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Microwave enhanced synthesis

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1. Introduction

Microwave technology has become very important in synthesis and it is reasonable to assert that there are now very few areas of synthetic organic chemistry that have not been shown to be enhanced using microwave heating. It has become recognised that many chemical reactions, which require heating are likely to proceed more rapidly using this different form of heating. In 1995 one of us wrote an article, which provided an overview of the area and since that time it has become clear that organic synthesis has greatly benefited from the development of microwave technology.[1] In this article we present a new overview of the area and include selected highlights of the innovative ways in which synthetic chemists utilise microwaves to achieve fast, clean and high-yielding transformations. The impact has been dramatic and now microwave heating is used to add value to synthetic transformations in undergraduate programmes,[2–4] in facilitating rapid discovery in medicinal chemistry[5–9] and of course in mainstream organic synthesis. Moreover, it is also finding utility in other areas such as nanoparticle synthesis[10] and PCR.[11,12] Part of the reason for the successful uptake has been the development of newer and more readily available instruments, which can allow microwave heating to be achieved in a controlled manner. The area is still burgeoning and this is in no small part due to the positive interaction between suppliers of microwave equipment and the research community.

The principles of microwave dielectric heating have been described on numerous occasions in books and review articles, and so for detailed description the reader is referred elsewhere.[13,14] Despite this, it is still occasionally found that the misconception

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that specific bonds can be activated using microwave heating persists. Microwave dielectric heating is a bulk effect and the heating is a consequence of dielectric loss. Thus, if one or more species in the reaction mixture has a permanent dipole then dielectric heating by irradiation with microwave energy, at 2.45 GHz, will be possible. Hence, solvents such as methanol, DMF, acetonitrile, ethyl acetate and water are commonly employed in microwave enhanced reactions. Hexane, and similar solvents, containing no dipole do not couple with microwave energy and in order for microwave dielectric heating to be successful another reaction component must contain a dipole. It should be noted that in the majority, if not all, cases the nature of the microwave enhancement can be directly attributed to a heating effect. However, it would be remiss not to note that there is a view that there may be other non-thermal microwave effects, although in recent years the numbers of such claims have diminished. However, there have been a number of useful articles, which discuss this topic at length and the reader is directed to those for a detailed discussion of the non-thermal effects.[15,16] Despite the interesting nature of some of the observations, it is still the case that non-thermal microwave effects, if they exist, are not widely understood.[17,18] Certainly not, to date, to such an extent to provide a platform for generic synthetic methodologies.[19] It is of course important to understand the potential role of non-classical effects, such as heterogeneity, especially when consideration is given to scale-up of microwave-mediated processes.[14,20–25]

It is clear that microwave chemistry can provide access to synthetic transformations, which may be prohibitively long or low yielding using conventional heating.[26] Moreover, there have been numerous technical developments in terms of instrumentation, which allows microwave heating with cooling, bespoke peptide synthesisers, and instruments, which allow larger scale reflux conditions. In addition, the academic community has been actively engaged in technological developments and in particular there has been intense activity directed towards the development of reactors to allow continuous flow. For example Bagley and Wood describe a simple microreactor and demonstrate its utility with substitution, Fisher indole and Bohlmann–Rahtz reactions.[27] Other contributions from Wilson,[28] Haswell,[29,30] Sahle-Demessie,[31] Kappe,[32] Kappe and Kunz,[33] Organ,[34–37] Leadbeater,[38] and Ley[39] have all provided important developments in reactor design for continuous-flow processes. Another area of technical development has been reported by Kappe[40,41] involving the development of bespoke silicon carbide microtitre plates, which can be used to carry out 48 reactions at a time. The plate itself couples with microwaves and therefore reactions containing no dipolar materials can be carried out at up to 20 bar.

In the area of reaction monitoring, Leadbeater[42,43] and Stone-Elander[44] have made some important contributions and Leadbeater has examined the integration of UV, IR and Raman spectroscopy with microwave instruments and, most recently, examining macroscopic effects by utilisation of a digital camera.[45] Leadbeater has also been interested in examining the benefits of multimode versus monomode, which is now available due to developments in instrumentation.[46]

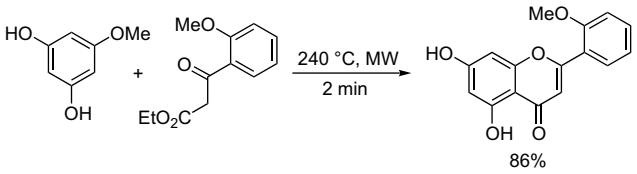
It has been known for some years that microwave heating can provide an excellent basis for the development of high quality preparation of analytical samples and Colmsjo has described the development of an apparatus for microwave enhanced dynamic extraction.[47] The protocol appears straightforward and provides similar efficiencies to conventional Soxhlet extraction, but in a much reduced time.

The growing importance of water as a solvent for organic transformations is particularly noteworthy and, given the high temperatures that can be achieved very rapidly under microwave heating, it is unsurprising that many microwave enhanced protocols utilise water as an alternative and preferable solvent to many more conventional organic transformations.[48,49] More specific examples of the use of water as a solvent in microwave enhanced reactions will be seen throughout the article.

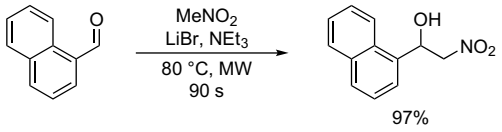
It should also be noted that over the years a number of general and specific review articles have been published and these have been valuable in promoting the area.[13,48,50–53] In this article, rather than attempting to provide an exhaustive treatment, we will focus on highlighting a few key examples of microwave enhanced reactions in the myriad areas of synthesis, which have now been studied.

2. General synthetic transformations

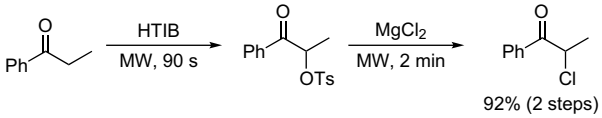
Although solvent-free reactions have been utilised for a long time,[54] it was found that microwave heating offers possibilities to extend and enhance such processes.[55,56] This has been a continuing area for development in recent years and Varma and Namboodiri have, for example, shown that a microwave-enhanced solvent-free approach can be used to make ionic liquids.[57] Seijas has recently described a route to functionalised flavones under microwave enhanced solvent-free conditions (Scheme 1).[58] Thus treatment of phloroglucinol with α-keto-esters leads directly to flavones in a few minutes and in good overall yields and this method provides a very nice complement to other methodologies for preparing this important class of compound. Wang has described a microwave-enhanced solvent-free approach to β-hydroxy nitro compounds via a Lewis acid mediated Henry reaction (Scheme 2).[59] Lee has described a two-step method for the synthesis of α-halo-carbonyls by α-keto-tosylation using Koser's reagent, [hydroxy(tosyloxy)iodo]benzene (HTIB), and then conversion into the halo-compound using MgX_2 (Scheme 3).[60] Both reactions are very rapid and the reaction appears to be applicable to iodides, bromides and chlorides.



Scheme 1.

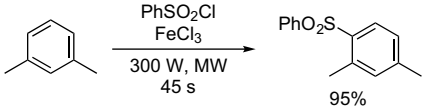


Scheme 2.



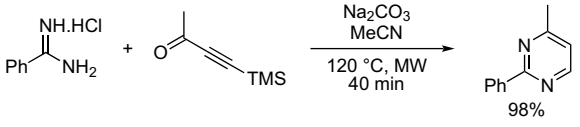
Scheme 3.

In the area of electrophilic aromatic substitution, Dubac and coworkers have described a solvent-free sulfonation of aromatics under microwave heating conditions (Scheme 4).[61] Thus, using benzenesulfonyl chloride and $FeCl_3$, *m*-xylylene underwent smooth sulfonation with 45 s of microwave heating to give the desired product.

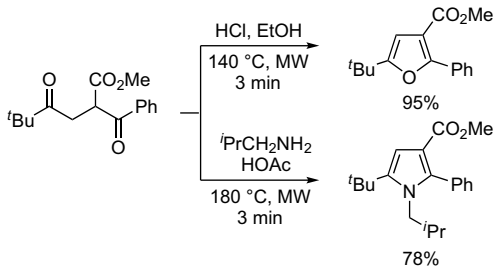


Scheme 4.

One of the early observations made was the enhancement of condensation reactions under microwave heating. It is likely that many of the advantages can be attributed to the ability of microwave heating to drive the reaction to completion by heating of the generated water. In a very simple, but important, practical example of this type of reaction Turnbull described the use of a microwave enhanced imine formation as a method for attachment of carbohydrates and amine containing labels and surfaces.[62] Bagley has, in a series of papers, described the synthesis of pyridines and pyrimidines using microwave enhanced sequences involving condensation reactions (Scheme 5).[63–65] In the synthesis of pyrroles and furans, microwave heating has enabled Taddei to enhance the Paal–Knorr synthesis (Scheme 6).[66]

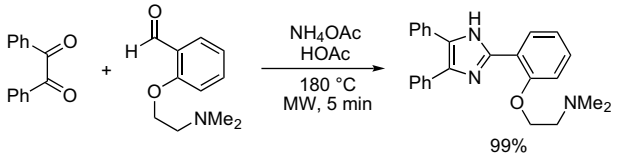


Scheme 5.

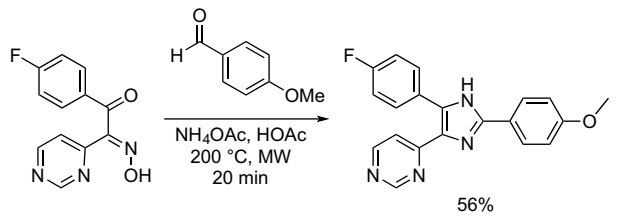


Scheme 6.

Imidazole synthesis has been improved utilising microwave heating and in two recent contributions the groups of Wolkenberg[67] and Combs[68] have developed two distinct microwave enhanced approaches to this important class of compounds (Scheme 7). Wolkenberg's approach utilises the condensation of an aldehyde with a 1,2-diketone and ammonium acetate in acetic acid at high temperature. Combs' approach relies on the microwave-assisted deoxygenation of an *N*-hydroxyimidazole (Scheme 8).

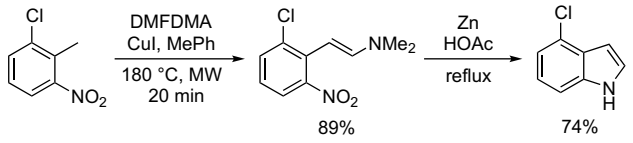


Scheme 7.



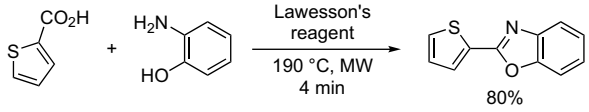
Scheme 8.

Ley has recently described a microwave enhanced indole synthesis based on the Leimgruber–Batcho synthesis (Scheme 9).[69] Thus, microwave irradiation provided a very practical approach to the required enamines, which could then undergo reductive cyclisation under standard or microwave-mediated conditions.

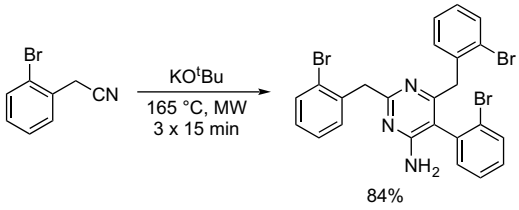


Scheme 9.

In a very nice example of heterocycle formation, Seijas reported the use of Lawesson's reagent to convert benzoic acids into benzoxazoles and benzothiazoles in a single step (Scheme 10).[70] The reactions proceed very well in a few minutes of microwave heating at 190 °C and these are carried out under open vessel conditions. Another nice example of heterocycle synthesis is described by Ley using a microwave induced trimerisation of nitriles to give pyrimidines in a single step (Scheme 11).[71] The protocol requires the use of potassium *tert*-butoxide and the nitrile is heated neat at 165 °C. It is notable that the process can be carried out on reasonable scale and so is ideal for production of monomer building blocks.

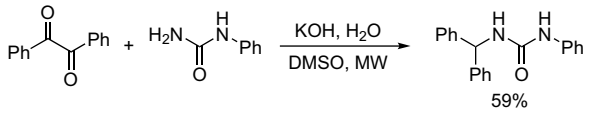


Scheme 10.



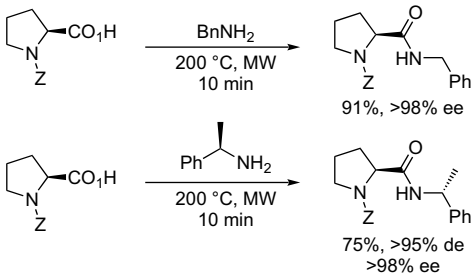
Scheme 11.

Lambert has described the synthesis of benzhydryl-phenyl ureas using a microwave-mediated rearrangement process in an open system (Scheme 12).[72] Treatment of a 1,2-diketone with a urea led to the isolation of a substituted urea via benzyl rearrangement followed by decarboxylation.



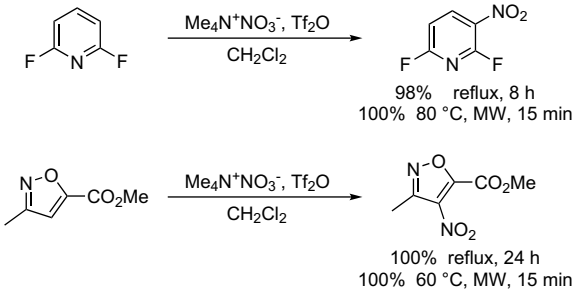
Scheme 12.

Orru[73] first and more recently Ferroud[74] have reported that carboxylic acids and amines undergo coupling directly and in the absence of any reagent at elevated temperatures (Scheme 13). Whilst the transformation has been described previously, it would appear that in this case a much wider range of amines can be coupled, including amino acids. A key to success appears to be the use of very high temperature, >200 °C, and Orru reports impressive yields.



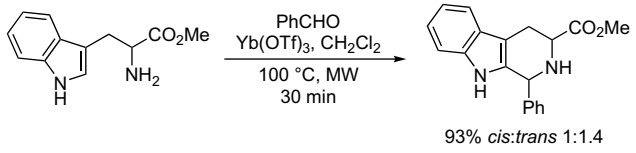
Scheme 13.

In synthetic aromatic chemistry there have been numerous contributions describing the potential value and importance of using microwave irradiation. Shackelford and co-workers have described the use of a microwave enhanced nitration protocol, which uses tetramethylammonium nitrate and trifluoromethanesulfonic acid (Scheme 14).[75] This reagent system generates nitronium triflate and allows the rapid and high-yielding nitration of aromatics and heteroaromatics to be achieved on reasonable scale and with very simple aqueous work-up required to give analytically pure material.



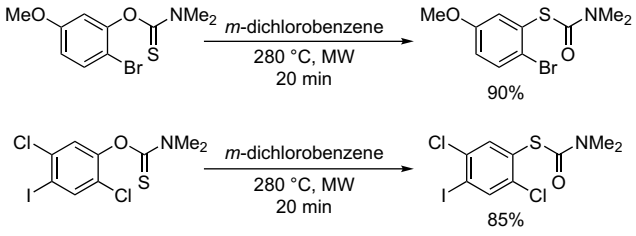
Scheme 14.

Ganesan and Srinivasan have described the microwave enhanced Pictet–Spengler reaction, which is used for the rapid Lewis acid catalysed synthesis of tetrahydro-β-carbolines (Scheme 15).[76]



Scheme 15.

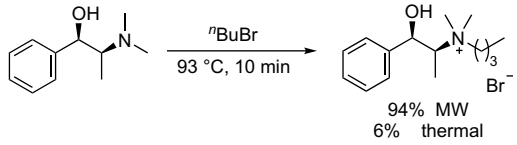
Moseley has reported the use of microwave heating to enhance the Newman–Kwart rearrangement, which is an excellent method for the preparation of 2-thiocarbamates from *O*-thiocarbamates (Scheme 16).[77,78] The authors describe a detailed optimisation protocol, which allows them to demonstrate that, in contrast to previous reports, it is possible to optimise reactions at lower temperatures even for some apparently more difficult classes of substrate.



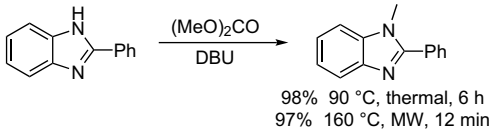
Scheme 16.

Microwave heating has long been known as an excellent method for improving the scope of substitution reactions and this has continued to be a valuable development. Thanh has shown the use of a microwave enhanced method for the preparation of ionic liquids (Scheme 17).[79] Although there are a number of reports on the use of microwave heating for the synthesis of ionic liquids, this report focuses on preparation of chiral variants from (−)-*N*-methylephedrine and the ability to *N*-alkylate under microwave conditions is an important part of the overall sequence. Shieh and co-workers report an interesting O- or N- methylation protocol utilising DBU (Scheme 18).[80] Thus, phenols, indoles or benzimidazoles could be readily methylated using dimethyl carbonate in good to excellent yields with microwave heating at 160 °C.

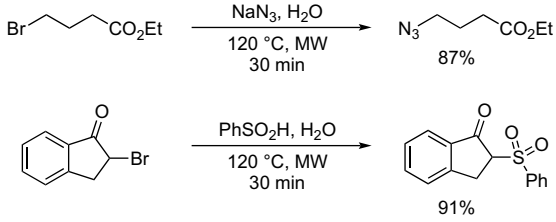
Given the renewed popularity of azides, particularly in cycloaddition chemistry, there is interest in simplified methods for their production. Varma reported a very convenient synthesis of azides from tosylates, chlorides and bromides under aqueous conditions (Scheme 19).[81] The method can be extended to other displacement processes, for example, to thiocyanates and sulfones.



Scheme 17.

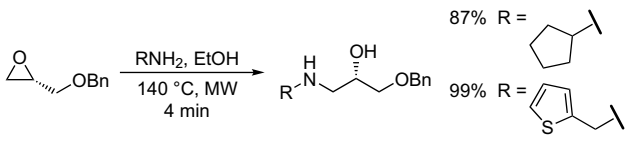


Scheme 18.



Scheme 19.

Epoxides are well established as good electrophiles and given the large number of methods available for their preparation they are attractive intermediates for organic synthesis. In a couple of recent contributions it is noted that microwave irradiation can provide a benefit to substitution reactions of epoxides. Flitsch developed an excellent microwave-mediated approach to aminopropanols as anti-parasitic agents and the key part of the library production was based around a smooth opening of an epoxide (Scheme 20).[82] Application to the asymmetric synthesis of analogues is notable and this simple methodology allowed the group to identify new anti-parasitic agents with promising levels of biological activity.

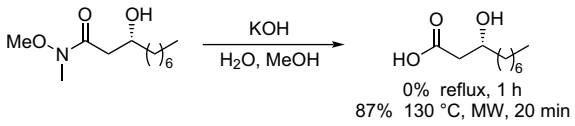


Scheme 20.

In an alternative method, Jacobs reported the chromium–salen catalysed opening of epoxides.[83] The conventional methodology provides a good route into enantiopure azido alcohols via desymmetrisation or kinetic resolution and so the interest here is to determine the effect of the microwave dielectric heating on the stereoselectivity. It was confirmed that in addition to reducing the reaction time these reactions could be carried out with equal efficiency under microwave heating. This shows a real advantage over conventional heating, which leads to an erosion of the observed selectivity.

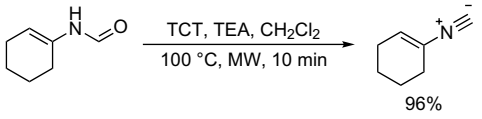
Pohl recently described the use of a microwave enhanced cleavage of a Weinreb amide (Scheme 21).[84] This is of particular

note because of the value of Weinreb amides in synthesis and the fact that the hydrolysis was unsuccessful under conventional thermal conditions.



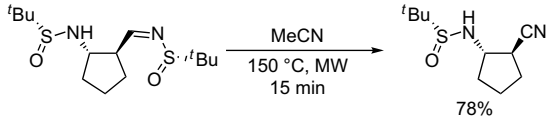
Scheme 21.

The ubiquitous application of isonitriles in the Ugi and other multi-component reactions provides an impetus for the development of improved protocols for their synthesis. Thus, Porcheddu found that the dehydration of formamides could be readily achieved using 2,4,6-trichloro[1,3,5]triazine (TCT) and this was applicable to aliphatic and aromatic formamides (Scheme 22).[85] An appealing feature of these reactions is the ability to simply filter the products and directly use the product isonitrile.



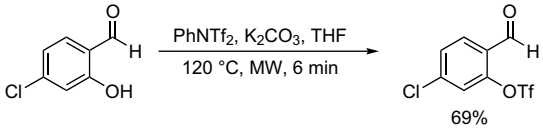
Scheme 22.

Moving from isonitriles to nitriles, Ellman has described the conversion of *N*-sulfinyl aldimines into nitriles (Scheme 23).[86] After describing an intramolecular self-condensation for the synthesis of cyclopentanes, they described that the aldimines can readily undergo elimination to give the corresponding nitriles with microwave heating.



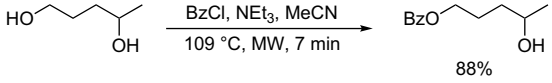
Scheme 23.

Another nice example of a simple, but potentially valuable, transformation was described by Larhed (Scheme 24).[87] This work provides an effective route to aryl triflates from alcohols using a microwave enhanced triflation using *N*-phenyltriflimide and the application to solid-phase synthesis is discussed.



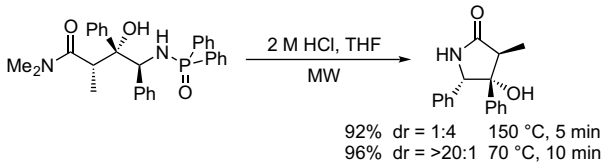
Scheme 24.

Caddick has reported a method for the selective benzoylation of diols, which classically would require a stannane to derive selectivity (Scheme 25).[88] However, judicious choice of base achieved selective benzoylation. The use of microwave heating is beneficial in that it helps avoid prolonged heating, which was shown to be detrimental to yield and selectivity.



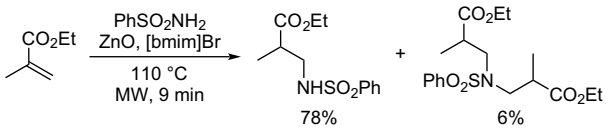
Scheme 25.

Scheidt has described a microwave enhanced cyclisation to generate γ-lactams and it is notable that, even with fairly sensitive functionality, further undesirable reactions such as elimination were not observed (Scheme 26).[89]



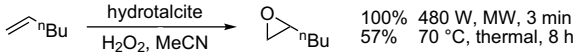
Scheme 26.

Conjugate addition reactions have also been shown to benefit from microwave heating. Zare has described the microwave enhanced conjugate addition of sulfonamides to α,β-unsaturated esters using zinc oxide in ionic liquids (Scheme 27).[90]



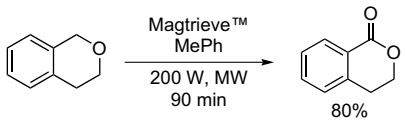
Scheme 27.

Oxidation reactions can be enhanced using microwave heating, although care often has to be taken to avoid the hazards associated with over-oxidation. In this arena, Sahle-Demessie reported olefin epoxidation on magnesium aluminium hydroxide carbonate, hydrotalcite, using hydrogen peroxide (Scheme 28).[91] The use of microwave heating was shown to have a very beneficial effect and facilitated reactions in a few minutes, as opposed to hours under conventional conditions.



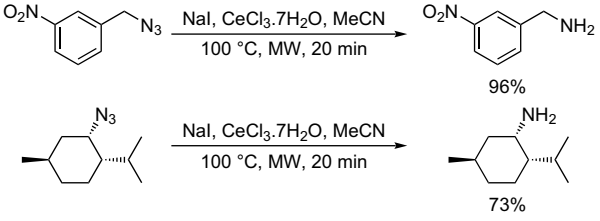
Scheme 28.

Bogdal has described the use of a microwave enhanced protocol for modification of aromatic side chains (Scheme 29).[92] Thus, using the DuPont catalyst Magtrieve™, it is possible to oxidise a range of aromatic compounds.



Scheme 29.

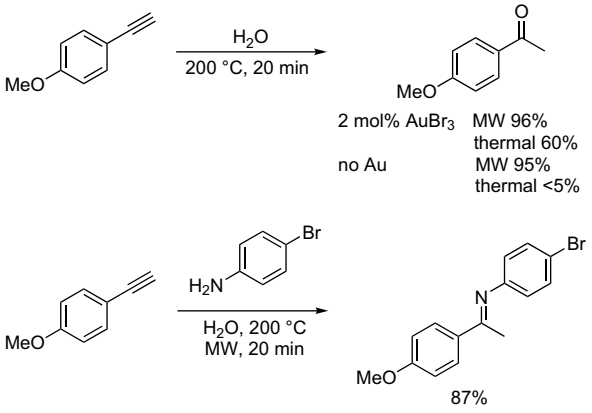
Moving from oxidation to reduction, Bartoli and Marcantoni have reported a simple and efficient method for the reduction of azides to primary amines (Scheme 30).[93] The method can be carried out under conventional heating, 24 h, or microwave heating,



Scheme 30.

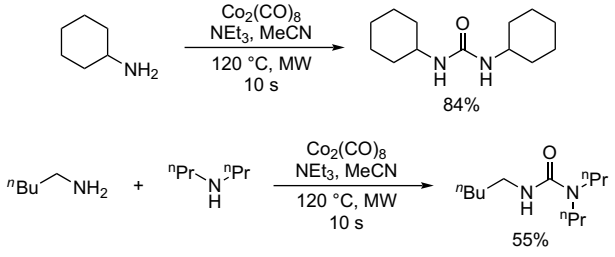
20 min, but irrespective of the mode of heating both methods rely on an excess of sodium iodide and $CeCl_3$.

Vasudevan reported hydration of alkynes to give ketones assisted by microwave heating (Scheme 31).[94] This transformation, originally mediated using gold catalysis, was found to proceed for electron-rich aryls in excellent yields without any metal catalysis. For electron-deficient examples the reaction was slow, but could be promoted using 2 mol% $AuBr_3$ without recourse to the more commonly employed acidic conditions. In a particularly elegant example of the work, the authors show alkyne hydration followed by imine formation. Thus, treatment of an alkyne and an amine in water leads to an imine directly.



Scheme 31.

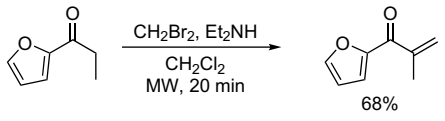
In another very useful transformation, Larhed has described the formation of ureas using $Co_2(CO)_8$ (Scheme 32).[95] The reaction has principally been used for the preparation of symmetrical ureas and there is evidence to suggest that it proceeds via an isocyanate. Successful application of this methodology to the synthesis of unsymmetrical ureas requires 5:1 stoichiometry of the amine partners. Unfortunately, even under these conditions the yields of unsymmetrical products were only modest.



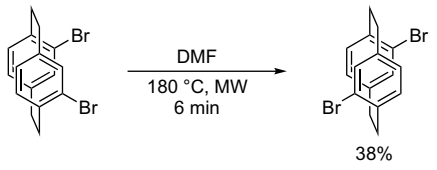
Scheme 32.

Hon has recently described the α-methylenation of ketones under microwave conditions (Scheme 33).[96] The reaction, which conventionally involves a very slow reaction even at reflux requiring large excesses of CH_2Br_2 and Et_2NH, can be reduced to less than 30 min using microwave heating.

In a nice example of a microwave-mediated isomerisation, Braddock described a microwave enhanced method for the isomerisation of paracyclophanes (Scheme 34).[97] These species are highly desirable and the present paper describes a very simple,



Scheme 33.

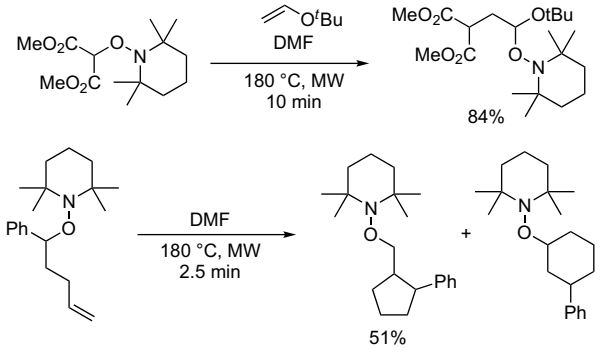


Scheme 34.

practical and scalable method for the isomerisation of the 4,16 isomer into the 4,12 species.

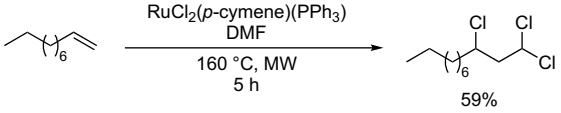
3. Radical chemistry

A small but growing number of contributions are being made in the area of microwave enhanced free-radical chemistry. There are likely to be increasing contributions in the area of microwave enhanced free-radical polymerisation methods.[98] However, in the synthetic organic chemistry community there is a growing recognition that radical chemistry can potentially benefit from microwave heating. Studer has been particularly interested in developing cleaner methods for carrying out free-radical chemistry (Scheme 35).[99–101] He has focused on the exploitation of the persistent radical effect and in a nice description of the approach that provides examples of inter- and intramolecular radical reactions, which rely on the homolytic cleavage of TEMPO derivatives. Because of the stability of the TEMPO radical it can reversibly capture other intermediate radicals and allow useful chain processes to take place. Microwave irradiation can significantly enhance both inter- and intramolecular variants of this methodology, allowing them to be carried out in minutes as opposed to days.



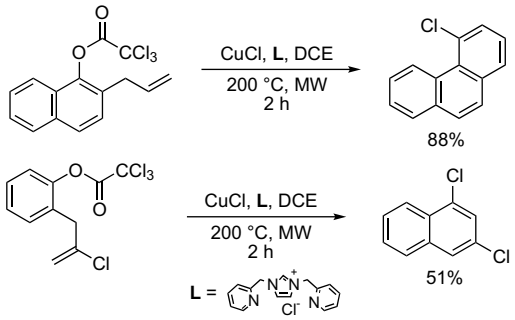
Scheme 35.

Demonceau has reported the microwave enhanced radical addition process mediated by ruthenium (Scheme 36).[102] This atom-transfer process is potentially synthetically useful but can be prohibitively slow, since after 300 h heating products were only isolated in 20% yield. However, after microwave heating for 5 h a 60% yield was obtained.



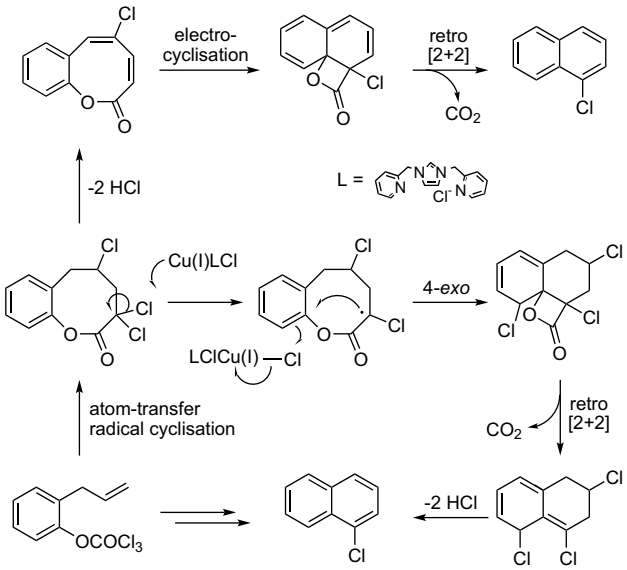
Scheme 36.

Remaining with atom-transfer radical processes, Quayle has reported a remarkable microwave induced benzannulation. Thus, treatment of trichloroacetates with catalytic CuCl under microwave conditions led to the isolation of a novel and unexpected arylation



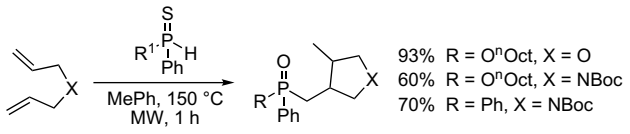
Scheme 37.

reaction.[103] The reaction does require a reasonably long period of irradiation, 2 h, and high temperatures but has been shown to be general in terms of applicability with a number of interesting examples presented (Scheme 37). The authors speculate that the mechanism involves an atom-transfer radical cyclisation followed by spirocyclic β-lactone formation and retro [2+2] cycloaddition (Scheme 38).



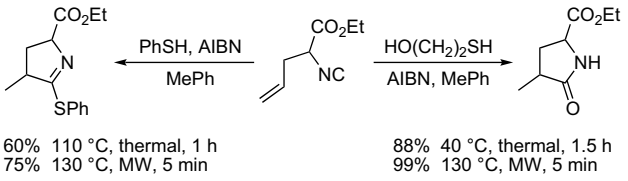
Scheme 38.

Parsons has further developed his phosphorus hydride mediated method for cyclopentane formation using microwave heating (Scheme 39).[104] Thus, by appropriate choice of substituent it is possible to promote phosphorus radical formation simply under microwave heating conditions and in the absence of an initiator. Given the significant difficulties that can be associated with initiation processes in radical chemistry, this type of approach has the potential to be generalised.



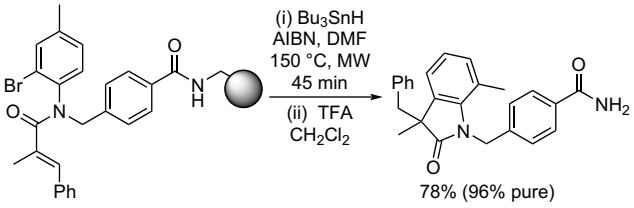
Scheme 39.

In addition, Kilburn has reported microwave enhanced radical cyclisations utilising isocyanides (Scheme 40).[105] The overall transformation is very appealing as it leads directly into functionalised cyclic imines. The use of microwave heating reduces the reaction time and increases the isolated yields.



Scheme 40.

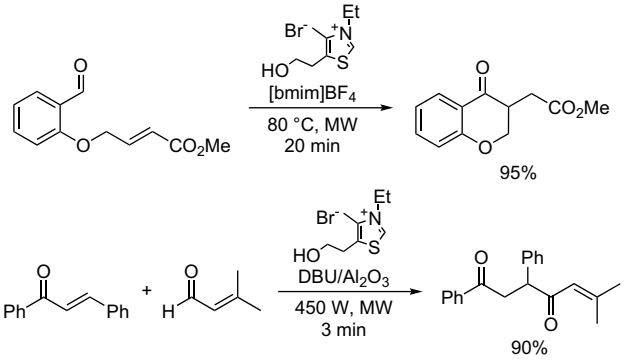
Radical chemistry has been successfully transformed onto solid phase and Fukase has described a microwave enhanced solid-phase radical cyclisation to give indole derivatives (Scheme 41).[106] Also, Bowman has extended work on *ipso* substitution to the solid phase and demonstrated the utility of microwave heating.[107]



Scheme 41.

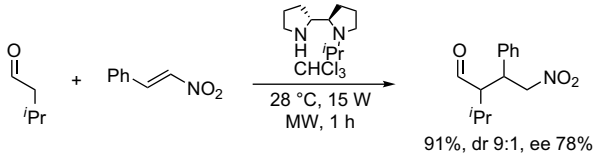
4. Organocatalysis

Organocatalysis has recently emerged as a major methodology for organic synthesis and there are examples of microwave enhanced protocols. For example, the groups of Yang[108] and Yadav[109] showed that the Stetter reaction can be enhanced under microwave conditions using solvent-free or ionic liquid protocols (Scheme 42).



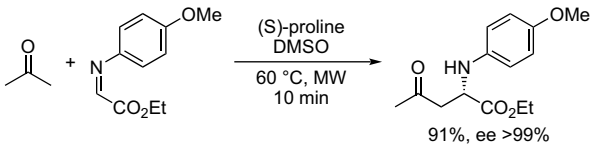
Scheme 42.

Of course, one of the most significant and important aspects of organocatalysis relates to its ability to deliver enantiomerically enriched compounds. Alexakis[110] (Scheme 43) and Kappe[111] (Scheme 44) have explored the impact of microwave energy on asymmetric organocatalysed transformations and shown that there are significant practical benefits associated with elevated temperature.

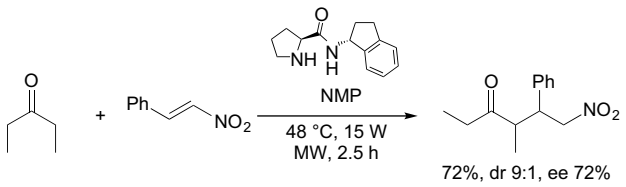


Scheme 43.

More recently, Najera has shown the positive impact that microwave heating can have on bifunctional prolinamide catalysed conjugate additions of ketones to unsaturated nitro compounds (Scheme 45).[112] In an unusual variant on the organocatalysis theme,

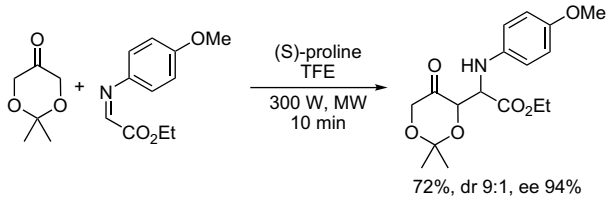


Scheme 44.



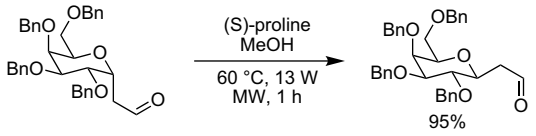
Scheme 45.

Westermann has reported the use of dihydroxy acetone in the diastereocontrolled organocatalytic Mannich-type reaction (Scheme 46).[113] In the latter cases the use of trifluoroethanol (TFE) and microwave heating allowed the reduction of the reaction time from 20 h to 5–15 min.



Scheme 46.

In a final example in this section, Massi and Dondoni describe an unusual organocatalytic reaction (Scheme 47).[114] Thus, they demonstrate that, using enamine catalysis under microwave irradiation, it is possible to induce anomerisation in carbohydrate derived aldehydes.

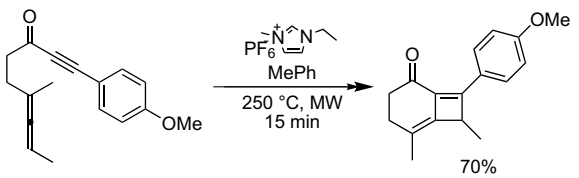


Scheme 47.

5. Cycloaddition

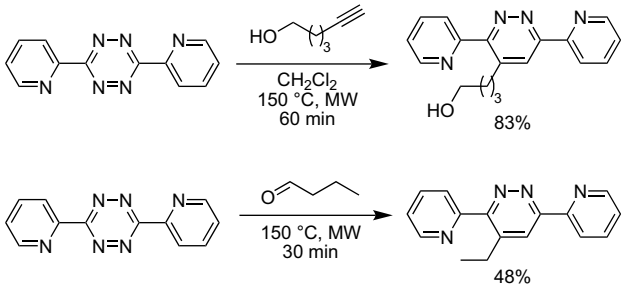
The benefit of microwave irradiation to a range of pericyclic reactions has been known since the early days of the development of this area.[115] There has been considerable activity in this area in recent years. For example, Brummond reported an interesting and relatively unusual [2+2] intramolecular cycloaddition between an alkyne and an allene (Scheme 48).[116] The reaction was optimised at relatively high temperatures, 250 °C, and the use of an ionic liquid as an additive was required to assist the dielectric heating. Under these conditions the intramolecular cycloaddition was successfully applied to a range of substrates.

More commonly, microwave radiation is used to assist or enhance Diels–Alder cycloadditions and as with the case in other areas of microwave chemistry the combination of technologies can be useful. For example, Kappe and van der Eycken have reported the benefits associated with combining high pressure methods with microwave chemistry, with the observation that pre-pressurisation of reaction vessels may offer significant benefits.[117] Moreover, the use of microwave chemistry can help mediate reactions that are in some way more environmentally benign than traditional methods.[118]



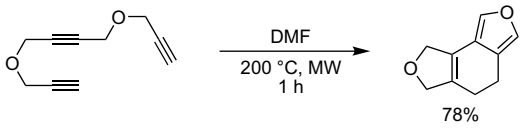
Scheme 48.

In an example of the use of microwave irradiation to mediate an unusual inverse-demand cycloaddition, Schubert described an interesting investigation into cycloadditions of tetrazines with alkenes and alkynes (Scheme 49).[119] The desired reactions work very well under microwave conditions. However, what is particularly notable is the finding that tetrazines react with aldehydes and ketones. The products are derived from reaction of the tetrazine with the enol tautomer of the aldehyde or ketone. Although the yields are not uniformly excellent this is a very appealing potential route to pyridazines derived from formal cycloaddition of gaseous dienophiles.



Scheme 49.

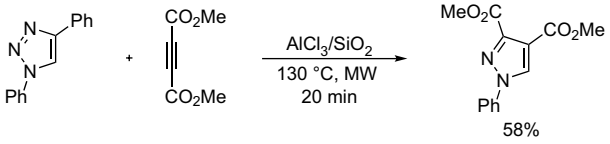
Ley has reported a microwave enhanced trimerisation metho dology based on alkynes (Scheme 50).[120] Thus, appropriately substituted triynes can undergo a much improved cyclotrimerisation using microwave heating.



Scheme 50.

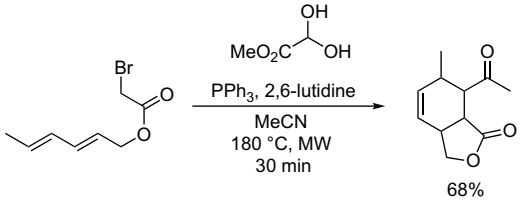
Solid-phase variations of microwave enhanced cycloaddition chemistry have also emerged in recent times. For example, van der Eycken reports the use of immobilised pyrazinones with dienophiles.[121] In general the cycloaddition/retrocycloaddition reactions are clearly shown to benefit from microwave heating conditions and the application of the method to a traceless methodology augurs well for the implementation of this approach into medicinal chemistry programmes.

In a somewhat different approach, Diaz-Ortiz and Prieto reported the use of a solvent-free cycloaddition between a 1,2,3-triazole and an alkyne (Scheme 51).[122] The reaction requires high temperature and employs silica-bound Lewis acids, the extrusion of a nitrile leading to substituted pyrazoles in moderate to excellent yields.



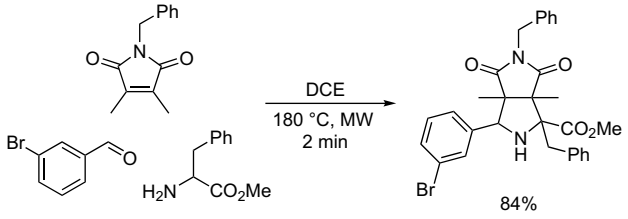
Scheme 51.

Dai has recently reported the development of a microwave enhanced tandem Wittig/Diels–Alder reaction, which exhibits significant rate enhancement upon microwave heating. However, some loss of some selectivity in the Wittig step is observed at elevated temperatures (Scheme 52).[123]



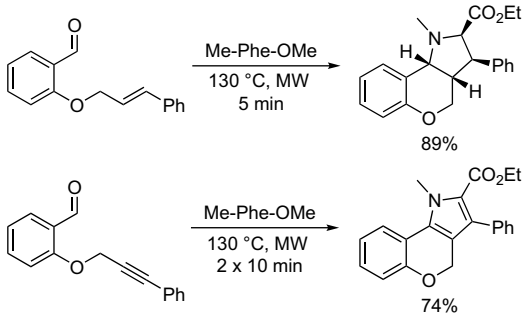
Scheme 52.

There has been a particularly high level of activity in the area of microwave enhanced [3+2] cycloadditions.[124] Azomethine ylides have been generated and employed in intermolecular cycloaddition reactions under microwave conditions. In a report by Sarko, an amino acid, an aldehyde and a maleimide are combined to give proline derivatives (Scheme 53).[125] This highly modular approach was exploited in the rapid synthesis of an 800-member collection of compounds.



Scheme 53.

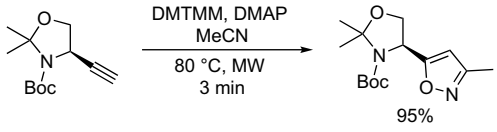
Bashiardes has reported a microwave enhanced intramolecular azomethine ylide cycloaddition (Scheme 54).[126] Once again, we see the potential for solvent-free reaction conditions and simple treatment of alkenyl or alkynyl aldehydes with an amino ester led to the isolation of cycloadducts in excellent overall yields and with significantly reduced reaction times.



Scheme 54.

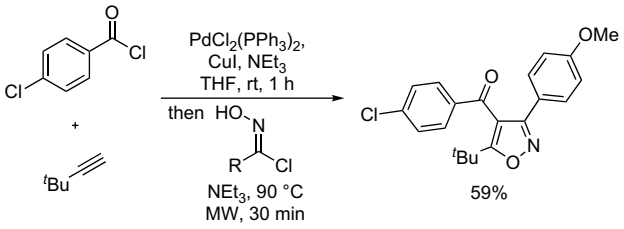
Nitrone cycloadditions have also been studied under microwave heating conditions. In the intermolecular sense, Fisera demonstrated that microwave heating could be used to enhance the rate of chiral nitrone cycloadditions, although it was noted that selectivity suffered as a result.[127] Under solvent-free conditions, Singh and coworkers report that intramolecular cycloaddition of nitrones benefits from microwave heating.[128]

The generation and cycloaddition of nitrile oxides have also been described under microwave heating. Hence, Giacomelli described a microwave enhanced route for the generation of nitrile oxides from nitro compounds using 4-(4,6-dimethoxy[1,3,5]-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM).[129] In an impressive one-pot protocol treatment of an alkyne with a nitro compound in the presence of DMAP and DMTMM in acetonitrile for 3 min led to the desired isoxazole in 95% yield (Scheme 55). Application to a solid-phase variant is also particularly notable.



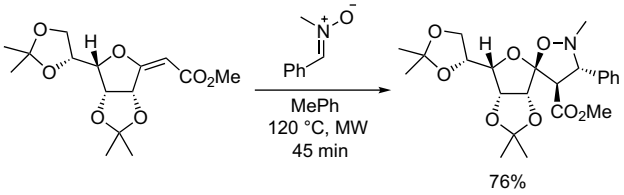
Scheme 55.

More recently, Muller has reported the reaction of nitrile oxides with alkynyl ketones (Scheme 56).[130] Again, the benefit in this case is the modular nature of the assembly of precursors, coupled with an efficient microwave enhanced cycloaddition.



Scheme 56.

In a nice illustration of the applicability of nitrile oxides and nitrone cycloaddition, Taillefumier and Chapleur described the participation of *exo*-glycals with dipoles in [3+2] cycloadditions (Scheme 57).[131] Of particular note are the nitrone cycloadditions, which are only successful under microwave heating conditions, with no product reported under thermal conditions.



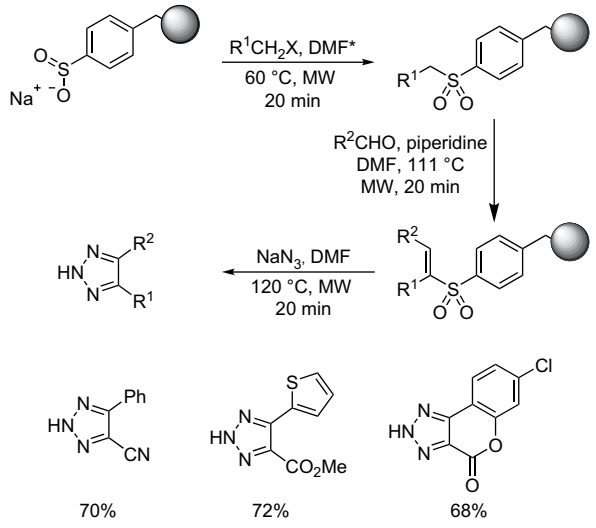
Scheme 57.

Unsurprisingly, the most significant area of development in microwave enhanced cycloaddition chemistry has been to promote the reaction of azides with alkynes and alkenes. Now known by many as 'click reactions', these cycloadditions have been recognised to be very useful, especially in biology and polymer science applications.[132]

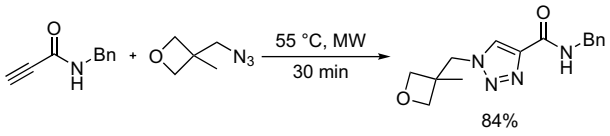
The most common cycloaddition reaction using an azide is probably now with an alkyne and this provides a route to triazoles. However, in a nice alternative, Lam described the cycloaddition of vinyl sulfones with azides (Scheme 58).[133] The work is directly applied to a solid-phase approach and provides very convenient access to triazoles. A microwave enhanced sequence involving sulfinate conversion into a sulfone, Knoevenagel condensation and finally azide cycloaddition is reported. It is notable that each step is enhanced under microwave heating.

Returning to the reaction of azides with alkynes, it is interesting to note the report by Katritzky who described the cycloaddition of azides with alkynyl amides (Scheme 59).[134] These alkynes are generally rather resistant to cycloaddition, but under microwave enhanced solvent-free conditions they occur cleanly and in high yield.

van der Eycken and Fokin have described a one-pot synthesis of triazoles using the copper catalysed version of the Huisgen 1,3-dipolar

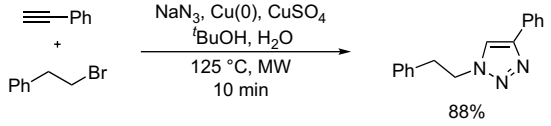


Scheme 58.



Scheme 59.

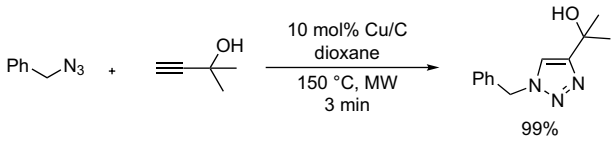
cycloaddition (Scheme 60).[135] Thus, reaction of an alkyl halide with an azide can be achieved in the presence of an alkyne and thence cycloaddition takes place, all in a single microwave enhanced protocol. The reactions are completely regiocontrolled and proceeded in good to excellent yields.



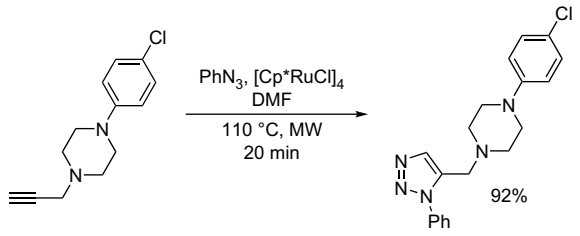
Scheme 60.

The use of copper to catalyse these cycloadditions has been an important development and in a recent advance, Lipshutz described the use of copper on charcoal for catalysis (Scheme 61).[136] This heterogeneous protocol offers advantages over existing catalytic methods, however, what is particularly noteworthy is the finding that under microwave heating the reaction can be carried out without base and with exquisite 1,4-selectivity in a few minutes. Moreover, the level of copper contamination is minimal and, indeed, ICP-AES analysis of the triazoles indicated that levels are so low that accurate measurement was not possible.

An alternative to the copper catalysed cycloaddition requires the use of alternative metals and Fokin has reported an interesting development of a new variant on ruthenium chemistry, which generates the 1,5-isoxazole, which cannot be accessed using Cu mediated or uncatalysed reactions (Scheme 62).[137] Hence, the use of pentamethylcyclopentadienylruthenium(II)chloride tetramer could be employed in DMF under microwave irradiation. Of particular note is the success reported when utilising aryl azides,



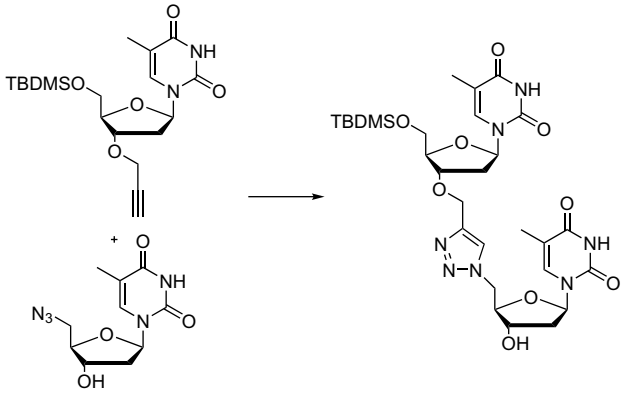
Scheme 61.



Scheme 62.

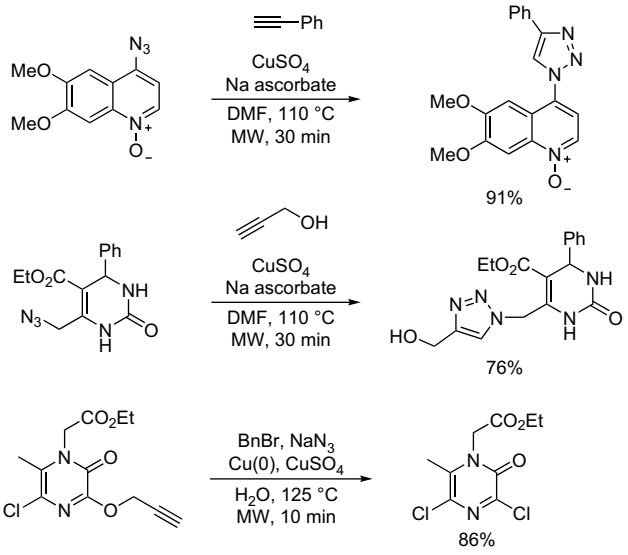
which are notoriously unreactive under most cycloaddition conditions.

Applications of the azide–alkyne cycloaddition are widespread and, here too, microwave heating can enhance reactivity. Zerrouki has reported the generation of triazole linked dithymidines making extensive use of microwave heating for both precursor synthesis, via alkylation reactions, and the cycloadditions themselves (Scheme 63).[138]

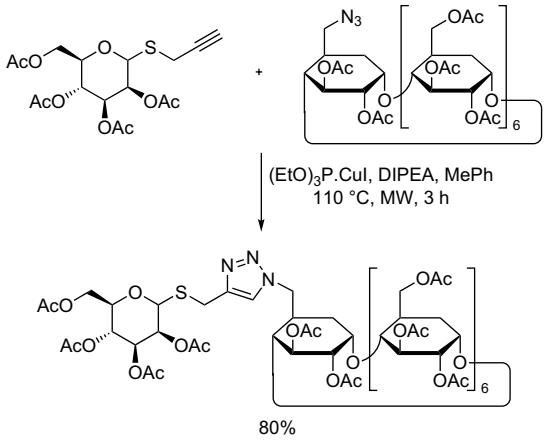


Scheme 63.

Kappe has made extensive use of microwave heating to enhance cycloaddition reactions of azides. For example, in the synthesis of 4-triazolyl-2(1*H*)-quinolones phenyl azides undergo microwave enhanced cycloaddition with alkynes, employing copper sulfate and sodium ascorbate (Scheme 64).[139] The same group has incorporated these microwave-enhanced cycloadditions into multicomponent reaction sequences in order to make known and new



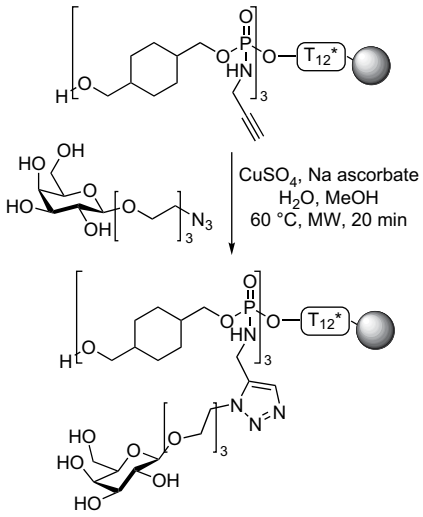
Scheme 64.



Scheme 65.

classes of heterocycle including dihydropyrimidinones and pyrazinones (Scheme 64).[140,141]

One of the major attractions for utilisation of this type of cycloaddition is the potential application to the synthesis of biologically important molecules or probes.[142] For example, Santoyo-Gonzales has reported that microwave enhanced cycloaddition of multivalent neoconjugates could be mediated employing $(Ph_3P)_3{\cdot}CuBr$ and $(EtO)_3P{\cdot}CuI$ as organic soluble catalysts (Scheme 65).[143] In Morvan's paper, microwave-enhanced cycloadditions of modified supported oligonucleotides with azide derivatives of sugars are described (Scheme 66).[144] As noted by the authors there are several advantages to this methodology including the ability to introduce several alkynes with good positional control, the rapid reactivity and the ease of purification.



Scheme 66.

Modified peptides have also been made utilising microwave-enhanced azide cycloaddition. For example, Liskamp reported the synthesis of peptide based polymers.[145] Variation of the reaction conditions led to different levels of products isolated from cycloaddition of the peptide based azido-alkyne. In particular, the use of microwave heating conditions apparently leads to high molecular weight polymers.

Application of microwave-enhanced azide cycloaddition chemistry to dendrimer synthesis and functionalisation has been reported by several groups. Weck has described the monofunctionalisation of dendrimers. Under copper catalysis with microwave heating these reactions proceed with extremely high yields.[146] Liskamp and Pieters describe the synthesis of glycodendrimers and dendrimeric peptides via microwave-enhanced cycloadditions.[147,148] In the latter work, access to smaller and larger peptide based systems with the potential as protein mimetics is provided (Scheme 67).

Finally in this section the application of microwave enhanced cycloaddition reactions to the functionalisation of fullerenes and nanotubes will be considered. Thus, azomethine ylides can undergo a regiocontrolled addition to C70 and the benefit of using microwave heating is the ability to modify the regiochemistry to give predominantly the 5–6 isomer.[149] The authors go on to propose that the regiocontrol can be explained by a kinetically controlled cycloaddition process. Diels–Alder cycloaddition of *o*-quinodimethane to single-wall carbon nanotubes has also been reported by Navarette and Langa.[150] More recently, Prato and Vazquez reported reversible microwave-enhanced cycloaddition of aziridines to single-wall nanotubes.[151] These results point to an important future development, as functionalised single-wall nanotubes are both desirable and presently fairly difficult to obtain. It is likely that this, along with the development of microwave enhanced nanoparticle synthesis, will be an area of considerable activity in the coming years.[10]

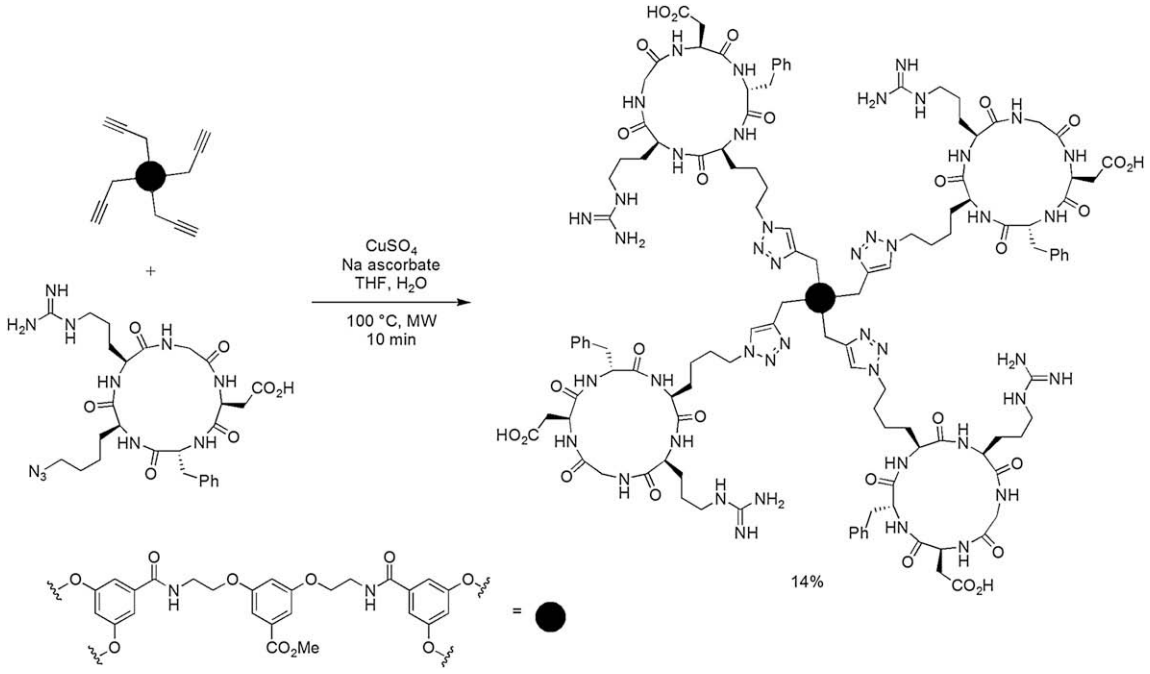
6. Metathesis

In recent times, there has been considerable interest in the application of microwave irradiation to a range of metathesis processes and this area has been the subject of recent reviews.[152,153] As expected, there is considerable benefit in the high temperatures that can be rapidly achieved with microwave conditions and the utilisation of reagents and catalysts containing thermally stable ligands, such as *N*-heterocyclic carbenes, provides ample opportunity for the enhancement of metathesis. Unsurprisingly, it has been ring-closing metathesis, which has been the focus of many studies and microwave enhanced ring-closing metathesis of dienes has been reported and in the main it appears that enhancement can be attributed to a heating effect.[154–156] Some additional benefits can be accrued by careful control of reaction conditions, for example, by carrying out the reactions under solvent-free conditions[157] or by using ionic liquids[158] or by combining microwave irradiation with inert gas sparging.[159] These protocols have been used for a variety of ring-closing metathesis applications and it is notable that application to natural product synthesis has been successfully achieved.[160] The application of several microwave enhanced transformations has been nicely illustrated by van der Eycken in approaches to buflavine analogues, which involve a microwave enhanced Suzuki–Miyaura reaction and a microwave enhanced ring-closing metathesis.[161]

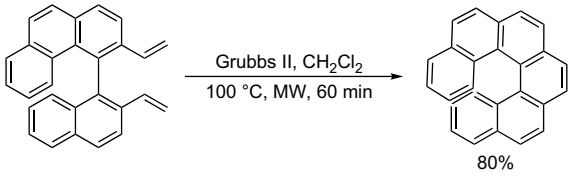
A particularly good example of the application of ring-closing metathesis in synthesis was reported by Collins for the synthesis of helicenes (Scheme 68).[162] As noted in the paper, the approach can be used to make 5-, 6- and 7-helicene in excellent yields and this method represents one of a small number of applications of metathesis to make aromatic ring systems.

Another nice application of microwave enhanced ring-closing metathesis towards strained systems is reported by Campagne in which a 1,5-enyne metathesis is mediated under microwave conditions using Grubbs–Hoveyda II catalyst (Scheme 69).[163] Although the yields are not outstanding these reactions do proceed better under microwave conditions and represent an important advance.

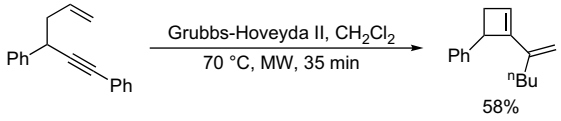
Microwave enhanced ring-closing metathesis has featured in the synthesis of peptides and peptide mimetics. In a seminal contribution, Leatherbarrow showed that solid-phase ring-closing metathesis could be used for the synthesis of Bowman–Birk inhibitor analogues (Scheme 70).[164] A similar approach was used by Robinson in the synthesis of analogues of α-conotoxin IMI (Scheme 71).[165]



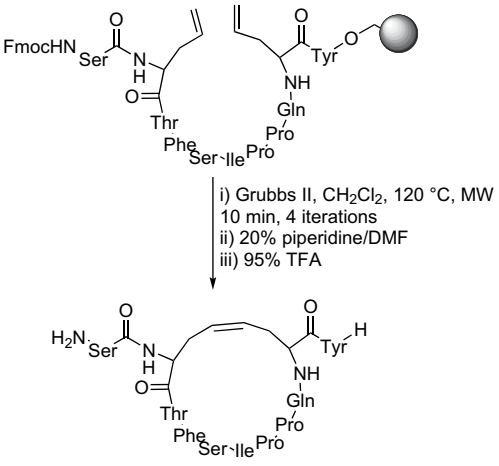
Scheme 67.



Scheme 68.



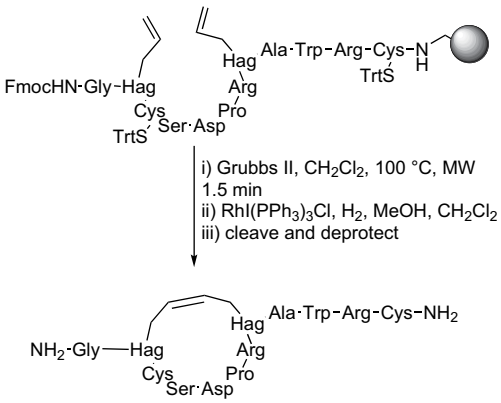
Scheme 69.



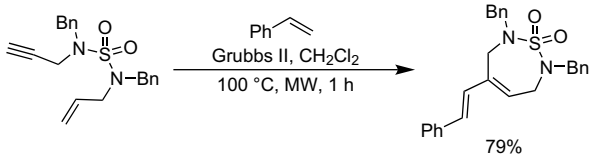
Scheme 70.

In a very nice sequential approach Brown demonstrated the use of tandem ring closing and cross-metathesis under microwave enhancement (Scheme 72).[166]

Whilst the latter example highlights the potential for utilising microwave enhancement in the realm of cross-metathesis, it is certainly the case that this is an area, which has attracted considerably less attention and there are significant opportunities for further development. In 2005, Murray reported microwave enhanced cross-metathesis of electron-deficient alkenes with an electron-rich alkene.[167] The benefits of using microwave enhancement are dramatic: conventional heating requires 2–6 h whereas with yields between 60 and 80%, under microwave heating the



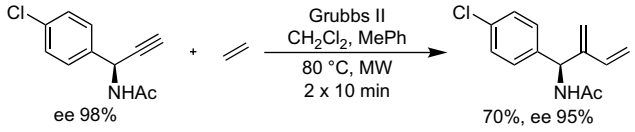
Scheme 71.



Scheme 72.

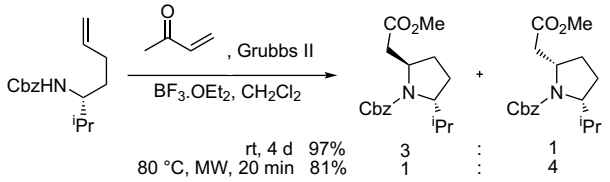
reactions require 1–15 min with yields of 50–80%. Rodriguez has examined a significant variety of alkene partners in alkene–alkene cross-metathesis and has concluded that not only does microwave heating reduce the reaction time but it also has a positive impact on the TON of the catalysts.[168]

In alkene–alkyne cross-metathesis, Botta has also demonstrated a very elegant approach to dienes (Scheme 73).[169] Treatment of an alkyne with ethylene using Grubbs II under microwave enhanced conditions leads to moderate to good yields of the desired products with no racemisation.



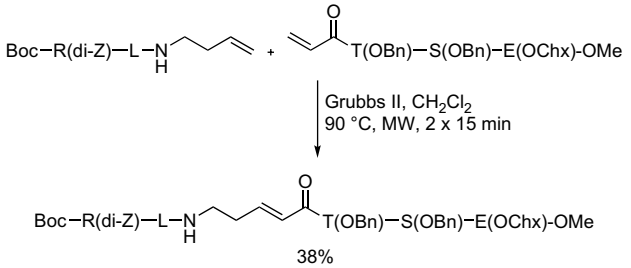
Scheme 73.

In another very elegant example of cross-metathesis, Fustero showed a powerful combination of microwave enhanced cross-metathesis of an electron-deficient alkene with a mono-substituted alkene bearing an amine (Scheme 74).[170] Under conventional conditions a modest yield of the desired product is isolated. However, under microwave irradiation the cross-metathesis product then undergoes intramolecular conjugate addition with the formation of the cyclic amine products in excellent yields. Although the reactions could be carried out under conventional heating conditions over a prolonged period of 4 days, they were more conveniently mediated over a 20 min period utilising microwave conditions.



Scheme 74.

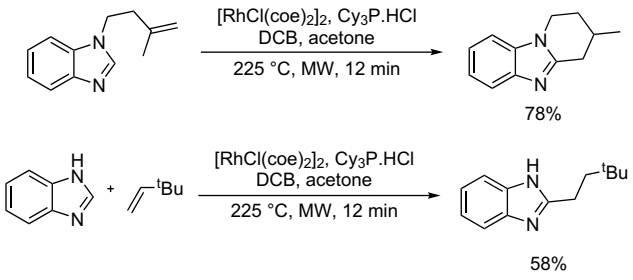
Finally in this area, cross-metathesis has been used as a method for joining peptide fragments. In an attempt to make main chain peptide mimetics, Caddick has reported cross-metathesis of alkene modified amino acids (Scheme 75).[171] In order for the reactions to proceed, there is a requirement for the use of Grubbs II and the reactions require careful gassing/purging. However, under these conditions a variety of microwave enhanced cross-metatheses have been mediated to give novel peptide mimetics.



Scheme 75.

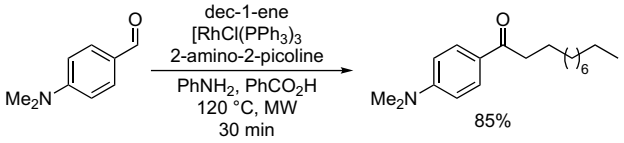
7. Metal mediated transformations

In the area of rhodium chemistry, Souers and co-workers have described a microwave enhanced C–H activation protocol.[172] This team showed that it is possible to mediate a benzimidazole CH activation using between 2 and 10% of a rhodium catalyst to allow the preparation of cyclic structures in good yields and with short reaction times. Careful selection of the solvent was an important factor in the successful optimisation of this protocol with 25% of acetone in *o*-dichlorobenzene (DCB) identified as being optimal (Scheme 76). A very impressive development was the extension to an intermolecular variant, which was successful in a modest 58% yield. A more recent report from Bergman and Ellman describes a detailed extension of the C–H activation approach and shows how aryl halide coupling can be carried out in addition to the original alkene carbometallation approach.[173]



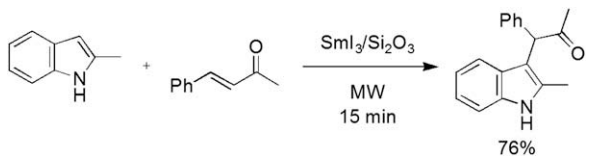
Scheme 76.

Rhodium mediated conjugate addition has also benefited from microwave irradiation and the groups of Loupy and Jun,[174] and Frost[175] have both made important contributions. The well known rhodium mediated hydroacylation of alkenes is explored under microwave conditions by Loupy and the key to their success is the use of a solvent-free method and the addition of 2-amino-3-picoline, aniline and benzoic acid (Scheme 77). In the work described by Frost, alkene functionalisation was carried out using a boronic acid and the reaction was rendered enantioselective via selective protonation.



Scheme 77.

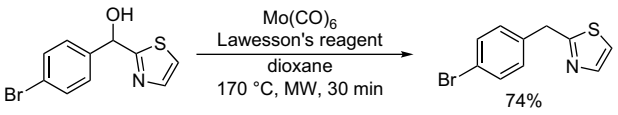
Zhan has also contributed to conjugate addition chemistry under microwave heating conditions. In their work, they utilise a samarium(III) catalysed conjugate addition of indoles to α,β-unsaturated ketones and nitro compounds (Scheme 78).[176] The method works well in that it proceeds to give good yields of product with reduced reaction times.



Scheme 78.

In the area of molybdenum catalysis, Larhed[177] and Moberg[178] have both described asymmetric allylic substitution under microwave enhanced conditions and in the latter case utilising a solid support. In the former case the ability to utilise $Mo(CO)_6$ as an air stable precatalyst is also noteworthy.

Alterman has recently described a interesting alcohol deoxygenation utilising $Mo(CO)_6$ and Lawesson's reagent under microwave conditions (Scheme 79).[179] The reaction is compatible with

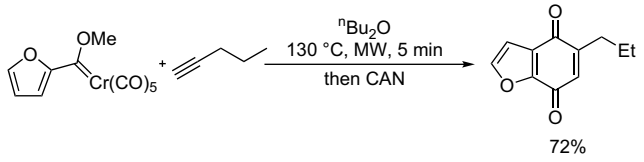


Scheme 79.

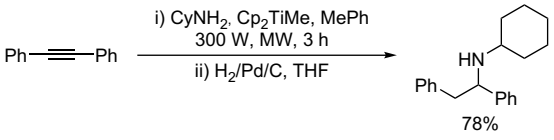
aryl halides and proceeds in modest to excellent yields with a variety of substrates.

Moving to nickel, Leadbeater has reported microwave enhanced halide exchange.[180] Thus, treatment of aryl iodides with nickel bromide or chloride led to moderate to good yields of the corresponding iodides or bromides. The reaction is also compatible with bromides and it is possible to convert chlorides into bromides. The protocol is simple and fairly quick, although it does require 1–2 equiv of the nickel salt.

Kerr recently described a very efficient Dotz annulation, which is remarkably rapid and in some cases very high yielding (Scheme 80).[181]



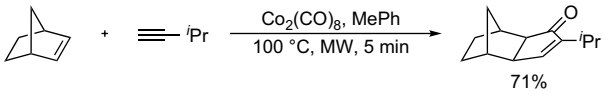
Scheme 80.



Scheme 81.

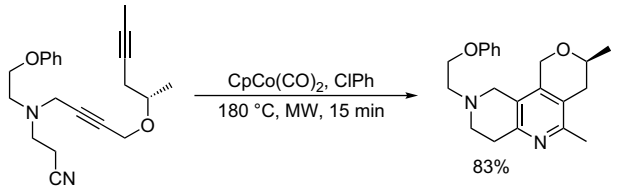
Remaining with alkyne functionalisation, Doye described a microwave enhanced alkyne amination protocol (Scheme 81).[182] Thus, treatment of a terminal or disubstituted alkyne with a range of primary amines employing around 3% Cp_2TiMe_2 under microwave conditions led to intermediate imines, which were then subjected to reduction to give unsymmetrical secondary amines.

Alkynes of course are well known for their participation in the remarkable Pauson–Khand reaction and Groth has reported the use of microwave heating to promote intermolecular and intramolecular cyclisation to generate enones (Scheme 82).[183] The benefit of the use of microwave conditions is that it allows the reaction to proceed with 20% of cobalt complex with no requirement for an additional source of CO.



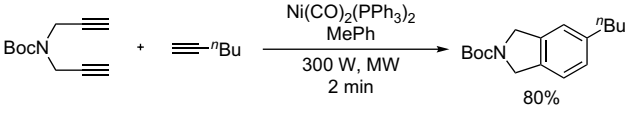
Scheme 82.

Microwave heating has been shown to have a beneficial effect on cyclotrimerisation of alkynes and related compounds and contributions have been made from a number of groups, who have utilised cobalt, nickel and ruthenium (see Scheme 11 and Scheme 50 above). Snyder showed that cobalt mediated [2+2+2] cyclisations are possible utilising a combination of nitriles and alkynes (Scheme 83).[184] This report provides a very interesting method for the production of unusual heterocyclic templates and the study contains some applications of interesting heteroatom-containing linking chains and chiral attachment points.

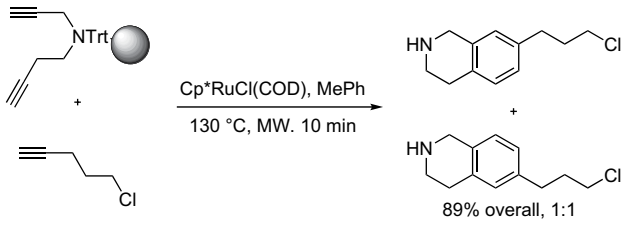


Scheme 83.

Dieter has also been active in this area and in two recent reports describes alkyne cyclotrimerisation using nickel and ruthenium.[185,186] The nickel protocol is carried out in solution phase and is applied to the construction of carbocycles (Scheme 84), whereas the ruthenium protocol is carried out on solid phase (Scheme 85).

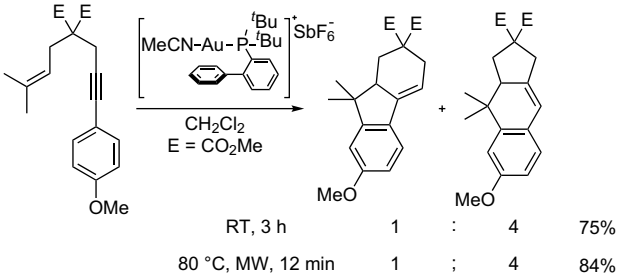


Scheme 84.



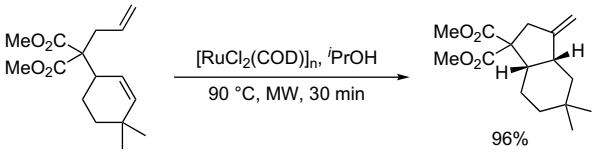
Scheme 85.

Moving from polyalkynes to enynes, Echavarren has explored the use of microwave heating for gold catalysed cycloaddition reactions. Although many of these reactions do proceed at ambient temperatures it is shown that many of them can be accelerated from hours/days to minutes with microwave heating (Scheme 86).[187] It is likely that the impact of microwave heating on gold catalysis will be an area of significant future development.



Scheme 86.

Diene cyclisations have also been shown to benefit from microwave heating. Thus, Fairlamb has examined the ruthenium catalysed diene cyclisation and found that increased yields and reduced reaction times result from microwave heating (Scheme 87).[188]



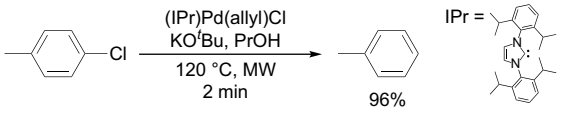
Scheme 87.

8. Palladium catalysed coupling reactions

This is an area of enormous significance in organic chemistry and there have been a very significant number of research investigations reported, which are focused on the use of microwave irradiation to enhance palladium catalysed coupling protocols and several review articles have provided a detailed analysis of this area so this section will only provide a selection of recent highlights.[189,190]

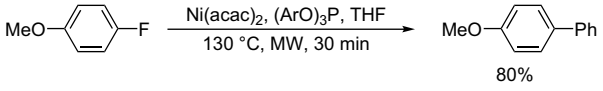
Given the powerful nature of palladium chemistry it is unsurprising that application of microwave enhanced protocols to diversity oriented synthesis is now being reported.[191] Similarly, applications of microwave enhanced solid-phase palladium catalysis are also becoming more commonplace and most commonly the ligand is being tethered to the solid support.[192,193] However, it is important to note that a robust linkage between the support and the ligand needs to be in place and it is not always clear that this will always be the case. Moreover, careful consideration of the impact of changes on the ligand structure, and indeed the ligand–metal stoichiometry, all need to be carefully considered when developing this type of heterogeneous approach.

Of course, a variety of bonds will undergo oxidative addition as a first step in the majority of palladium catalysed protocols and under usual circumstances the aim is to make a C–C, C–N, C–O or C–S bond. However, there are occasional reasons for wishing to carry out some form of reduction. In an interesting observation, Nolan has reported that using a microwave-mediated protocol, employing (NHC)Pd(allyl)Cl complexes they can achieve good yields for reduction of aryl chlorides (Scheme 88).[194]



Scheme 88.

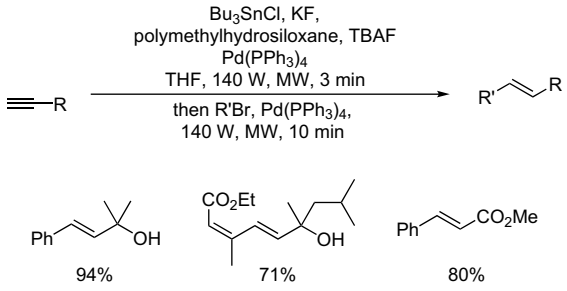
In an interesting study, Dankwardt has explored the use of aryl fluorides in coupling with Grignard reagents. Some success is achieved using a microwave-mediated protocol with moderate to good yields obtained in coupling of aryl fluorides with aryl Grignard reagents under palladium and nickel catalysis (Scheme 89).[195]



Scheme 89.

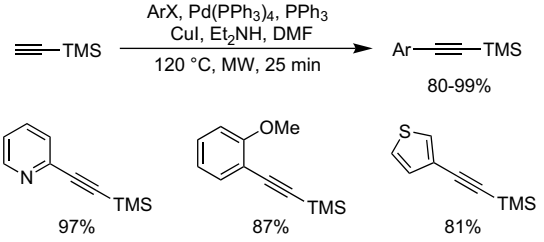
Given the interest in development of different types of palladium catalyst it is not surprising that many researchers are investigating the interplay between reagent and method of heating and some notable useful developments have resulted. Some interesting protocols based on palladium nanoparticles have recently been described and of course this is particularly useful as often many of the organic ligands utilised in palladium chemistry can by themselves add limitations to coupling reactions.[196,197] One of the advantages of using nanoparticles is that it has the potential to deliver a methodology that requires very small quantities of palladium. In a recent report, Cravotto and Palmisano have studied a range of Suzuki couplings using ligandless conditions and, using a novel flow reactor, were able to combine both microwave and ultrasound to give excellent yields of biaryls with very short reaction times.[198]

Although not quite as widely used as in the past, the Stille reaction is still useful for organic synthesis and recent illustrations in the steroid area and polythiophene synthesis highlight the potential value of using microwave enhancement.[199,200] In a particularly good example, Maleczka reported a microwave enhanced one-pot protocol, which allows the conversion of an alkyne into a vinylstannane and thence direct coupling with a vinyl iodide. The conversions are good to excellent and this allows the synthesis of functionalised alkenes and dienes using simple and practical procedures (Scheme 90).[201]



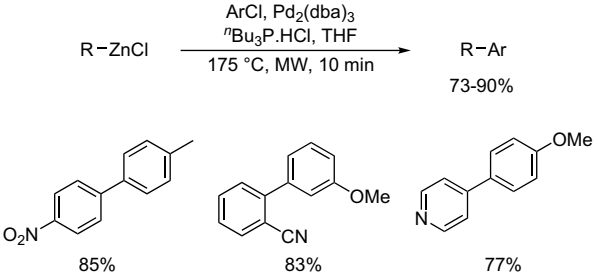
Scheme 90.

The Sonogashira reaction of an alkyne with an aryl halide has also been subjected to microwave enhancement.[202] Erdeyli has shown that aryl halides and triflates will undergo a rapid coupling with alkynes in good yields (Scheme 91).[203] The same group has shown that this work can be extended to a solid-phase variant by attachment of the aryl halide onto an appropriate resin.[204]



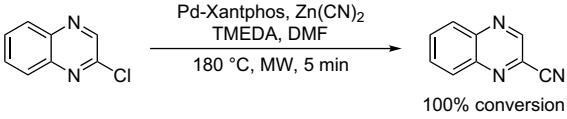
Scheme 91.

Both the Negishi and Kumada reactions have also been enhanced using microwave heating. Kappe has reported that a variety of factors are important for optimisation of these reactions (Scheme 92).[205] The microwave dielectric heating is an important factor not only in the coupling reaction but also for the preparation of the organometallic coupling partner.[206] Extension to a solid-supported variant has also been discussed by Kappe.[205]



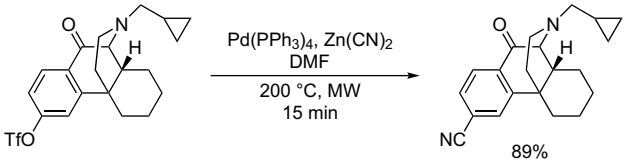
Scheme 92.

The introduction of a nitrile via palladium catalysed coupling of aryl halides can be a useful alternative to other methods and has been the subject of some investigation. Thus, Pitts described a microwave enhanced method, which could be used for multi-gram synthesis via batch or flow processes (Scheme 93).[207] Similarly,



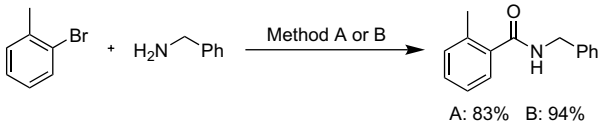
Scheme 93.

Neumeyer reported cyanation of triflates under microwave irradiation specifically for the synthesis of functionalised morphinans (Scheme 94).[208]



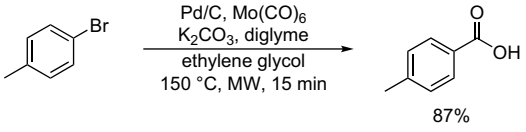
Scheme 94.

The related transformation involving carbonylation has also been successfully improved/enhanced using microwave chemistry. Larhed reported that aminocarbonylation can be readily mediated using molybdenum hexacarbonyl and this provides a route into biaryl amides (Scheme 95).[209] The author also reported the use of DMF as an alternative to molybdenum.[210] In addition, he has described the conversion of aryl halides into their corresponding carboxylic acids (Scheme 96).[211]



Method A: $Mo(CO)_6$, [Pd], DBU, THF,150 °C, MW, 15 min
Method B: $Pd(OAc)_2$, dppf; imid., KO^{t}Bu; DMF; 190 °C, MW, 20 min

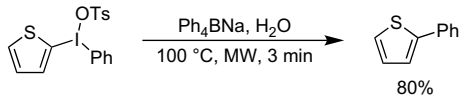
Scheme 95.



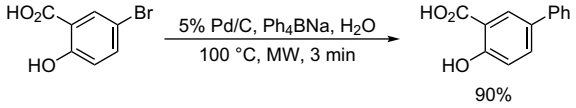
Scheme 96.

There have been a significant number of reports on the successful improvement of the Suzuki, Suzuki–Miyaura and similar reactions using microwave conditions. For example, Yan has described the direct coupling of iodonium salts with sodium tetraphenylborate (Scheme 97),[212] whereas Xu derived similar products from the palladium catalysed coupling of sodium tetraphenylborate and aryl bromides in water with very low catalyst loading, 0.05 mol % (Scheme 98).[213]

Water is being utilised increasingly as a solvent for palladium catalysed couplings.[214,215] For example, Leadbeater showed the use of palladium acetate at low catalysts loading, 0.4 mol %, in water for the coupling of arylboronic acids with aryl bromides and then more recently the use of palladium on carbon for the analogous reaction utilising aryl chlorides.[216,217] Key to this latter work is the utilisation of the heating–cooling protocol, which the authors suggest will prolong the lifetime of the aryl chloride during the reaction.

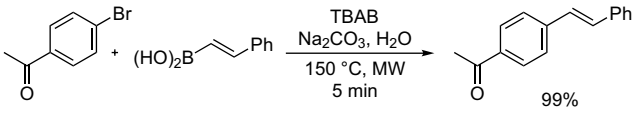


Scheme 97.

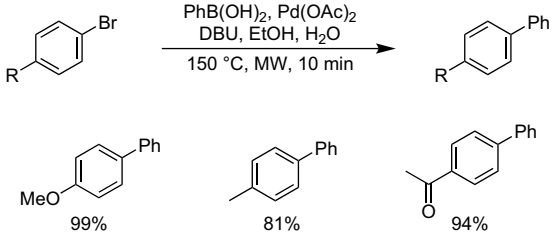


Scheme 98.

The same author has also reported a microwave enhanced Suzuki reaction, which can proceed with ultra-low levels of metals present in bases commonly employed in Suzuki reactions (Scheme 99).[218] More recently, the same group has reported the use of the bases DBU and DABCO as alternatives in aryl halide couplings of this type (Scheme 100).[219]



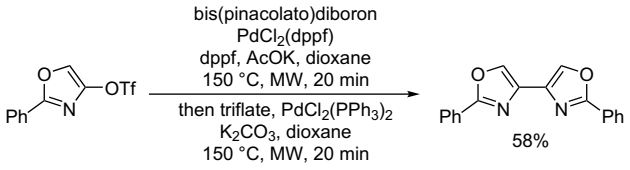
Scheme 99.



Scheme 100.

Remaining with the theme of water, Varma has also used a water-based system for a ligandless Suzuki reaction in water. In this case, the key to success was the utilisation of polyethylene glycol, which serves as an alternative to more conventional solvent systems.[220] Freundlich described the arylation of bromophenols using palladium on carbon and which is enhanced using microwave irradiation.[221] Microwave enhanced Suzuki reactions have also found utility in poly(thiophene) synthesis. For example, Barbarella has described solution phase and solvent-free microwave enhanced Suzuki couplings employing thiopheneboronic acids.[222,223] Kabalka has reported solvent-free Suzuki couplings using palladium doped onto potassium fluoride alumina.[224] In a very nice development, the Ley group has described the use of a microwave enhanced Suzuki protocol utilising their palladium EnCat catalyst.[225] This encapsulated metallic species can be used in flow and batch protocols and has wide applicability for Suzuki couplings.

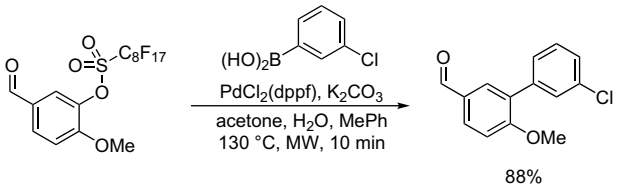
The majority of Suzuki and related coupling reactions are carried out utilising bromides and iodides. However, Greaney has used triflates in an efficient microwave enhanced synthetic approach to functionalised oxazoles. Thus, arylboronic acids could be coupled effectively to triflates, illustrated particularly well by a one-pot approach to bis-oxazoles (Scheme 101).[226]



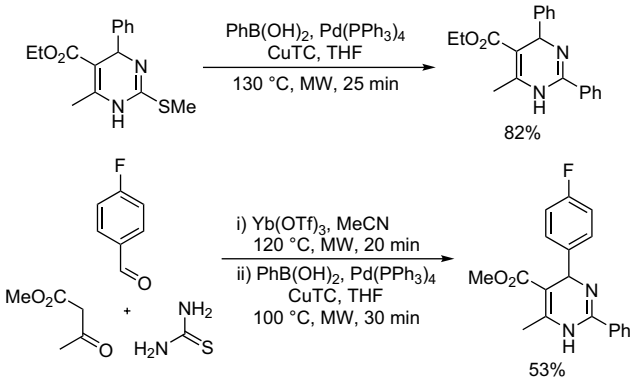
Scheme 101.

Zhang has described the use of fluorous-phase sulfonates as participants in Suzuki-type couplings (Scheme 102).[227] This is advantageous because of the ease of purification of intermediates that have this type of fluorous tag. The couplings proceeded very well under microwave conditions and offer an alternative to classical triflates.

Kappe has reported the use of thiones as coupling partners with arylboronic acids (Scheme 103).[228] Thus, direct coupling of



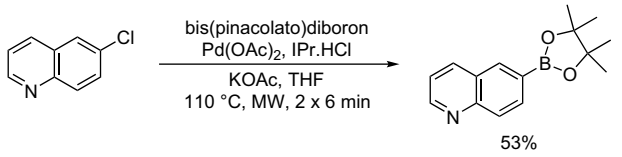
Scheme 102.



Scheme 103.

a thioamide with a phenylboronic acid, employing palladium catalysis in the presence of Cu(I) thiophene-2-carboxylate, CuTC, under microwave conditions gives the aryl dihydropyrimidines. One of the appealing features of this work is that the precursors can be prepared in a rapid microwave enhanced multi-component reaction and, in two steps, a large collection of substituted dihydropyrimidines can be prepared.

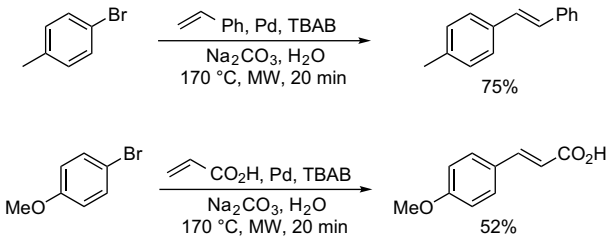
Of particular importance in palladium chemistry is the ability to use aryl chlorides and it is often found that microwave chemistry can be useful in helping render this class of compound useful for Suzuki coupling. There are now numerous methods for mediating Suzuki coupling reactions using aryl chlorides.[229] However, a particularly good example of the use of chlorides in palladium catalysis is provided by Furstner (Scheme 104).[230] In this study, a microwave enhanced coupling was utilised to develop a route to aryl pinacol boronates from aryl chlorides and bis(pinacolato)diboron, employing an imidazolium chloride (IPr·HCl) and microwave heating.



Scheme 104.

It is also the case that microwave enhancements have been commonly observed in the Heck reaction. For example, classical Heck reactions using aryl bromides and acrylates can be accelerated and proceed in good yield when carried out under microwave irradiation using ionic liquids.[231,232] The ionic liquid has been shown to be recyclable and the products were easy to isolate from these reaction conditions. Cravotto has described a Heck protocol with relatively low levels of palladium, 0.01 mol %.[233] In this case, they utilise an organic solvent, but the key to their success is the application of microwave irradiation and ultrasound.

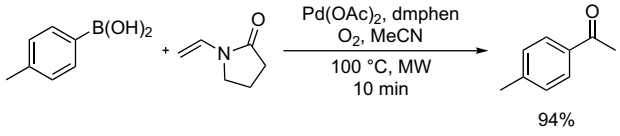
Another area of development for the microwave enhanced Heck reaction has been the use of water as a solvent and in concert with very low levels of palladium. Thus, Leadbeater and co-workers have reported Heck reactions of electron-rich and electron-deficient alkenes using aryl bromides under microwave conditions in water (Scheme 105).[234] Very low levels of 1 ppm palladium have been employed and this protocol looks potentially useful for scale-up. The use of a stoichiometric quantity of tetrabutylammonium bromide and potassium carbonate is required and the reactions proceed in moderate to good yields.



Scheme 105.

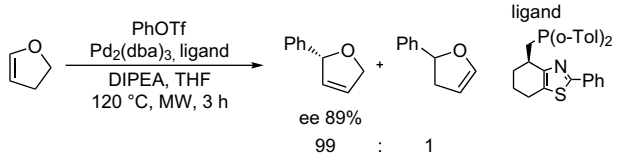
Najera has also reported a water-based protocol for the mono and double Heck arylations of electron-deficient alkenes. In this work, several protocols are recommended for different classes of substrate. However, a unifying feature is the use of an oxime-derived palladacycle as the catalyst.[235–237]

One of the key issues in the Heck reaction is that of regiochemistry and it is most common to observe β selectivity for addition to mono-substituted alkenes. In a very elegant piece of work, Larhed described the development of a microwave enhanced oxidative Heck reaction (Scheme 106).[238,239] Thus, using arylboronic acids under an oxygen atmosphere electron-rich alkenes, including enol ethers and amides, undergo α-arylation and the use of microwave irradiation reduces the reaction time to 10 min. In a related report, the same group also report the synthesis of β-disubstituted alkenes via Heck arylations utilising aryl chlorides employing a palladacycle and Fu's $[(^tBu_3)PH]BF_4$ pre-ligand.[240]

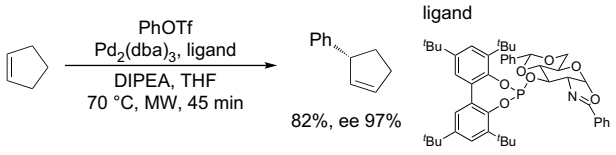


Scheme 106.

Another key issue in the microwave enhanced Heck reaction is asymmetric induction and Larhed has made important contributions in this area.[241] Thus, high levels of enantioselectivity can be obtained when carrying out the Heck reaction of dihydrofurans using aryl triflates, employing a palladium–phosphineoxazoline catalyst. The use of microwave irradiation is beneficial, but it does tend to compromise the levels of asymmetric induction. However, by judicious design of the catalyst Andersson has demonstrated that excellent levels of enantioselectivity can be achieved (Scheme 107).[242] Dieguez and co-workers have also been active in this area and have developed a microwave enhanced asymmetric Heck reaction employing sugar-based oxazolines. With their optimised system, they are able to mediate Heck reactions with cyclopentene and other less commonly studied alkenes (Scheme 108).[243]

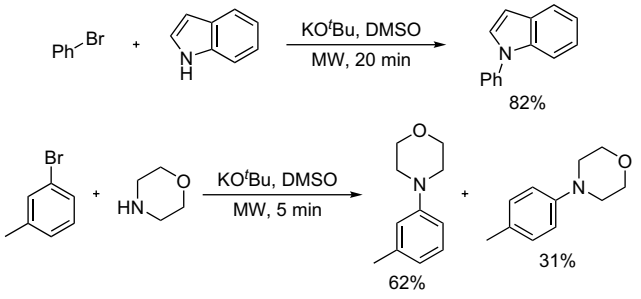


Scheme 107.



Scheme 108.

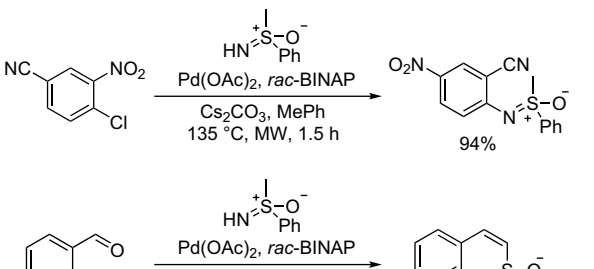
C–N bond formation has also been an area of considerable activity and Tu recently reported a microwave-mediated amination via the base-mediated generation of a benzyne. Yields are high and the reaction times are short and this provides a useful extension of methods for generating aryl amines (Scheme 109).[244]



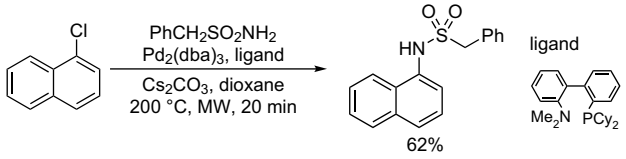
Scheme 109.

Caddick has used a palladium–imidazolium salt protocol to mediate amination of aryl chlorides under microwave conditions and has compared the use of these in situ methods with the application of bis-carbene–palladium complexes.[245] In a more demanding case, Harmata showed that sulfoximines can undergo N-arylation with aryl chlorides under microwave conditions. Careful choice of substrates in this study allows the authors to demonstrate the potential for utilising this method for the synthesis of heterocycles (Scheme 110).[246] Remaining with C–N bond formation, Cao has also used N-arylation, employing chlorides. However, in this case the amine component is a sulfonamide and this method provides a good route into *N*-aryl substituted sulfonamides (Scheme 111).[247]

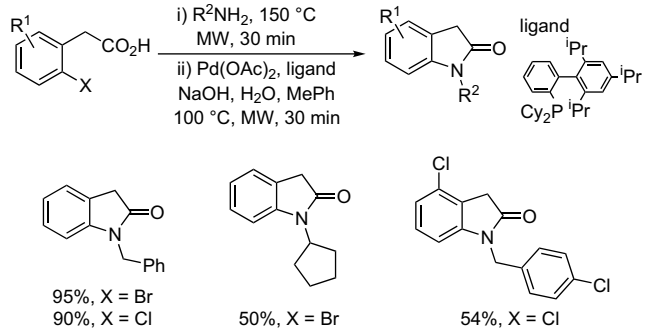
Intramolecular N-arylation is also very useful and, in a very elegant example, Turner not only demonstrated the value of microwave enhanced aryl amination, but also used microwave protocols to assemble the cyclisation precursor (Scheme 112).[248] Thus, direct condensation of a carboxylic acid with an amine took place under solvent-free conditions and then the reagents were introduced for the intramolecular amination step. The overall yields of this transformation are good and this provides a very rapid entry into oxindoles.



Scheme 110.



Scheme 111.

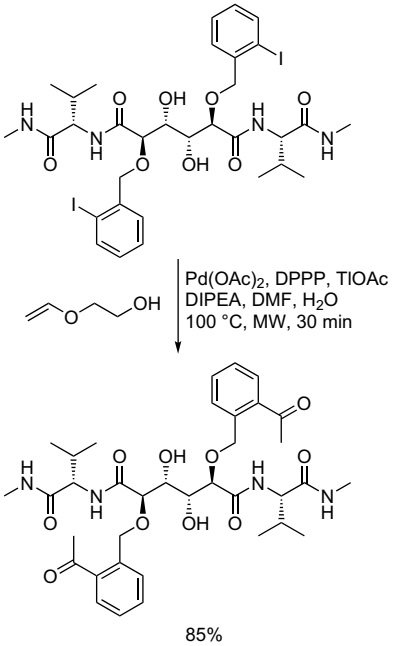


Scheme 112.

In a very nice example of the generality of microwave-enhanced palladium catalysed transformations, Wannberg demonstrated the prospect for functionalisation of peptides from an aryl iodide (Scheme 113).[249] Thus, the iodide undergoes functionalisation via Heck, Suzuki, Suzuki–Miyaura and Sonogashira reactions. The prospect for protein functionalisation in the future is very clear from this very interesting piece of work.

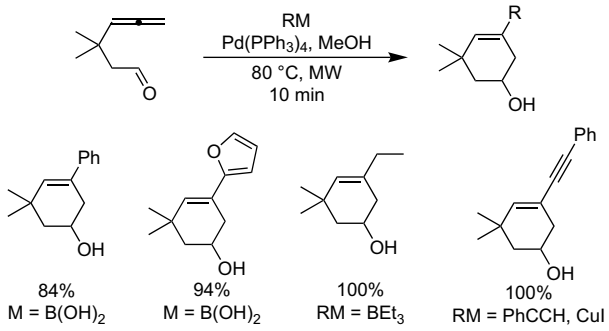
Although all of the work considered in this section have been focused on aryl halides/triflates, it is important to note that other modes of reactivity can be usefully enhanced by utilising microwave heating. For example, microwave-enhanced palladium catalysed allylic substitution can provide a useful route to enantiomerically pure dicarbonyl compounds.[250,251]

More recently, Tsukamoto has reported an elegant microwave-enhanced palladium catalysed cyclisation of allenyl aldehydes with concomitant alkylation, originating from an arylboronic acid.[252] Thus, under microwave conditions an undesirable allene arylation can be suppressed leading to the desired cyclisation. The method is

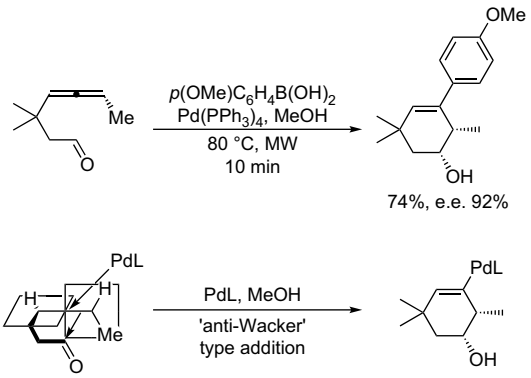


Scheme 113.

applicable to an interesting variety of ring systems and by use of a range of boronic acids a variety of substituents can be introduced (Scheme 114). The authors demonstrate the transfer of chirality from an enantiomerically enriched allene and this is not only synthetically useful, but also informs us about the mechanism. On the basis of these results, the authors invoke a trans-specific addition of the arylboronic acid to the palladium complexed allene (Scheme 115).



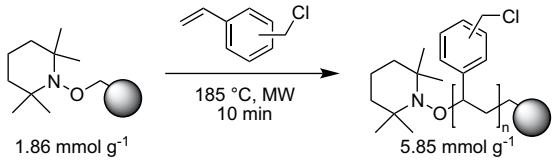
Scheme 114.



Scheme 115.

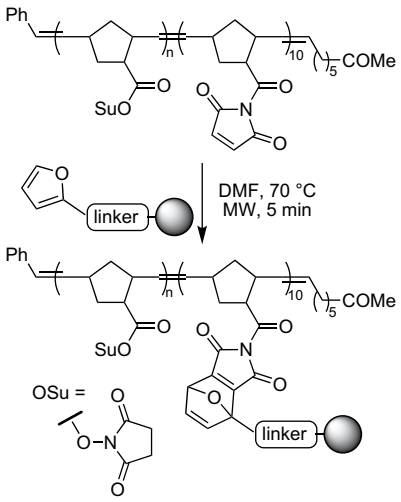
9. Combinatorial and solid-phase chemistry

This has been an area of enormous growth and has been the subject of a variety of review and summary articles.[253–260] One of the areas of recent development has been that of microwave enhanced polymer synthesis.[261–263] In the area of living polymerisation, Wisnowksi described the use of microwave-enhanced living free-radical polymerisation (Scheme 116).[264] In this report, the TEMPO-methyl resin is heated with a styrene derivative to give very large and high loading "rasta" resins around 150 times faster than conventional methods. Not only does microwave heating speed up the process, but it also seems to lead to much improved functionality.



Scheme 116.

In the area of ring-opening metathesis polymerisation (ROMP), Kiessling has reported an immobilisation strategy to enable the solid-phase synthesis of polymers (Scheme 117).[265] Thus, polymers



Scheme 117.

derived from ROMP were immobilised via a microwave enhanced Diels–Alder reaction between a resin-bound furan and a maleimide functionalised block co-polymer. Using microwave irradiation, the capture of the polymer was very effective (>90%).

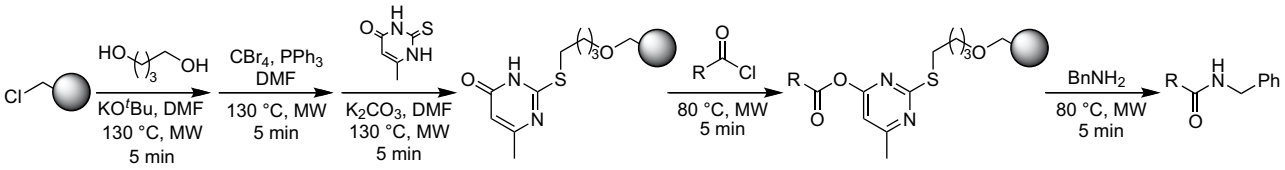
Another area of considerable development has been solid-supported reagents and microwave heating has been shown to impart a significant benefit to such reactions. A number of groups have utilised microwave enhanced coupling reactions such as acylations.[266] In an elegant example, Corelli and Botta show that they can synthesise a solid-supported acylating agent using a sequence, which is entirely carried out under microwave conditions and they then demonstrate the applicability of this reagent to promote acylation of amines, alcohols and thiophenols (Scheme 118).[267]

Taddei has reported a modified PS-Mukaiyama reagent for a microwave enhanced acylation process enabling the rapid synthesis of carboxylic esters in high purity.[268] Wang and co-workers described the synthesis of oxadiazoles from carboxylic acids and amidoximes in high yields and with good levels of purity using microwave enhanced dehydration with polymer-supported reagents (Scheme 119).[269]

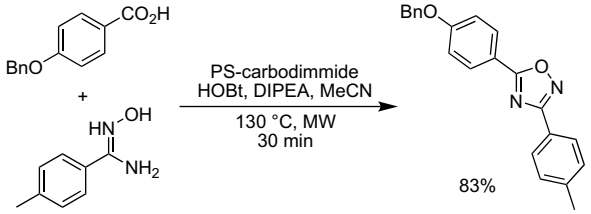
Westman has developed a microwave enhanced solid-phase protocol for Wittig olefination, which relies on the use of a supported triphenylphosphine reagent (Scheme 120).[270] The reaction is very appealing, as it allows a fast one-pot protocol for the synthesis of alkenes from aldehydes, phosphines and alkyl halides.

Porco has reported the development of a solid-supported anthracene derivative as a scavenger for dienophiles in a recent paper (Scheme 121).[271] Thus, microwave-enhanced cycloadditions of flavones with dienophiles can be carried out in the presence of a solid-phase scavenger, which then allows easy purification of the products.

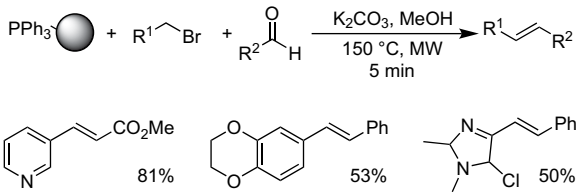
The Ley group has been one of the pioneers of the use of microwave heating to enhance polymer-supported reagent chemistry. For example, they have demonstrated the use of a polymer-supported oxazophospholide for the synthesis of isocyanides. Thus isothiocyanates were smoothly converted into isocyanides under microwave irradiation utilising a polymer-supported reagent system (Scheme 122), and these were then incorporated into a multicomponent reaction array employing the Ugi reaction.[272] Ley has also reported the development of a polymer-supported thionating agent, which can promote effective thiocarbonyl formation under microwave heating (Scheme 123).[273] A key component here is the importance of the addition of a small quantity of an ionic liquid to facilitate the dielectric heating. More recently, the synthesis of



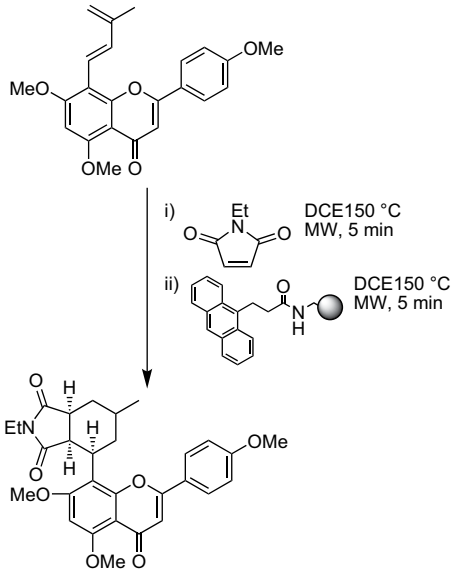
Scheme 118.



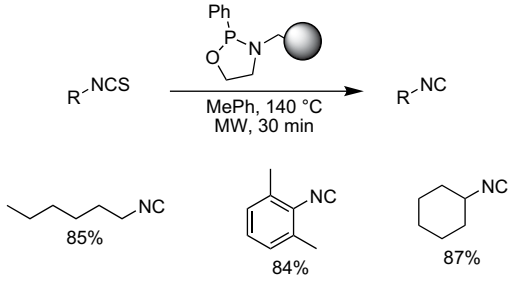
Scheme 119.



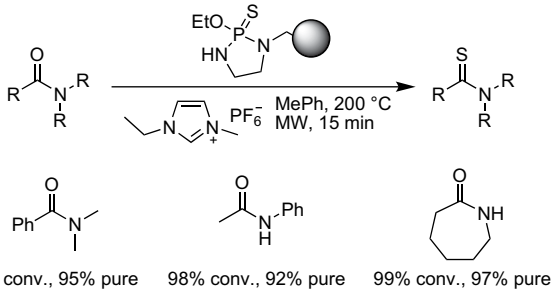
Scheme 120.



Scheme 121.



Scheme 122.



Scheme 123.

more than 1500 2-aminosulfonamide substituted oxadiazoles has been reported using supported reagents under microwave irradiation.[274]

The Ley group has also pioneered the use of polymer-supported reagent chemistry in the area of total synthesis.[275] In an impressive example of multi-stage natural product synthesis, the group describes the total synthesis of plicamine.[276] The synthesis is multi-step and each step involves a supported reagent, thus negating the requirement for silica-gel chromatography. Moreover, in a couple of steps, the use of microwave heating enhanced the yields and selectivity of the transformations (Scheme 124).[277]

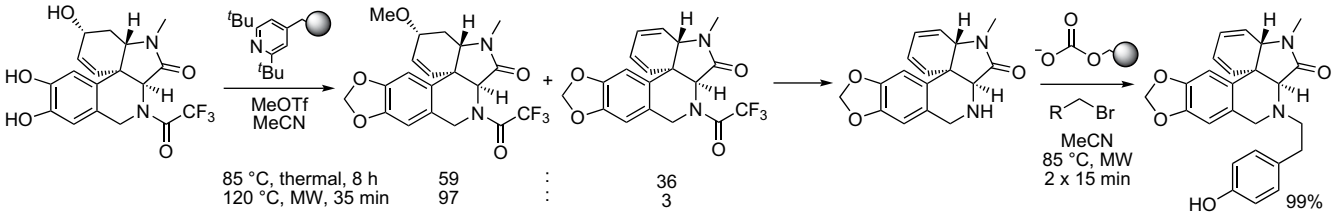
Microwave heating has also been shown to have a beneficial impact on solution-phase combinatorial chemistry. For example, Lehn described the benefit of using microwave heating to enhance the scandium(III) mediated coupling of a hydrazone and a bis-hydrazinopyrimidine.[278] This is a useful reaction as it underpins the development of dynamic libraries of molecular helices.

Fluorous technology has emerged as an important method for enabling combinatorial chemistry and the Zhang group has made extensive use of the microwave enhanced variant for multi-component and combinatorial chemistry applications.[279] For example, they use fluorous-tagged sulfonates to enable them to carry out dipolar cycloadditions, palladium catalysed coupling reactions and Ugi reactions.[280–282]

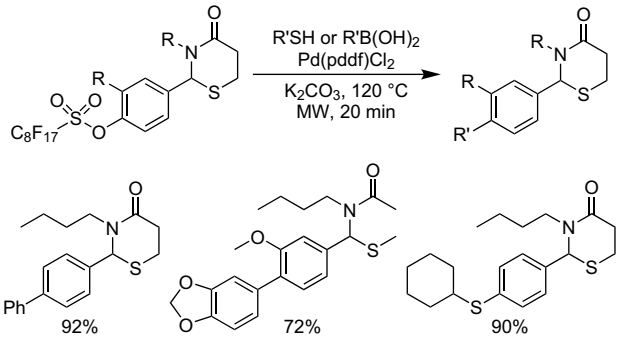
Yan has described the use of microwave enhanced fluorous chemistry to carry out the synthesis of compound collections based on thiazolidinone and thiazinone libraries (Scheme 125).[283] The use of a fluorous-tagged benzaldehyde in a coupling with mercapto-acetic acids and amines was reported. The use of a microwave-enhanced palladium catalysed, fluorous cleavage/biaryl coupling is particularly noteworthy.

In the area of solid-phase chemistry, there have been many developments and the attachment and cleavage of materials under microwave heating conditions are now well established.[284] For example, Dai has reported a resin-linker construct, which contains a poly-glycine unit, which is used to capture a copper ion required for heterocycle formation (Scheme 126).[285,286]

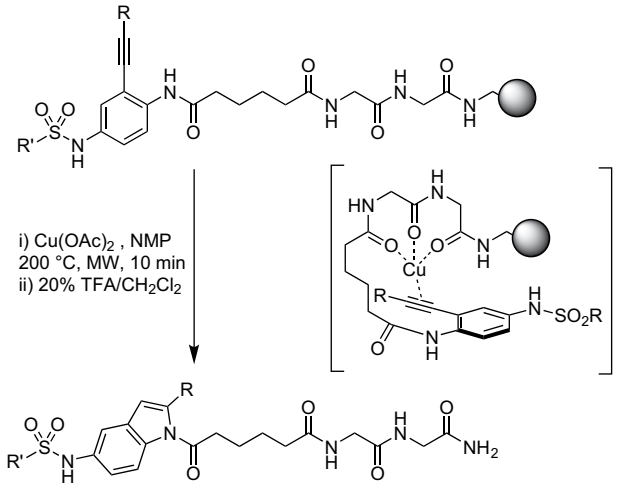
In a series of papers, Blackwell has reported the development of small-molecule macroarrays, which have exciting possibilities for drug discovery and chemical biology.[287] This approach leads to the immobilisation of discrete compounds on a cellulose support and microwave irradiation has been important in developing the methodology. For example, the attachment of a linker via tosyl



Scheme 124.

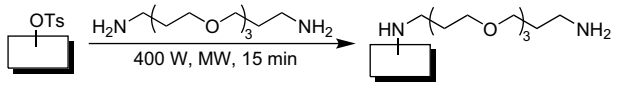


Scheme 125.

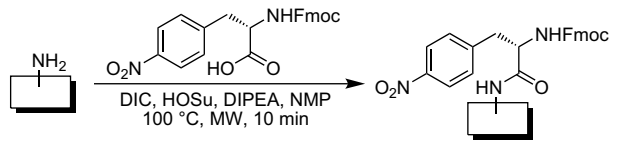


Scheme 126.

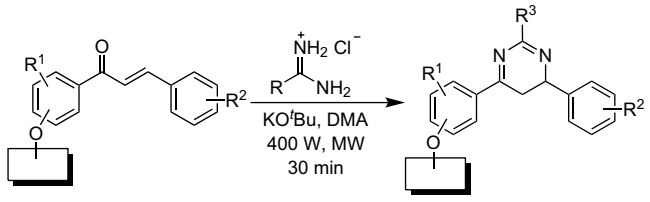
displacement using an amine has been enhanced using microwave heating (Scheme 127).[288] Moreover, microwave enhanced amide bond formation (Scheme 128) and dihydropyrimidine chemistry have been described (Scheme 129).[289,290] This methodology is very simple and potentially very powerful, in part because of the tolerance of biological assays to the cellulose, thus allowing direct screening, without the requirement for removal of the compounds



Scheme 127.



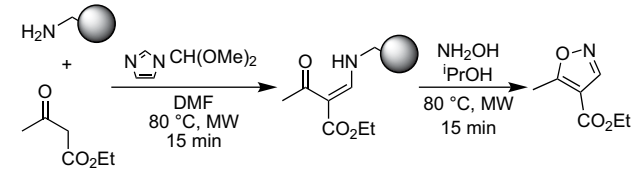
Scheme 128.



Scheme 129.

from the support. However, if cleavage is required it is easily achieved using TFA.

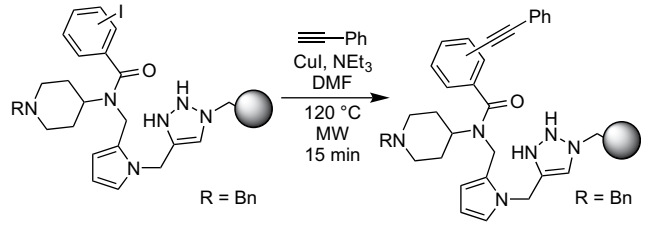
Porcheddu has also reported on the development of cellulose-based systems (Scheme 130).[291] Using an amino-derivatised cellulose bead they carry out microwave enhanced pyrazole and oxazole synthesis. It is noteworthy that these new supports are compatible with the high temperatures often associated with microwave heating and can be recycled up to 10 times with no significant loss of yield when microwave radiation is employed.



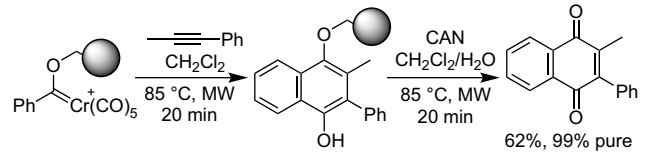
Scheme 130.

Gmeiner has described the use of a microwave-enhanced palladium catalysed coupling on solid phase. Specifically, they find that they can enhance Sonogashira couplings (Scheme 131).[292]

Finally in this section, Martinez has described a solid-supported approach to the Dotz benzannulation (Scheme 132).[293] They show that a solid-supported chromium carbene precursor undergoes a microwave enhanced annulation with alkynes to generate bicyclic



Scheme 131.



Scheme 132.

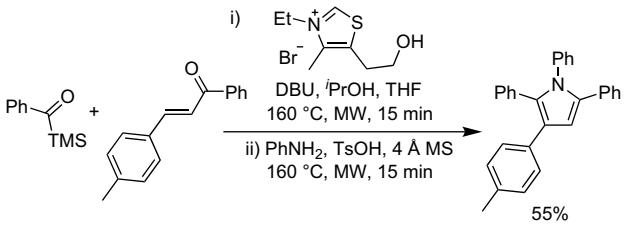
aromatics. The group reports a sixfold reduction in reaction time and the reactions proceed in moderate to good yield.

10. Multi-component and tandem reactions

In pursuit of enhanced functionality chemists often aspire to make compound collections in order to populate a wide area of physico-chemical space and, in this arena, multi-component reactions continue to hold considerable utility. For this reason, there is continued appetite for the development of new variations on the multi-component reaction theme and many of these have been neatly summarised in recent review articles.[294] It is striking that many of these review articles highlight the importance of microwave heating. Although there is still always ongoing debate surrounding the microwave effect, it appears that in most cases the enhancements can simply be attributed to elevated temperature along with the occasional use of open vessels, allowing rapid evaporation of solvent and/or volatile products, e.g., water. It is notable that multi-component reactions based on condensation, using, for example, 1,3-dicarbonyl compounds, are particularly susceptible to enhancement, and a variety of interesting compound collections based on heterocyclic templates have been prepared rapidly and efficiently using microwave irradiation.[295]

Although there are a number of interesting examples, which illustrate the importance of these reactions, for example, the Hantzsch dihydropyridine synthesis,[296] it is notable that there has been considerable attention paid to the benefit that microwave heating can have on the Biginelli reaction, and an early pioneer to demonstrate the potential benefit of microwave heating was Kappe.[297] This group along with others has shown that this reaction can under appropriate conditions be automated and Orru showed that this approach can be extended to a four-component approach leading to a considerable product diversity.[298] Other useful contributions in this area include the use of water,[299] solvent-free conditions,[300] and the use of soluble polymers to generate PEG-bound dihydropyrimidinones, which could be readily cleaved.[301]

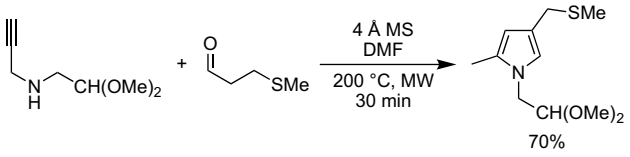
Scheidt reported a very elegant one-pot microwave enhanced sila–Stetter/Paal–Knorr approach to pyrroles (Scheme 133).[302] In this work, a silyl-ketone is combined with an unsaturated ketone in the presence of a thiazolium catalyst to generate a 1,4-dicarbonyl, which then undergoes condensation with an amine to generate tetrasubstituted pyrroles. Although the reaction works quite well under conventional conditions, it is notable that the reaction can be carried out in 3% of the time when using microwave heating. Remaining with pyrroles, Organ has described a one-pot approach to functionalised pyrroles from a sequence involving an aza-Claisen rearrangement, imine–allene approach (Scheme 134).[303]



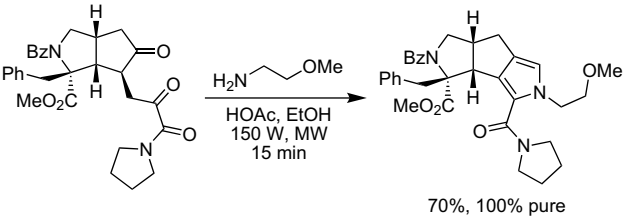
Scheme 133.

In an example of a more complex pyrrole synthesis, Werner applied a microwave enhanced condensation reaction to give heavily functionalised pyrroles (Scheme 135).[304] The reactions are rapid, high yielding and, in this case, have been applied to a wide range of amines.

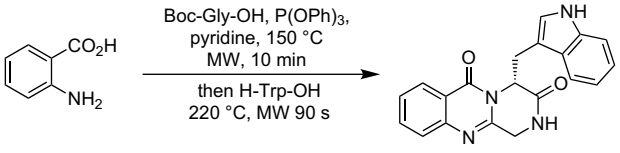
An expeditious approach to pyrazino[2,1-*b*]quinazoline-diones is to be found in the work of Liu (Scheme 136).[305] In this



Scheme 134.



Scheme 135.

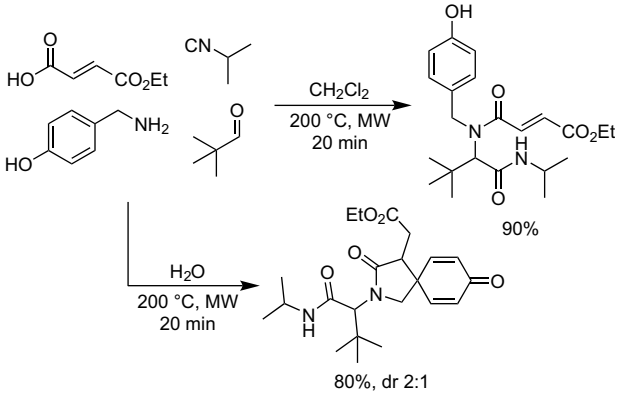


Scheme 136.

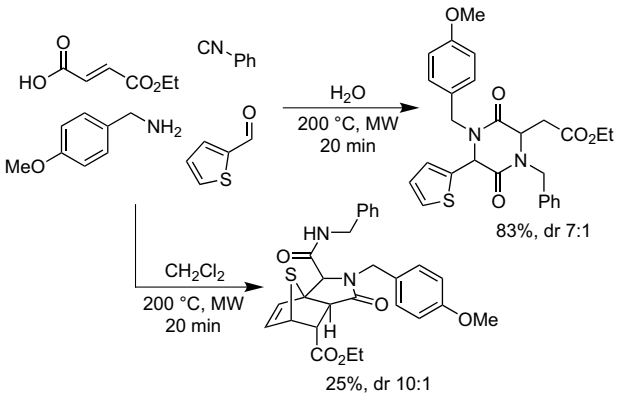
three-component approach, a Boc-protected amino acid is combined with an anthranilic acid and the intermediate benzoxazin-4-one reacted with another amino acid derivative to give the target heterocycles rapidly in good yield when carried out with microwave heating.

In another example of a one-pot protocol, Andreana demonstrates an even greater potential for diversity by utilising bifunctional acceptors in microwave-assisted multi-component cascades.[306] Multi-component Ugi reactions were high yielding (Scheme 137) and displayed a range of subsequent reactivity, dependent upon the substrate and solvent (Scheme 137 and Scheme 138), for example, Ugi products containing phenol-derived γ-lactams via Michael addition in protic media (Scheme 136). However, Ugi products containing other electron-rich aromatics gave diketopiperazines, via an aza-Michael process, in protic media, but gave tricyclic lactams, via an intermolecular Diels–Alder reaction, when the reactions were carried out in CH_2Cl_2 (Scheme 138).

Although common, it is not inevitable that a multi-component reaction will be utilised for the production of polycyclic systems. For example, Tu has developed a synthetic route to functionalised propargylic amines from the combination of an aldehyde, amine

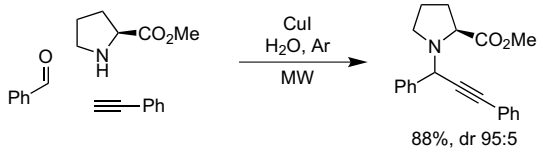


Scheme 137.



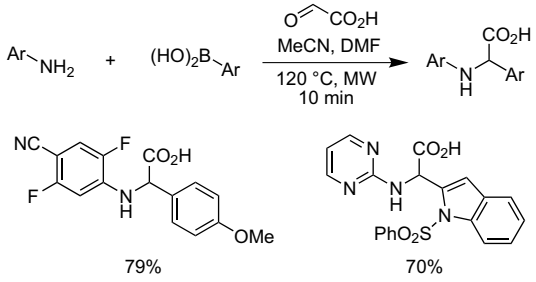
Scheme 138.

and alkyne (Scheme 139).[307] Under microwave conditions in water, the reactions are rapid and are catalysed using a relatively inexpensive copper salt as a catalyst. The authors go on to show that the protocol can be extended to a diastereoselective variant and propose a mechanism for the transformation involving the addition of an alkynylcopper to an iminium.



Scheme 139.

The Petasis reaction has also been shown to benefit from microwave enhancement by Follmann (Scheme 140).[308] The synthesis of a range of amino acids derived from aromatic boronic acids has been considerably improved when using microwave heating.



Scheme 140.

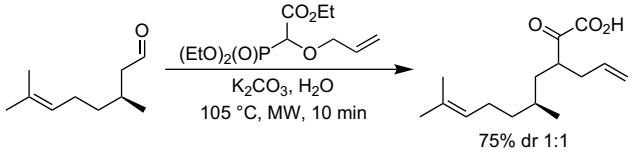
Of course, multi-component reactions have benefited greatly from microwave enhancement and there are a number of opportunities for microwave chemistry to provide an advantage. For example, it may be possible to enhance the overall value of a multi-component reaction if microwave irradiation benefits each component of the process. However, oftentimes the benefit is associated with enhancement of one reaction step in the overall sequence, for example, in Bonnaterre's synthesis of oxindoles in which the intramolecular Buchwald–Hartwig process is accelerated utilising microwave irradiation.[309]

In the area of tandem reactions, there have also been some very nice developments assisted by the use of microwaves. Taylor has described a microwave induced tandem sequence involving an olefination/Claisen rearrangement sequence (Scheme 141).[310] Lindsay has described a microwave enhanced aza-Cope/Mannich scheme (Scheme 142).[311] Moody has described a Mitsunobu/Claisen sequence to phenols (Scheme 143),[312] and Barriault describes an oxy-Cope/ene sequence (Scheme 144).[313]

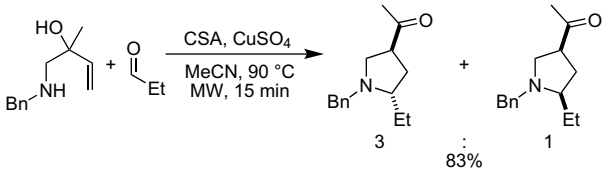
Finally in this section, Stevens reports an intriguing approach to functionalised isoindoles via microwave induced cascade (Scheme 145).[314] Thus, an amino phosphonate ester bearing pendant alkynes rearranges to an isoindole in moderate to good yield, with the reaction only really becoming feasible using microwave conditions.

11. Natural products and target synthesis

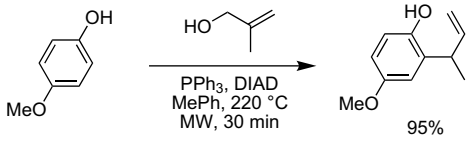
One of the greatest tests of any synthetic methodology is the application into complex molecules, in particular natural products, and in recent times it has become clear that many complex systems can tolerate the high temperatures associated with microwave heating, at least for short periods. Alternatively, such heating can, in some cases, lead to novel modes of reactivity of complex natural products.[315] Moreover, it is also clear that microwave heating can rescue a synthetic route and be an important part of a successful target synthesis endeavour.[316] Bagley has developed very short synthetic sequences to medicinally important target molecules by exploiting microwave heating.[317,318] A variety of microwave enhanced cycloaddition reactions have been used by Trost,[319] Moody[320] and Romo.[321]



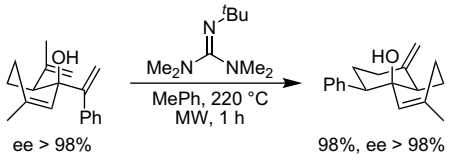
Scheme 141.



Scheme 142.



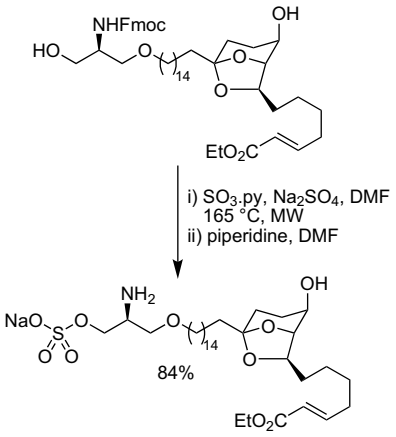
Scheme 143.



Scheme 144.

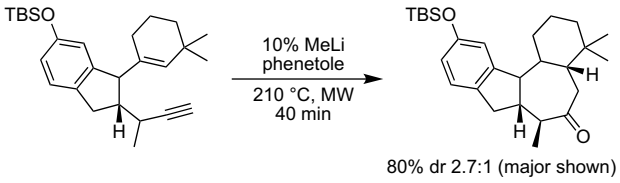
Scheme 145.

In the total synthesis of (+)-didemniserinolipid B, Ley[322] and Burke[323] have independently both exploited a microwave enhanced O-sulfation in order to complete their respective syntheses (Scheme 146).



Scheme 146.

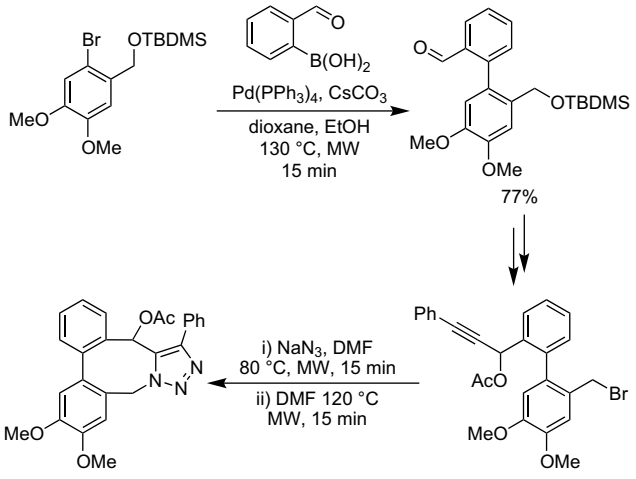
In an approach to frondosin C, Ovaksa reported a cyclisation–Claisen rearrangement sequence, which is more efficient using microwave heating (Scheme 147).[324,325]



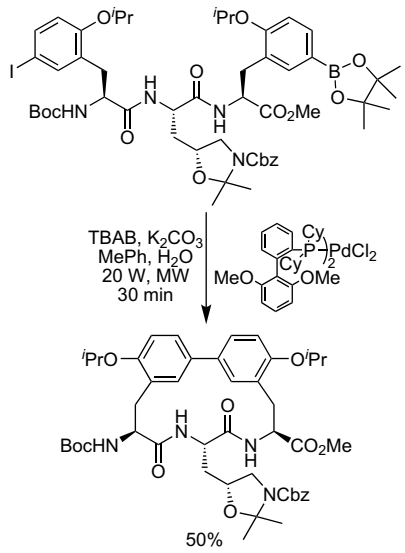
Scheme 147.

In an impressive approach to steganacin and steganone analogues, van der Eycken described a microwave enhanced Suzuki protocol (Scheme 148).[326] At a later stage in the synthetic route, the authors again use a microwave protocol, but this time to enhance a 1,3-dipolar cycloaddition and complete their synthesis.

A Suzuki–Miyaura coupling was essential for the successful completion of the synthesis of the macrocycle biphenomycin B by Zhu (Scheme 149),[327] in which an intramolecular coupling could be readily carried out with microwave enhancement using either $Pd(OAc)_2$ or more effectively using a hindered phosphine.

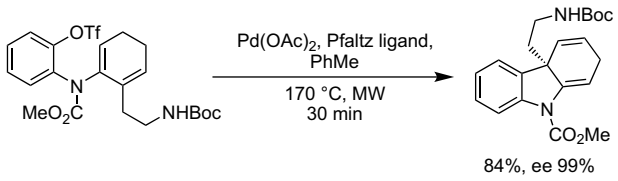


Scheme 148.



Scheme 149.

Palladium catalysed Heck reactions are also well established under microwave conditions and Overman has exploited this technique in an asymmetric Heck cyclisation as part of their successful synthetic approach to the strychnos alkaloid minfiensine (Scheme 150).[328] Under conventional heating, the reaction was slow, but it could be accelerated using microwave heating, from 100 h to 30 min, with no loss of enantioselectivity compared to the thermal case.

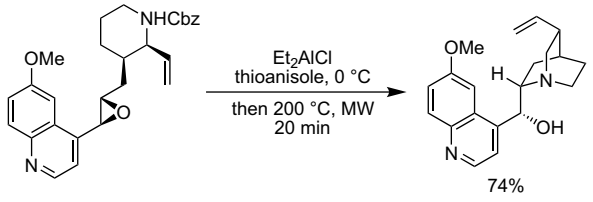


Scheme 150.

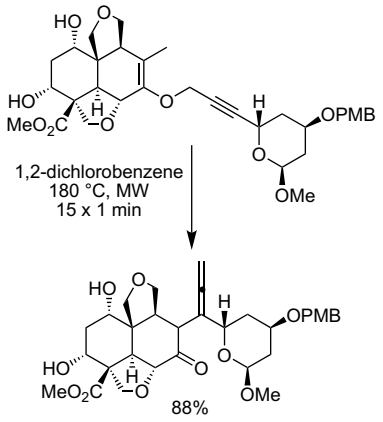
In order to complete their total synthesis of the cinchona alkaloids quinine and quinidine, Jacobsen used a microwave enhanced deprotection/nucleophilic substitution sequence (Scheme 151).[329] All other approaches led to poor yields and/or unacceptable reaction times and the microwave protocol was complete within 20 min.

As part of the development of what was to become the successful total synthesis of azadirachtin, Ley showed that consecutive pulses of microwave irradiation led to reproducibly high yields in the key Claisen rearrangement (Scheme 152).[330]

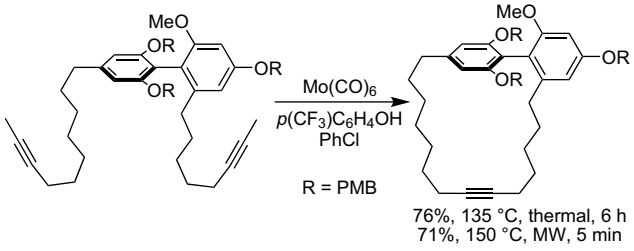
As was seen earlier in this article, the area of metathesis has also benefited from microwave enhancement. In an elegant application in natural products synthesis, Furstner has used an intramolecular alkyne metathesis employing molybdenum-based catalysts (Scheme 153).[331]



Scheme 151.

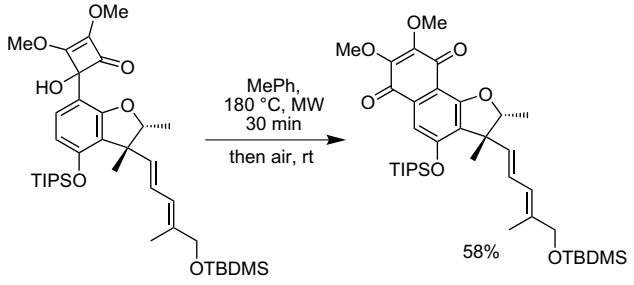


Scheme 152.



Scheme 153.

In addition to microwave enhanced reagent-based protocols, microwave enhancement has also been used to help mediate bond reorganisation/isomerisations. For example, in his synthetic approach to furaquinocin, Trost utilised a microwave enhanced cyclobutenone to quinone rearrangement (Scheme 154).[332] It should be noted that under other more conventional conditions the reactions did not reach 100% conversion.



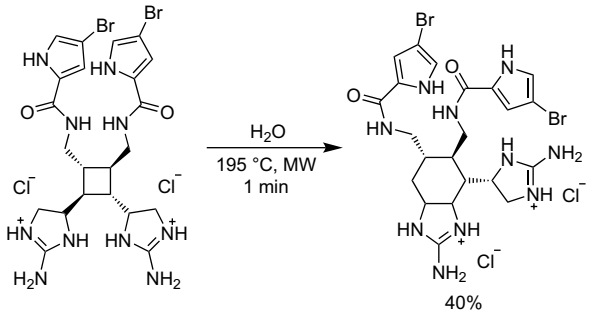
Scheme 154.

Finally, in a very elegant example of the power of microwave enhancement, Baran described a fascinating reorganisation of sceptrin to ageliferin, which could only be achieved by using a microwave enhanced methodology (Scheme 155).[333] This is a remarkable transformation and it provides a powerful case for the use of microwave heating in natural products synthesis.

12. Peptides, proteins and enzymes

12.1. Coupling protocols

Significant developments in microwave enhanced peptide and protein chemistry have been a highlight of the last five years and this is to a large extent a consequence of specific instrumentation,

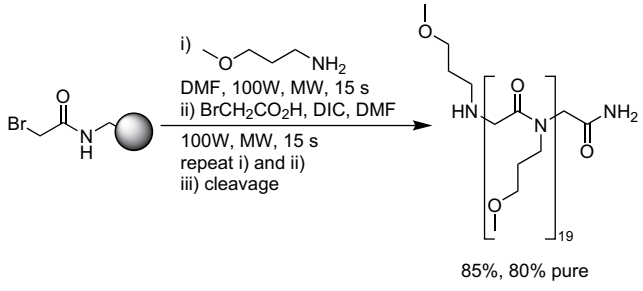


Scheme 155.

which can allow both solution and solid-phase peptide chemistry to be carried out readily and effectively.[334] It has been known for some time that the use of microwave irradiation can have a beneficial impact on amide bond formation.[335] This of course has led to a more detailed assessment of the potential benefits of using microwaves to make amide bonds in the context of peptide synthesis. Bradley utilised microwave irradiation to enhance couplings using secondary amines utilising DIC and HOBt in DMF.[336] The coupling proceeds with an improvement over the conventional PyBroP protocol with a shorter reaction time and more efficient use of monomer. It is also noteworthy that the protocol allows the use of substrates, which contain the Fmoc protecting group, which is known to be sensitive to elevated temperature. In addition, fluorescein–peptide coupling with peptoids were also reported to be significantly improved under microwave conditions. The work demonstrates that complex peptides requiring labelling can potentially benefit from microwave-mediated protocols and that under these circumstances the use of microwave chemistry may obviate the use for more expensive and elaborate peptide-coupling agents. In a nice extension to this work, the same group has applied this methodology to the construction of peptoid dendrimers.[337]

Microwave enhanced DIC coupling features in Kodadek's solid-phase synthesis of peptoids (Scheme 156).[338] Their synthetic strategy involves coupling of α-halo amides with primary amines. The appeal of this sequence is its rapidity, with the individual steps only requiring a reaction time of 1 min, and the efficiency of the coupling. In a very important variation, Blackwell discovered that this methodology could be extended to unreactive secondary amines.[339]

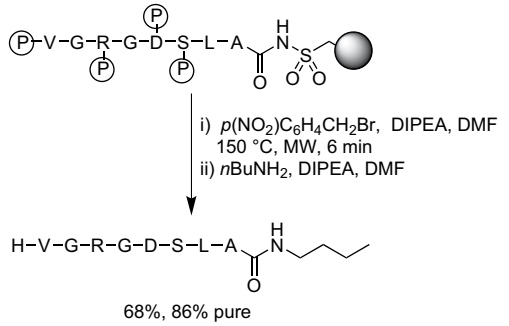
Of course, the rapid synthesis of complex peptides through microwave enhanced coupling is potentially very beneficial, particularly in view of the inherent inefficiency of any linear synthetic sequence. It has become clear that rapid coupling using microwave irradiation can be very powerful. However, concerns must be raised about the prospect for racemisation, particularly in view of the fact that very early work identified that irradiation of amino acids can lead to very effective racemisation. However, careful consideration of the specific reaction conditions is clearly critical in developing synthetic sequences for peptide synthesis and this can be done in



Scheme 156.

a manner, which avoids the problems of racemisation. In a very interesting study, Collins carried out a detailed evaluation of the impact of microwave irradiation on synthetic transformations utilised in Fmoc solid-phase peptide synthesis.[340] In a model system, it was found that several amino acids are prone to racemisation during SPPS, but that lowering the temperature can help minimise these problems. It appears that there is a temperature dependency on the stability of the activated esters of the amino acids.

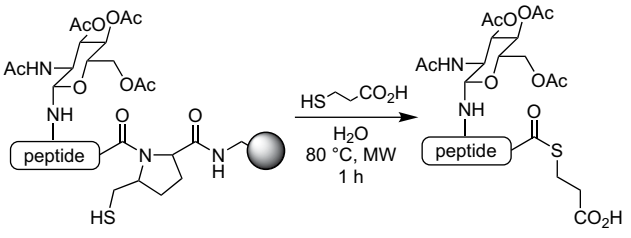
In an elegant example, Liskamp showed how microwave enhanced alkylation can be important for the development of protocols for modification of peptides (Scheme 157).[341] In this work, *N*-acyl sulfonamides can be activated efficiently with electrophiles under a microwave enhanced protocol, whilst avoiding the more common TMS–diazomethane activation. This allows the efficient cleavage of these species with a variety of amines. The benefit of this work is that it overcomes some of the previous limitations in using acylsulfonamides in peptide synthesis.



Scheme 157.

Of particular note is the recent report by Nakahara, who described an approach to the synthesis of peptide thioesters (Scheme 158).[342] These species are highly desirable because of their potential utilisation in protein ligations. The production of peptide thioesters incorporating glycosyl residues can be a particular problem, but this now appears to be more readily achieved via a microwave enhanced N/S acyl thioester exchange.

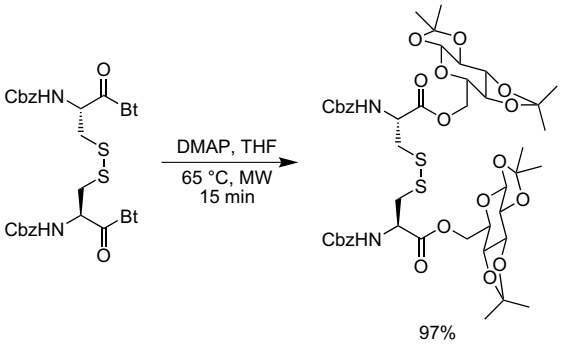
What has become clear is that the development of microwave enhanced methods can underpin the linear peptide synthesis.[343–345] Some very nice recent examples include Kappe's approach to the calmodulin binding peptide and Gellman's combinatorial approach to 14-helical β-peptide libraries.[167,346–349] Of particular note in the latter example is the considerable enhancement in synthetic efficiency in the latter stages of the synthesis. This indicates that microwave conditions may offer unexpected advantages for the preparation of difficult sequences. Shepartz has also shown very significant benefit associated with microwave enhanced linear peptide synthesis in their very impressive approach to Z28.[350] It will be of interest to see whether it is generally the case that the synthesis of longer peptides is optimised using a microwave enhanced protocol. Moreover, it will be important to understand the basis for any such enhancement, which may potentially be attributable to microwave-mediated disaggregation



Scheme 158.

effects associated with a developing secondary structure in longer peptides as they are synthesised. A final example reported by Nishimura illustrated the application of enhanced coupling protocols to the synthesis of glycopeptides.[351] In the synthesis of MUC1, coupling of N-terminal amino acids with glycosylated Fmoc-protected amino acids could be significantly enhanced under microwave conditions with a dramatic reduction in the overall reaction time, from 4 days to 7 h.

The coupling of sugars to peptides can also be enhanced using microwave-based protocols. In this area, Katritzky utilises aminoacyl benzotriazoles, which couple well with sugars under microwave conditions (Scheme 159).[352] Papini has also synthesised *N*-glycosyl amino acids utilising microwave enhanced coupling utilising a triazine-based coupling reagent.[353]



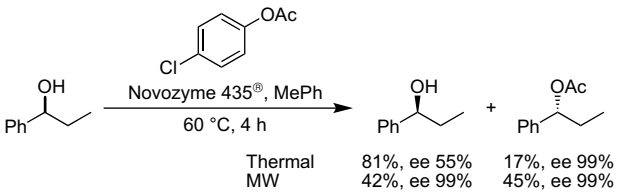
Scheme 159.

12.2. Peptide/protein analysis

It has been known for many years that microwave irradiation can be invaluable for digestion of samples to ensure high quality analysis and so it is interesting to see the emergence of microwave-assisted protein digestion, as an aid to proteomics/protein analysis. Over the last few years, there have been a few interesting papers describing a number of protocols. In a relatively early study, Bose and co-workers described a variety of proteolysis procedures using trypsin or lysine C in systems for analysis of cytochrome C, ubiquitin, lysozyme, myoglobin and interferon α-2b.[354] In these systems, the benefit is associated principally with the rapid availability of the peptides for MS analysis. This approach has been extended by Juan and co-workers to the direct trypsin digestion of proteins excised from 2-D gels.[355] More recent applications have sought to examine the effectiveness of acid-based digestion protocols and considerable success has been reported. For example, Lee has reported partial hydrolysis of tryptic glycopeptides using triflic acid;[356] and Sze has shown that C-terminal asp cleavage can be mediated by careful hydrolysis using formic acid.[357] This type of approach has been further developed by Basile, who developed an online variant, which involves the attachment of a microwave flow cell directly to an MS instrument.[358]

12.3. Enzymes

The use of microwave radiation to enhance enzyme processes has been explored with some success and a brief overview highlighting the potential of this area has been published.[359,360] In a couple of recent papers, Brimble[361] and Cao[362] have independently examined a lipase catalysed kinetic resolution of secondary alcohols using Novozyme 435 and it is reported that higher values of efficiency are associated with microwave enhancement (Scheme 160).



Scheme 160.

13. Concluding remarks

It is clear that microwave heating effects have a major impact on many areas of preparative science and particularly in the area of synthetic chemistry. It is notable that the impact has probably been far greater than many other technological developments and that microwave heating methods have become mainstream. Numerous laboratories have commercial instruments, particularly as they have become very reliable, safe and relatively inexpensive. It has become clear that, unlike many new technologies, microwaves have genuinely become an acceptable and routinely applied method for synthesis.

So where next for microwave enhanced science? Continued efforts by the suppliers of instruments should hopefully make the technology available to every bench chemist and perhaps even every bench scientist who needs to heat a sample. Although costs have dramatically reduced in recent years, we have yet to see them reduce to a point where the instruments become viewed as a standard piece of individual laboratory equipment. If that does happen then we could see further dramatic developments in the uptake of this valuable technology. The size of instruments may also need to reduce a little such that every laboratory bench could readily accommodate an instrument. So, further developments from equipment suppliers could continue to enhance the field further.

Scientifically, we can envisage still further attempts to speed up processes. One of the most exciting developments has probably been in peptide chemistry and the idea that we might at some point be able to make large-scale synthetic proteins in a day is an appealing prospect. Further major impacts on sample preparation for biology, materials science, nanotechnology, and polymer science are all likely to result in the next 5–10 years. Although there have been exciting developments, there are still many opportunities for microwave heating to revolutionise these areas.

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Richard Fitzmaurice completed his MChem at the University of Southampton in 2000 and obtained his Ph.D. in 2004 from the same institution under the supervision of J.D. Kilburn in 2004. He then took up a postdoctoral position at UCL with S. Caddick where he has remained and is now Senior Research Fellow. His research interests are principally in the area of synthetic methodology with particular focus on diversity oriented synthesis.