingly, while a change of solvent from THF to THP has little effect on the rate or yields of reactions carried out in a 50 kHz ultrasonic bath, no reaction was observed in diethyl ether under these conditions.⁶⁰ However, the reaction in diethyl ether was facilitated when ultrasonic irradiation of 500 kHz frequency was employed. The reason for this is not clear but it is tempting to suggest that at this higher frequency the cavitation bubbles, filled with volatile ether vapour, do not exceed the collapse limit radius before the compression cycle.

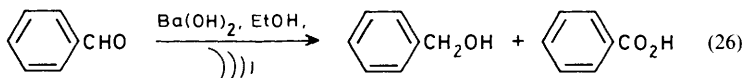


The Bouveault intermediates (6) derived from aryl halides and formamide with a chelating group such as (7) can be regioselectively *ortho*-lithiated. A great simplification of this method is made by sonication of the aryl halide and amide with excess lithium for 15 min followed by the dropwise addition of 1-bromobutane (instead of *n*-butyllithium), sonication for a further 30 min, followed by addition of the electrophile. For example, when the electrophile is iodomethane, a 70% yield of 2-substituted benzaldehyde [(8), E = Me] is obtained (equation 24).⁶¹



Good yields of alkenes are obtained by methylation of carbonyl compounds using zinc and diiodomethane in THF when the reaction is performed in an ultrasonic cleaning bath (53W, 41 kHz) at room temperature (equation 25).⁶² Higher yields are obtained with aldehydes than with ketones.

The Cannizzaro reaction under heterogeneous conditions (solid-liquid) catalysed by barium hydroxide is greatly accelerated by low intensity ultrasound (cleaning bath). Thus 100% yields of disproportionation products are obtained after 10 min sonication of benzaldehyde whereas no reaction is observed during this period in the absence of ultrasound (equation 26).⁶³



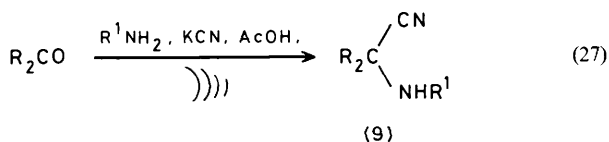
⁶⁰ J. Einhorn and J.-L. Luche, *Tetrahedron Lett.*, 1986, **27**, 1791.

⁶¹ J.-L. Luche, *Ultrasonics*, 1987, **25**, 40.

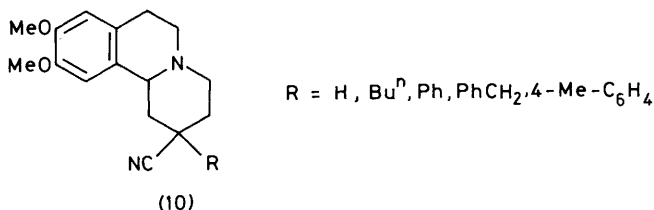
⁶² J. Yamashita, Y. Inoue, T. Kondo, and H. Hashimoto, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 2335.

⁶³ A. Fuentes and J. V. Sinisterra, *Tetrahedron Lett.*, 1986, **27**, 2967.

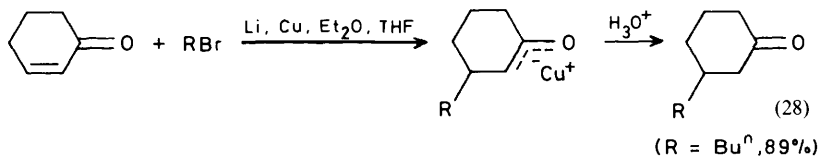
Ultrasonic acceleration of reaction is also observed in the Strecker synthesis of aminonitriles (9) (equation 27).⁶⁴



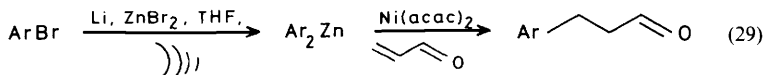
Using a simple cleaning bath the reaction times of these homogeneous reactions for the synthesis of aminonitriles (10) are reduced from 12 d to 20–25 h and yields are increased by up to 60%.



(ii) *Reactions at C-C Multiple Bonds.* 1,4-Addition to α,β -unsaturated carbonyl compounds. Traditionally organocopper reagents are used for these reactions.⁶⁵ Luche *et al.*³¹ have observed significant improvements in yields, rates, and ease of experimental technique when organocopper compounds generated by sonication (bath 50 kHz) of copper(I) compounds, organic halide, and lithium sand in diethyl ether-THF at 0 °C are allowed to react with α -enones (equation 28).



Ultrasonically generated (cleaning bath) arylzinc compounds are also excellent reagents for the 1,4-addition to α -enones and α -enals in the presence of catalytic quantities of Ni(acac)₂ (equation 29).⁶⁶



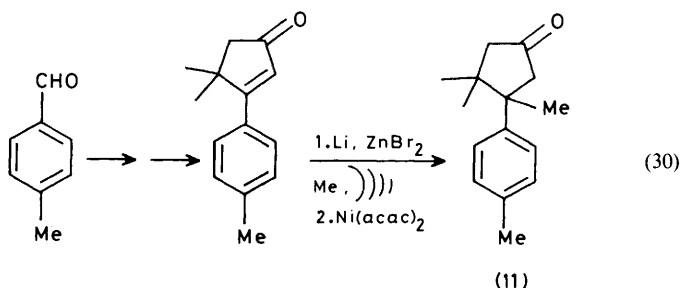
⁶⁴ J. Menedez, G. G. Trigo, and M. M. Sollhuber, *Tetrahedron Lett.*, 1986, **27**, 3285.

⁶⁵ G. H. Posner, *Org. React. (N.Y.)*, 1972, **19**, 1.

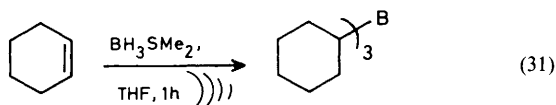
⁶⁶ J. C. S. Barboza, C. Petrier, and J.-L. Luche, *Tetrahedron Lett.*, 1985, **26**, 829.

Reactions with α -enals are performed at -40°C whereas those with α -enones are carried out at room temperature.

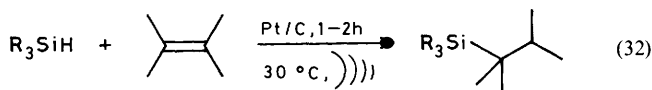
Extension of the method to include alkyl halides requires more intense sonication which is provided by a sonic horn (30 kHz) and a better medium for cavitation such as toluene-THF.^{30,67} Under these conditions good yields of alkyl-substituted ketones are obtained. The method has been successfully exploited to provide an efficient synthesis of β -cupranone (11) (equation 30).⁶⁸



Hydroboration. Low intensity ultrasound has a marked accelerating effect on hydroborations, which are traditionally very slow.⁶⁹ The effect is particularly marked in heterogeneous systems. For example, the preparation of tricyclohexylborane by hydroboration with $\text{BH}_3\cdot\text{SMe}_2$ in THF traditionally requires 24 h at 25°C , however, with irradiation, in an ultrasonic bath (50 kHz, 150 W) the reaction is complete in 1 h (equation 31).



Hydrosilation. Dramatic improvements in the platinum-catalysed hydrosilation of alkenes are obtained when reactions are carried out in an ultrasonic cleaning bath at 30°C , which is the lowest reported temperature for Pt-C catalysis (equation 32).^{70,71}



Hydroalkylation of alkynes and dienes. Ultrasonically promoted hydroperfluoro-

⁶⁷ C. Petrier, J.-L. Luche, and C. Dupuy, *Tetrahedron Lett.*, 1984, **25**, 3463.

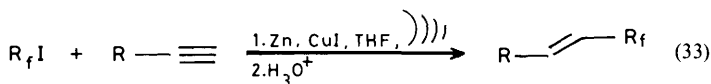
⁶⁸ A. E. Greene, J. P. Lansard, J.-L. Luche, and C. Petrier, *J. Org. Chem.*, 1984, **49**, 931.

⁶⁹ H. C. Brown and U. S. Racherla, *Tetrahedron Lett.*, 1985, **26**, 2187.

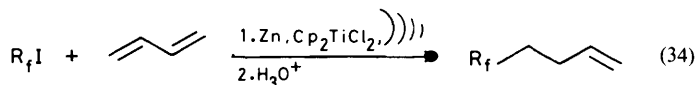
⁷⁰ B. H. Han and P. Boudjouk, *Organometallics*, 1983, **2**, 769.

⁷¹ B. H. Han and P. Boudjouk, *Tetrahedron Lett.*, 1981, **22**, 2757.

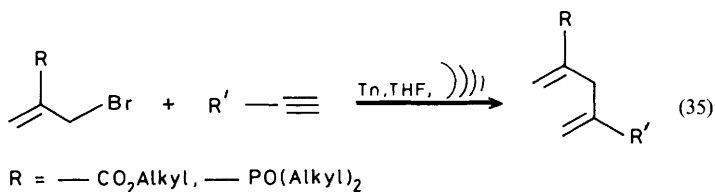
alkylation of alkynes with perfluoroalkylcuprates, which are generated *in situ* from the reaction of perfluoroalkyl halides with zinc and copper(I) iodide in THF, gives good yields of fluoroalkyl substituted alkenes. The reaction is regioselective but not stereospecific (equation 33).^{27,52}



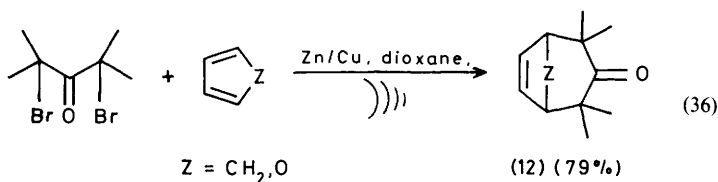
Similar results are obtained for the perfluoroalkylation of dienes catalysed by Cp_2TiCl_2 (equation 34).²⁷



Sonochemically generated highly functionalized allyl zinc intermediates readily add to alkynes to give dienes which can be used in various cyclizations (equation 35).²⁵



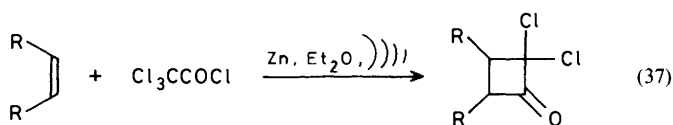
Cycloaddition. The zinc-promoted cycloaddition of α,α' -dibromoketones to 1,3-dienes is facilitated by ultrasound; highly hindered bicyclo[3.2.1]oct-6-en-3-ones (12) are easily accessible by this method (equation 36).⁷² This reaction in the absence of ultrasound gives only low to moderate yields and requires long reaction times (24 h).



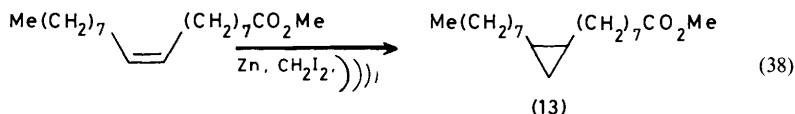
The [2 + 2] cycloaddition of dichloroketene to alkenes is also improved by ultrasound (equation 37).⁷³

⁷² N. Joshi and H. M. R. Hoffmann, *Tetrahedron Lett.*, 1986, **27**, 687.

⁷³ G. Mehta and H. S. P. Rao, *Synth. Commun.*, 1985, **15**, 991.



Short reaction times, good yields, ambient temperatures, and the use of ordinary zinc dust, instead of a zinc–copper couple, are significant advantages of this method. *Cyclopropanation.* In 1982 Repic described a sonochemical modification of the Simmons–Smith reaction using sonochemically activated zinc which avoided the sudden exotherm normally associated with the reaction. Thus (13) could be produced in 91% yield compared with 51% by the normal route.⁷⁴ Existing methods for this reaction relied upon activation of the zinc by using zinc–silver or zinc–copper couples and/or the use of iodine or lithium. In the sonochemical procedure no special activation of the zinc was required, indeed equally good and reproducible yields were obtained using zinc dust or even the metal in the form of mossy, rods, or foil. The ultrasonic source was again a cleaning bath (50 kHz). This methodology has been successfully scaled-up to run in a 22 dm³ vessel immersed in a 50 gallon bath.⁷⁵ For this scale-up the zinc was cast in two 800 g lumps (using 125 cm³ conical flasks as moulds). The reagents were methyl oleate (0.6 kg), diiodomethane (1.3 dm³), and dimethoxyethane (2.7 dm³). Under nitrogen at 100 °C the reaction yielded (13) 0.5 kg (82%) after 2.25 h (equation 38). The method



has several advantages over the normal method of cyclopropanation as a result of changing from zinc powder to the metal: there is a reduction in foaming (normally associated with ethene and cyclopropane formation); the exotherm is more evenly distributed (only a small clean area of metal is available throughout the reaction); the reaction can be controlled by removing the lump of metal from the reaction (this is not unlike the use of fuel rods in a nuclear reactor); the residual metal can be removed from the reaction as a lump.

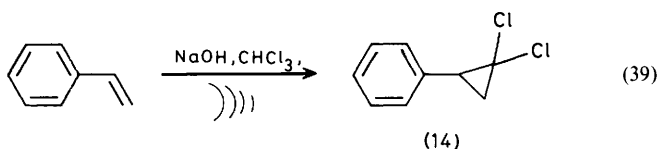
Ultrasound, when used in a solid–liquid reacting system, shows promise as a method of avoiding the use of phase-transfer catalysts. This has been found to be particularly relevant in the generation of dichlorocarbene by the direct reaction between powdered sodium hydroxide and chloroform.⁷⁶ The reported procedure is both simple and efficient in that irradiation (bath 45 kHz) of a stirred mixture of powdered NaOH in chloroform containing an alkene generates high yields of the corresponding dichlorocyclopropanes in 4 h at 40 °C. The results make it quite

⁷⁴ O. Repic and S. Vogt, *Tetrahedron Lett.*, 1982, **23**, 2729.

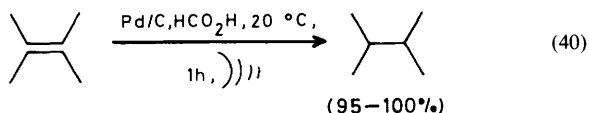
⁷⁵ O. Repic, P. G. Lee, and N. Giger, *Org. Prep. Proc. Int.*, 1984, **16**, 25.

⁷⁶ S. L. Regen and A. Singh, *J. Org. Chem.*, 1982, **47**, 1587.

clear that both mechanical stirring and ultrasonic irradiation are necessary for high reactivity, thus styrene is converted into (14), 96% in 1 h with both sonication and stirring, but the yield is reduced to 38% (20 h sonication only) and 31% (16 h stirring only) (equation 39).



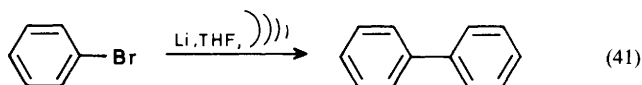
Hydrogenation. Formic acid and palladium-on-carbon are an effective couple for the hydrogenation of a wide range of alkenes at room temperature in the presence of low intensity ultrasonic fields (cleaning bath, 50 kHz) (equation 40).⁷⁷



Similarly, the hydrazine–palladium-on-carbon couple is also useful for the hydrogenation of alkenes in ethanol at room temperature using an ultrasonic bath.⁷⁸

A commercially useful example of a sonochemically enhanced catalytic reaction is the ultrasonic hydrogenation of soybean oil.⁷⁹ A three-phase non-aqueous system is used comprising liquid oil, H₂ gas, and solid catalyst. The catalyst was either 1% copper chromite or 0.1% Nysel (25% nickel) at 115 psig and 180 °C. The method employs a flow-through cell operating at 0.5–2.0 l h⁻¹ providing sonication at 20 kHz and leading to a tube reactor of dimension 120 feet × $\frac{1}{8}$ inch. This has considerable advantages over the currently used batch methods which require much longer reaction times.

(iii) *Coupling Reactions of Organometals and Organic Halides.* Ultrasonic radiation has been shown to be effective in promoting the homocoupling of organometallic intermediates. Good yields of homocoupled products obtained by reaction of alkyl, aryl, or aryl halides with lithium wire in THF immersed in an ultrasonic bath (117 W, 50 kHz) (equation 41).^{71,80} In the absence of ultrasound little or no reaction occurs.



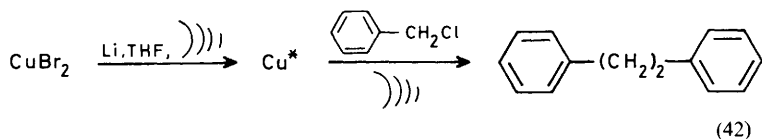
⁷⁷ P. Boudjouk and B. H. Han, *J. Catal.*, 1983, **79**, 489.

⁷⁸ D. H. Shin and B. H. Han, *Bull. Korean Chem. Soc.*, 1985, **6**, 247.

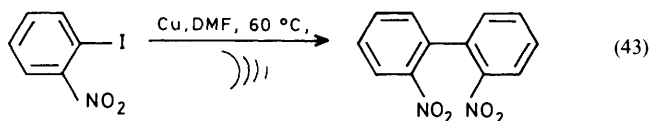
⁷⁹ K. J. Moulton, S. Koritala, and E. N. Frankel, *J. Am. Oil Chem. Soc.*, 1983, **60**, 1257.

⁸⁰ T. D. Lash and D. Berry, *J. Chem. Educ.*, 1985, **62**, 85.

Coupling of benzyl halides in the presence of copper or nickel powder generated by lithium reduction of the corresponding halides in the presence of ultrasound gives high yields of dibenzyl (equation 42).³⁹ The yields obtained when sonication is applied throughout the reaction are higher than those obtained in mechanically stirred reactions.

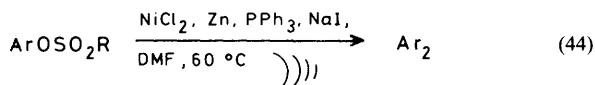


Ullmann coupling of activated aryl halides in DMF with high intensity ultrasound from a sonic horn gave a 64-fold increase in rate over a mechanically stirred control reaction (equation 43).⁴⁶

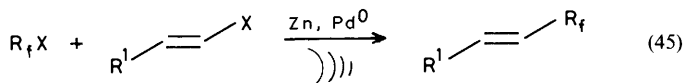


In this work a fourfold decrease in the particle size of the Cu was observed (see above), however, this alone was insufficient to explain the large rate increases observed when sonication was continued throughout the reaction. It would appear that ultrasound assists in the breakdown of reaction intermediates and/or the desorption of products.

An interesting Ullmann-type coupling of aryl sulphonates promoted by *in situ* generated nickel(0) complexes is also facilitated by ultrasound (equation 44).⁸¹ The method works best for triflates (R = CF₃); for tosylates (R = 4-methylphenyl) the rate is significantly lower.

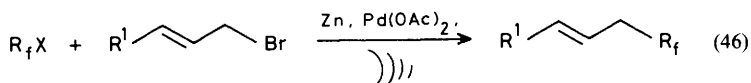


Sonication using a cleaning bath (35 or 45 kHz) has a beneficial effect in the cross-coupling reactions of perfluoroalkylzinc reagents with vinyl, allyl, or aryl halides (equations 45 and 46).^{27,52,53}

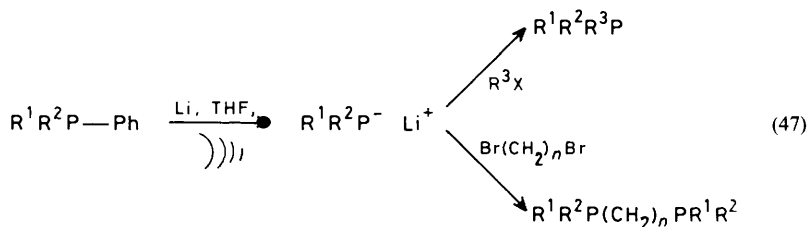


Aryl phosphorus bonds are readily cleaved by lithium in THF in the presence of low intensity ultrasound (cleaning bath) to give lithium dialkylphosphides which

⁸¹ T. Yamashita, Y. Inoue, T. Kondo, and H. Hashimoto, *Chem. Lett.*, 1986, 407.

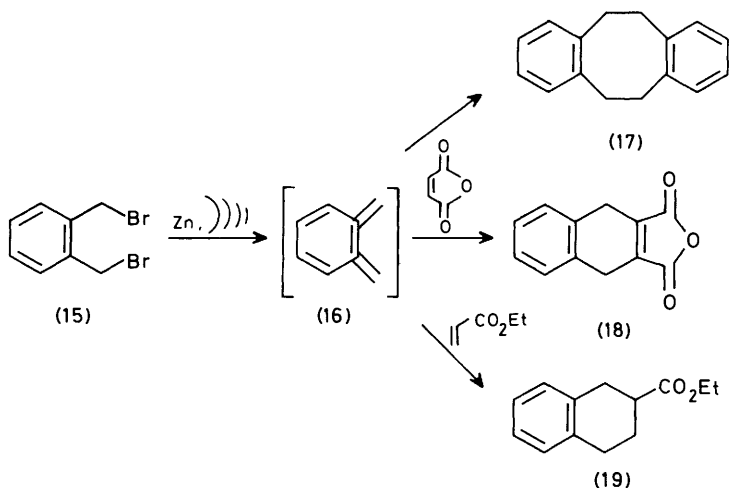


readily couple with alkyl halides to produce high yields of phosphanes (equation 47).^{82,83} Much higher rates are observed than for reactions using mechanical stirring.



(iv) *Dehalogenation.* Ultrasonic irradiation during the reaction between zinc and α, α' -dibromoorthoxylene (15) in dioxane yields a xylylene intermediate (16) which readily adds to any dienophiles in the reaction mixture affording high yields of adducts (18) and (19) as shown in Scheme 7.²⁶

In the absence of dienophile, polymer and about 10% of the dimer (17) are formed, although an 80% yield of the dimer can be obtained by reaction of (15) with



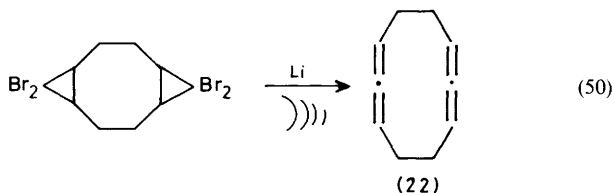
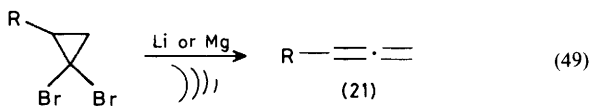
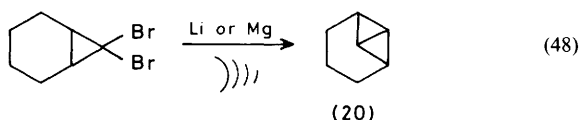
Scheme 7

⁸² T. S. Chou, J.-J. Ying, and C.-H. Tsao, *J. Chem. Res. (S)*, 1985, 18.

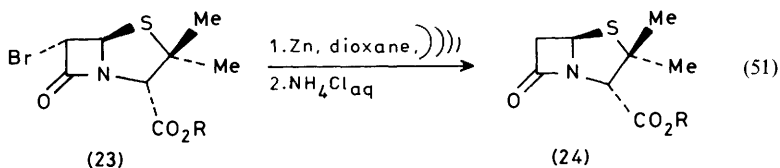
⁸³ T. S. Chou, C.-H. Tsao, and S. C. Hung, *J. Org. Chem.*, 1985, **50**, 4329.

Li (1 equiv.) in an ultrasonic bath.⁸⁴ There is no reaction in the absence of ultrasound. This technique for the generation of (16) has also been used in carbohydrate chemistry to produce compounds with A ring similarities to anthracyclonones.⁸⁵

Under the influence of ultrasound cyclopropylidines can be generated, without induction period, by the reaction of *gem*-dihalogenocyclopropanes and lithium, sodium, or magnesium in THF (but not pentane), which again emphasizes the importance of solvent in sonochemical reactions.⁸⁶ All three products (20) (equation 48), (21) (equation 49), and (22) (equation 50) were obtained in <20 min at 20 °C. Similar results were obtained for the less reactive dichloro-compounds using sodium sand in xylene.



Good yields of penicillinate esters (24) are obtained by the sonochemical debromination of the 6-bromopencillinate ester (23) with zinc (equation 51).⁸⁷



This method is more efficient, cleaner, and less expensive than those employing

⁸⁴ P. Boudjouk, R. Sooriyakumaran, and B. H. Han, *J. Org. Chem.*, 1986, **51**, 2818.

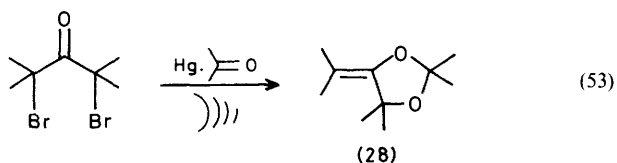
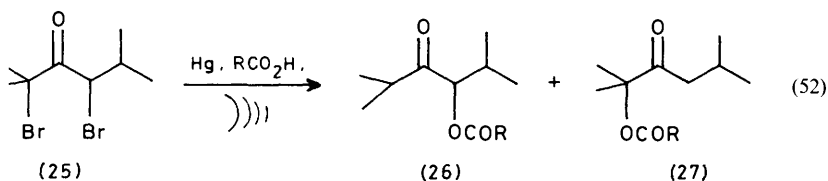
⁸⁵ S. Chew and R. J. Ferrier, *J. Chem. Soc., Chem. Commun.*, 1984, 911.

⁸⁶ L. Xu, F. Tao, and T. Yu, *Tetrahedron Lett.*, 1985, **26**, 4231.

⁸⁷ J. Brennan and F. H. S. Hussain, *Synthesis*, 1985, **8**, 749.

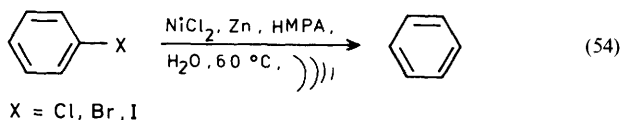
the more usual debrominating agents Bu_3SnH or $\text{Pd-C}/\text{H}_2$ recommended for this reaction.

Sonically dispersed mercury emulsions are efficient in the reductive debromination of α,α' -dibromoketone (25) in acetic acid to give α -acetoxyketones (26) and (27), (equation 52).³ Using ketones as solvents the products are isopropylidene-1,3-dioxolan derivatives *e.g.* (28) (equation 53).⁸⁸

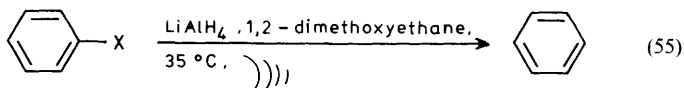


The rate of electrodechlorination of polychlorobiphenyl to give biphenyl at a stirred mercury pool electrode is enhanced 2- to 3-fold when the reaction is performed in an ultrasonic cleaning bath.⁸⁹

The reductive dehalogenation of aryl halides with nickel(II) chloride and zinc in aqueous HMPA is facilitated by low intensity ultrasound (equation 54).⁹⁰



Ultrasound also gives substantial rate enhancement in the reductive dehalogenation of aryl halides using lithium tetrahydroaluminate (equation 55).⁹¹ Thus a 97% yield of benzene was obtained in 5 h from bromobenzene compared with only 21% in 24 h under non-ultrasonic conditions.



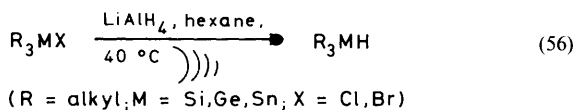
⁸⁸ A. J. Fry, G. S. Ginsberg, and R. A. Parante, *J. Chem. Soc., Chem. Commun.*, 1978, 1040.

⁸⁹ T. F. Connors and J. F. Rusling, *Chemosphere*, 1985, **13**, 415.

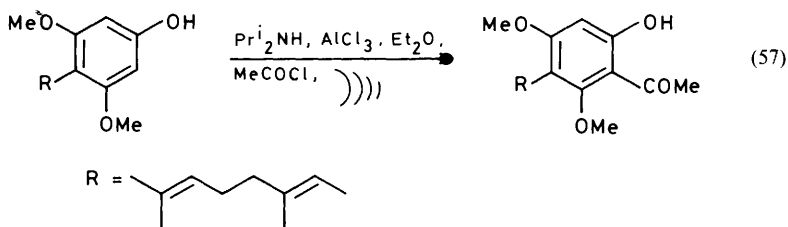
⁹⁰ T. Yamashita, Y. Inoue, T. Kondo, and H. Hashimoto, *Bull. Chem. Soc. Jpn.*, 1985, **58**, 2709.

⁹¹ B. H. Han and P. Boudjouk, *Tetrahedron Lett.*, 1982, **23**, 1643.

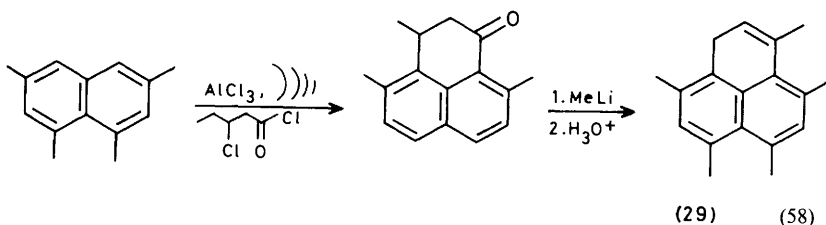
This method has also been extended to good advantage with the synthesis of group IVB element hydrides from the corresponding halogeno, alkoxy, or amino derivatives (equation 56).⁹²



(v) *Substitution.* Ultrasound facilitates the Friedel–Crafts acylation of aromatics (equation 57).⁹³



A combined Friedel–Crafts acylation/alkylation is a key step in the synthesis of hexamethylphenalene (29) (equation 58). The use of low intensity ultrasound has enabled the number of steps in the synthesis to be reduced from 15 to 4.⁹⁴



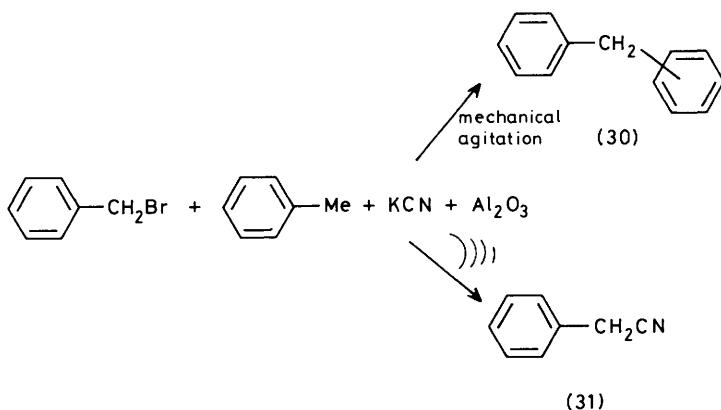
An interesting change in direction of the alumina-catalysed reaction of benzyl bromide with toluene and potassium cyanide is observed on sonication, Scheme 8.⁹⁵ Thus the mechanically stirred reaction gave 83% of the Friedel–Crafts product (30) and none of the substitution product (31), whereas the ultrasonic method gave no Friedel–Crafts product and 76% of the substitution product (Scheme 8). The probable explanation involves ultrasonic dispersion of KCN on the alumina surface which decreases its Friedel–Crafts activity whilst promoting the nucleophilic displacement of the CN⁻ on its surface.

⁹² E. Lukevics, V. N. Gevorgyan, and Y. S. Goldberg, *Tetrahedron Lett.*, 1984, **25**, 1415.

⁹³ B. M. Trost and B. P. Coppola, *J. Am. Chem. Soc.*, 1982, **104**, 6879.

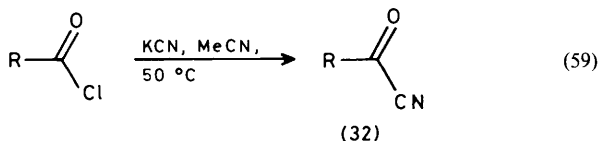
⁹⁴ P. Boudjouk, W. H. Ohrbrom, and J. B. Woell, *Synth. Commun.*, 1986, **16**, 401.

⁹⁵ T. Ando, S. Sumi, T. Kawate, J. Ichihara, and T. Hanafusa, *J. Chem. Soc., Chem. Commun.*, 1984, 439.



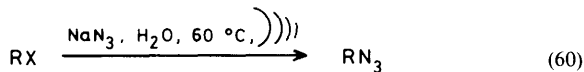
Scheme 8

In the ultrasonic preparation of aromatic acyl cyanides (32) (R = H, 2-Me, 3-Me, 4-Me, 4-MeO) (equation 59) by the reaction of the corresponding acyl



chlorides with solid KCN in acetonitrile, good yields of products have been achieved (70–85%) even in the absence of phase-transfer catalysts.⁹⁶ Under non-ultrasonic conditions this reaction is facilitated by the presence of traces of water but proceeds very slowly, whereas the ultrasonic reactions are not significantly affected by water. A possible rationale for this may be that the role of the water is to attack the crystal lattice to reveal sites which may well be more easily exposed by ultrasound.

The preparation of azides from primary alkyl halides and aqueous sodium azide also benefits from low intensity ultrasound (equation 60).⁹⁷ Higher yields are obtained when R = propargyl or allyl (60–91%) than for R = alkyl (20%).

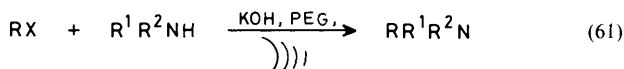


Rate enhancements are noted in several other heterogeneous substitutions which involve the use of phase-transfer catalysis (PTC), in several instances the use of ultrasound enables cheaper PTC reagents to be used. Thus the efficiency of *N*-

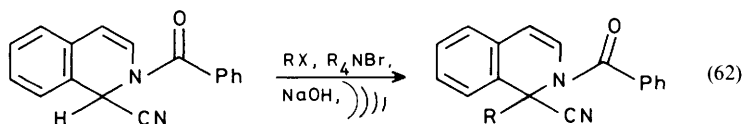
⁹⁶ T. Ando, T. Kawate, J. Yamawaki, and T. Hanafusa, *Synthesis*, 1983, 637.

⁹⁷ H. Priebe, *Acta Chem. Scand., Ser. B*, 1984, **38**, 895.

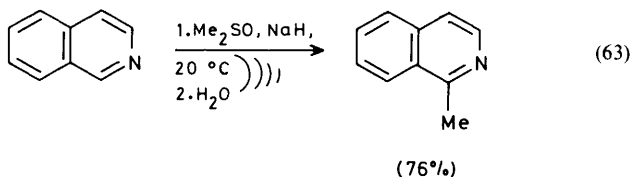
alkylation of amines with alkyl halides in toluene in the presence of KOH and PEG methyl ether is markedly increased (equation 61).⁹⁸ When R = benzyl and R¹ = R² = phenyl the yield is 98% in 1 h at 25–50 °C under sonication compared with only 70% after 48 h under reflux. In the absence of PTC there was no reaction under sonication, emphasizing that the increase in reactivity is not simply a matter of increasing interfacial contact area.



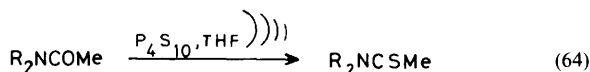
Ultrasound also enhances the rate of thiocyanation of alkyl halides using tetraalkylammonium halides as phase-transfer catalysts.⁹⁹ Increased yields of products are obtained using ultrasound in the PTC alkylation of the isoquinoline derivatives (33) (equation 62).¹⁰⁰



The generation of the methyl sulphanyl carbanion from sodium hydride and dimethylsulphoxide is facilitated by sonication (800 kHz, 200 W).¹⁰¹ When this reaction is carried out in the presence of isoquinoline good yields of 1-methylisoquinoline are obtained (equation 63).¹⁰² This reaction gives only slightly higher yields than existing methods, but for speed and simplicity it is superior.



Ultrasound has been found to give increased rates for the preparation of thioamides by reaction of their respective amides with P₄S₁₀ in dry THF (equation



⁹⁸ R. S. Davidson, A. M. Patel, A. Safdar, and D. Thornthwaite, *Tetrahedron Lett.*, 1983, **24**, 5907.

⁹⁹ W. P. Reeves and J. V. McClusky, *Tetrahedron Lett.*, 1983, **24**, 1585.

¹⁰⁰ J. Ezquerro and J. Alvarez-Builla, *J. Chem. Soc., Chem. Commun.*, 1984, 54.

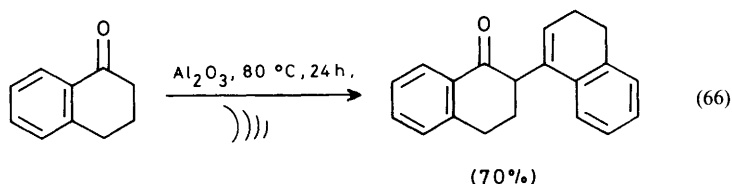
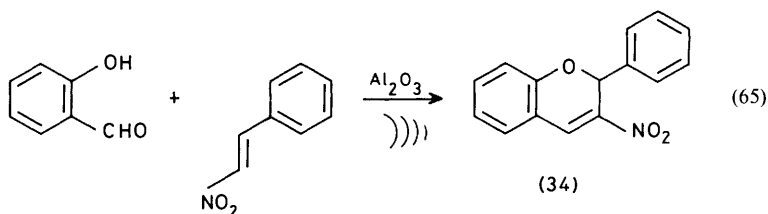
¹⁰¹ K. S. Sjöberg, *Tetrahedron Lett.*, 1966, 6383.

¹⁰² J. Ezquerro and J. Alvarez-Builla, *Org. Prep. Proc. Int.*, 1985, **17**, 190.

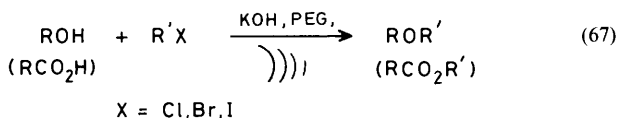
64).¹⁰³ This method has the additional advantage of requiring only 1—1.5 equiv. of P_4S_{10} rather than the large excess used in the traditional method.

(vi) *Condensations*. The rates at which *o*-hydroxybenzaldehydes condense with β -nitrostyrene derivatives using basic alumina catalyst can be increased by sonication.¹⁰⁴ The method which uses a 60 kHz cleaning bath is a convenient one-pot route to 3-nitro-2*H*-chromenes (34) (equation 65).

Ultrasound was also found to improve yields and rates for the aldol dimerization of ketones catalysed by basic alumina (equation 66).¹⁰⁵ Some of the conclusions drawn from the above work have, however, proved to be controversial.¹⁰⁶



Low intensity ultrasound (cleaning bath) has beneficial effects in the synthesis of ethers and esters (equation 67).¹⁰⁷ Using this method an 80% yield of ethyl phenyl ether was obtained in 2 h compared with only 44% in a stirred control reaction.



(vii) *Hydrolysis*. Ultrasound has a pronounced effect on the rate of saponification of carboxylic esters.¹⁰⁸ Thus methyl 2,4-dimethylbenzoate and sodium hydroxide

¹⁰³ S. Raucher and P. Klein, *J. Org. Chem.*, 1981, **46**, 3558.

¹⁰⁴ R. S. Varma and G. W. Kabalka, *Heterocycles*, 1985, **23**, 139.

¹⁰⁵ B. C. Barot, D. W. Sullins, and E. J. Eisenbraun, *Synth. Commun.*, 1984, **14**, 397.

¹⁰⁶ J. Muzart, *Synth. Commun.*, 1985, **15**, 285.

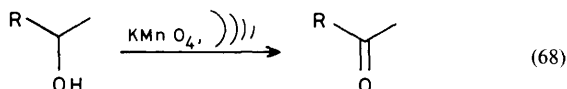
¹⁰⁷ R. S. Davidson, A. Safdar, J. D. Spencer, and D. W. Lewis, *Ultrasonics*, 1987, **25**, 35.

¹⁰⁸ S. Moon, L. Duchin, and J. Cooney, *Tetrahedron Lett.*, 1979, 3917.

solution (20%) after sonication (20 kHz probe) for 1 h gave a 94% yield of acid whereas only a 15% yield of acid was obtained after refluxing for 1.5 h.

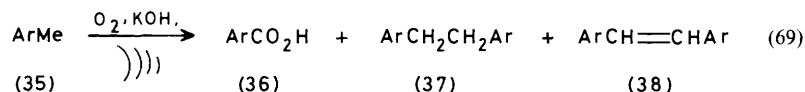
Saponification of commercially important substances, such as glycerides, rape seed oil, and wool waxes is greatly accelerated by sonication.¹⁰⁷ These heterogeneous reactions can be carried out at much lower temperatures than is usual and lead to products exhibiting less colour. While experiments on a 10 g scale were carried out in an ultrasonic cleaning bath, scale-up was achieved by use of a whistle reactor.

(viii) *Oxidation.* The oxidation of alcohols by solid potassium permanganate in hexane and benzene is significantly enhanced by sonication in an ultrasonic bath (equation 68).¹⁰⁹



Comparisons with mechanical stirring reveal increases in yield at 50 °C for the oxidation of octan-2-ol (R = C₆H₁₃) from 2.6% to 92.8% (5 h) and for 3-phenylprop-2-en-1-ol from 4.5% to 82.8% (3 h). When the KMnO₄ was supported on alumina, however, normal reactivity was enhanced and ultrasound had no additional effect.

Attempted autoxidation of 4-nitrotoluene (35) (Ar = 4-NO₂C₆H₄) (equation 69) in the presence of O₂ using KOH and PEG 400 as PTC gives a mixture



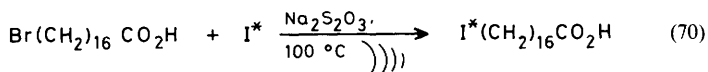
consisting entirely of the dimers (37) and (38) with combined yields ranging from 19.3 to 38.7% depending on O₂ pressure and reaction conditions. Sonication not only reduces reaction times by a factor of three but, more significantly, effects the selectivity of such reactions.¹¹⁰ At the same temperature (25 °C) and with reaction times of 1 h the product distribution of the reaction is changed by irradiation such that the carboxylic acid (36) is the main product with yield % (acid:total dimer) as high as 43.1% to 2.3% depending on conditions.

(ix) *Isotopic Labelling.* A quantitative isotopic yield of carrier-free [17-¹²³I]heptadecanoic acid is obtained by halogen exchange between the bromoacid and iodine-123-sodium thiosulphate in butan-2-one at 100 °C under sonication (ultrasonic bath, 50 kHz) for 20 min (equation 70).¹¹¹

¹⁰⁹ J. Yamakawi, S. Sumi, T. Ando, and T. Hanafusa, *Chem. Lett.*, 1983, 379.

¹¹⁰ R. Neumann and Y. Sasson, *J. Chem. Soc., Chem. Commun.*, 1985, 616.

¹¹¹ J. Mertens, W. Vanryckeghem, A. Bossuyt, P. V. den Winkel, and R. Vandendriessche, *J. Labelled Comp. Radiopharm.*, 1984, **21**, 843.



The Raney nickel-catalysed hydrogen–deuterium exchange in cerebroside and monosaccharides in THF–D₂O proceeds under mild conditions in an ultrasonic cleaning bath.¹¹² The mild conditions employed lead to enhancement of site selectivity for the exchange.

3 Sonochemistry Equipment

A. Ultrasonic Apparatus.—(i) *Whistle Reactor.* This type of mechanical transducer device is predominantly used for homogenization/emulsification. In a sense these devices can be considered almost as 'passive' rather than 'active' sonicators in that the power of the sonication is fixed by the flow of fluid across the vibrating plate. Most of the chemical effects observed using these reactors can be attributed to the generation of very fine emulsions rather than the ultrasonic irradiation itself. An obvious benefit of such a system is that it can be used for flow-processing large volumes.

(ii) *Ultrasonic Cleaning Bath.* This is undoubtedly the most accessible and simplest equipment available. There are, however, three factors that should be borne in mind when using this method.

- (a) The amount of power reaching the 'reaction' immersed in the bath is not readily quantifiable because it will depend on the size of the bath, the reaction vessel type (and thickness of its walls), and the position of the reaction vessel in the bath.¹¹³
- (b) Temperature control is not easy in this system. Most cleaning baths warm up during operation, especially over a prolonged period of use. This is not a problem if a heater is used to establish thermal equilibrium but can lead to inconsistent results when working around room temperature or below. Two solutions are available: (i) operating for very short periods over which the temperature can be assumed to remain essentially constant or (ii) circulating cooling water or adding ice. If ice is used, however, it must be borne in mind that solids will alter the characteristics of sonic wave transmission. Whatever method is chosen it must be emphasized that it is the temperature inside the reaction vessel which must be monitored as this is often a few degrees above that of the bath liquid.
- (c) Cleaning baths do not all operate at the same frequency and this may well lead to difficulties, particularly in attempts to reproduce results reported in the literature.

¹¹² E. Cioffi and J. H. Prestegard, *Tetrahedron Lett.*, 1986, **27**, 415.

¹¹³ B. Pugin, *Ultrasonics*, 1987, **25**, 35.

(iii) *Direct Immersion Sonic Horn*. An ultrasonic probe can be placed directly in the reacting system and this is the type of equipment often used for biological cell disruption. It is undoubtedly the most efficient method of transmitting ultrasonic energy into a reaction.

The vibrating motion generated by the piezoelectric transducer used in such equipment is normally too low for practical use and so it is necessary to magnify or amplify this motion. This is the function of the horn (or probe) attached to the transducer. Normally the horn is half a wavelength long. The most popular horn designs are shown in Figure 1.

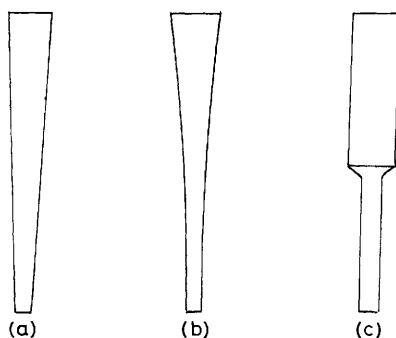


Figure 1 Horn designs (a) linear taper (b) exponential taper (c) stepped

(a) *Linear taper*. This is simple to make but its potential magnification is limited to approximately fourfold.

(b) *Exponential taper*. This design offers higher magnification factors than the linear taper but its shape makes it more difficult to manufacture. Its length and the small diameter of the working end makes this design particularly suited to micro applications.

(c) *Stepped*. For this design the magnification factor is in the ratio of the end areas.

The potential magnification is limited only by the dynamic tensile strength of the horn material. This is a useful design and easy to manufacture. Gains of up to 16-fold are easily achieved with this type.

The material used for the fabrication of acoustic horns should have high dynamic fatigue strength, low acoustic loss, resistance to cavitation erosion, and chemical inertness. The most suitable material by far is titanium alloy. A number of such devices are on the market (normally called cell disruptors), the majority operating at 20 kHz, and a range of different metal probes (horns) are available. The advantages of this method over a bath are threefold:

(a) Much higher ultrasonic powers can be used since energy losses during the transfer of ultrasound through the bath media and reaction vessel walls are eliminated.

- (b) These devices can be tuned to give optimum performance in the reaction mixture over a range of powers.
- (c) The ultrasonic intensity and size of sample to be irradiated can be matched fairly accurately for optimum effect.

Although the probe has these advantages over the bath it does suffer from the same difficulties of temperature control and operation at a fixed frequency, plus two additional problems. These are that with direct sonication it is possible to generate radical species by the action of the probe tip on the solvent and that with prolonged use some erosion of the tip occurs which may mean contamination of the reaction under study by small metallic particles.

(iv) *The Cup Horn.* This system (Figure 2) was also originally designed for cell disruption but is both more controllable than a cleaning bath (in terms of power and temperature) and less drastic in action than a sonic horn. The use of such a system allows more quantitative and reproducible studies of sonochemical effects than a cleaning bath. The frequency is fixed and the power is tuneable but, unlike the direct sonic horn, no radicals or fragments of metal are generated in the reaction mixture itself.

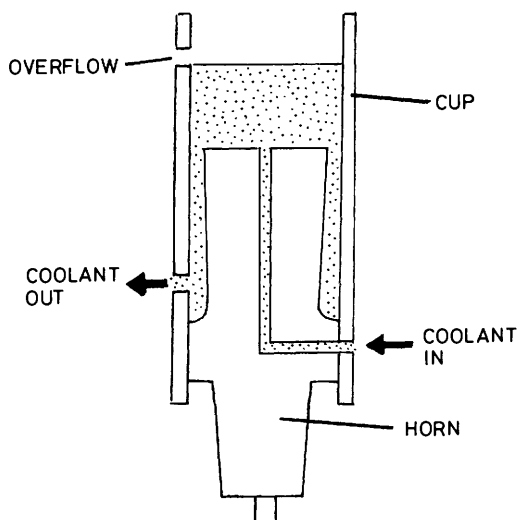


Figure 2 *Cup horn*

The major disadvantages of the cup horn compared with the direct immersion sonic horn are (i) the reduction in power and (ii) the restriction in size of the reaction vessel which can be placed inside the cup horn.

B. Reactor Design.—(i) *Batch Reactions.* Although the direct insertion of a probe into the reaction mixture is by far the most effective method of introducing ultrasound into a reaction, there are a number of problems associated with it. These

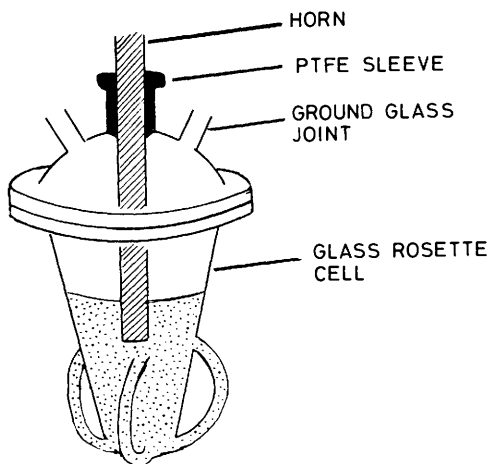


Figure 3 *Rosette cell*

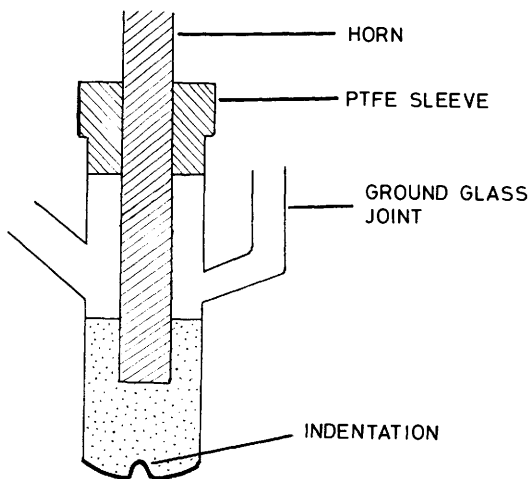


Figure 4 *Indented cell*

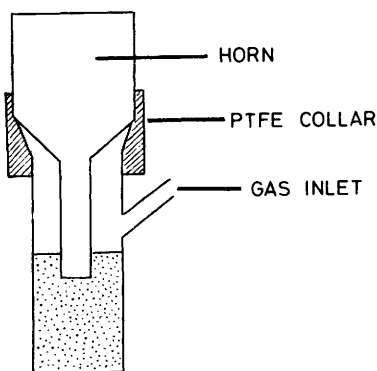


Figure 5 *Pressure reactor*

centre around the maintenance of temperature stability, vapour tightness, and (where necessary) pressure.

Some of the simplest types of laboratory scale reactor are described below. A glass rosette cell with flanged lid is shown in (Figure 3). The design of the rosette cell allows the irradiated reaction mixture to be sonically propelled from the end of the probe around the loops of the vessel and thus provides both cooling (when the vessel is immersed in a thermostatted bath) and efficient mixing. A PTFE sleeve provides a vapour-tight fit for the probe through the glass joint.

As an alternative to this an ordinary reaction vessel can be adapted for sonic mixing by providing an indentation on its base which acts to disperse the sonic waves as they are reflected from the base (Figure 4).

If the reaction vessel is simply immersed in an ultrasonic bath then it will be necessary to provide additional mechanical stirring.

In situations where gas pressures above atmospheric need to be used a useful reactor has been described by Suslick (Figure 5).⁴³

Luche has described a simple apparatus for organometallic preparations involving the direct reaction of metals with a liquid (Figure 6).⁶⁸

(ii) *Flow Systems.* An obvious limitation of the electromechanical systems described above is the batch nature of the processing involved. A favourite method of avoiding this is to use a flow-cell in a continuous or circulating system (Figure 7). This bears some relationship to the whistle reactor described above except that the sonication is provided through a probe and is therefore of controllable power.

(iii) *Large Scale Applications.* On a production scale the volumes treated will be very much larger than those considered in the laboratory. Almost certainly the type of process will govern the choice of transducer energy density required and it could well be that some processes would be suited to a low intensity sonication whereas others may need the higher intensity of the probe system.

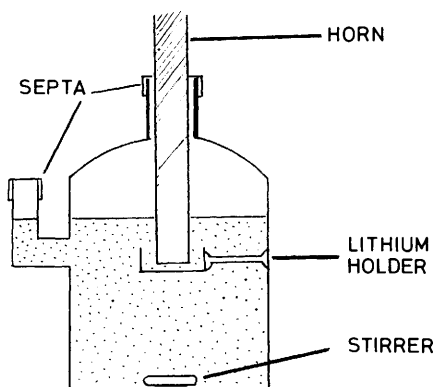


Figure 6 Organometallic reactor

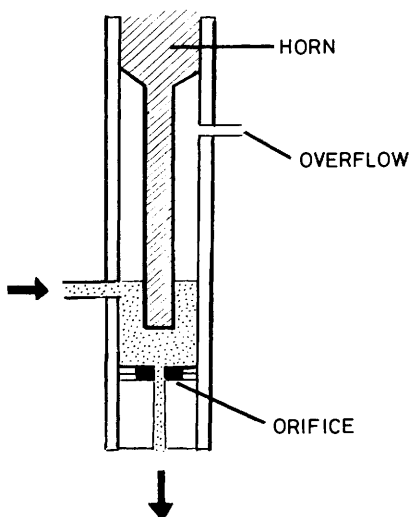


Figure 7 Flow cell

In the case of low intensity treatment the reacting liquids could be flowed in a controlled manner through an ultrasonic tank and out over a weir to the next process. A number of such sonically activated stages could be connected in line. The tanks would be constructed in an appropriate grade of stainless steel, or if plastic tanks were to be used then the transducer could be bonded on to a stainless steel or titanium plate and bolted with a gasket into the tank. Alternatively a sealed submersible transducer assembly could be employed.

If high intensity treatment were needed it would be possible to couple a probe

transducer into a flow pipe by means of a T section. A number of such transducers could be employed in this manner. The actual number and position in the process line would need to have been determined during the process development phase.¹¹⁴

¹¹⁴ R. A. Holl, U. S. Patent, 1978, 4,071,225.