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Recent Developments in Microwave-Assisted, Transition-Metal-Catalysed C–C and C–N Bond-Forming Reactions

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A selective overview of the recent developments of microwave-assisted, transition-metal-catalysed C–C and C–N bond-forming reactions is presented. Microwave-assisted chemistry is a comparatively novel technique in the present-day synthetic world and has recently grown in an exponential manner, stretching from academia to a widely practiced technique in industry. Transition-metal-catalysed C–C and C–N bond-forming reactions represent one of the most interesting and well-investigated type of microwave-assisted reactions, evident from the plethora of available literature and patents in this area. Given the large number of articles published on the subject, we have made a very concise selection from the recent literature, covering manuscripts dealing with the subject from the period of the end 2004 until the first part of 2007.

Introduction

Transition-metal-catalysed carbon–carbon and carbon–heteroatom bond-forming reactions are of prime interest in present-day chemistry owing to their widespread applications in the synthesis of, for example, drug-like molecules and natural products. There has been a plethora of literature published in the last two decades dealing with the efforts directed at improving transition-metal-mediated methodologies as well as the application of protocols developed for the synthesis of novel molecules with interesting properties.[1] Microwave-assisted organic synthesis (MAOS)[2] is a relatively new technique in the present-day synthetic world and has grown extensively in the last decade from a mere academic tool to a heartily used technique in the industrial research laboratory. Homogeneous transition-metal-catalysed reactions, typically needing rather long reaction times, represent one of the most important and best studied reaction types in MAOS, as is evident from the numerous recent scientific manuscripts, reviews and patents published in this field.[3] It is apparent from the recent literature that microwave irradiation mostly results in a dramatic acceleration of reactions, most often resulting in cleaner outcomes and increased yields.

Given the amount of literature published on microwave-assisted transition-metal-mediated protocols and the limited space available for this review, we have made a selection from the recent literature of microwave-assisted C–C and C–N bond-forming reactions rather than trying to give a full overview. Manuscripts dealing with the subjects are covered from the period of the end 2004 until the first part of 2007. For the sake of clarity we have divided the collected literature into six subchapters: 1) Suzuki–Miyaura and Stille reactions, 2) Heck and Sonogashira reactions, 3) transition-metal-mediated carbonylation reactions, 4) transition-metal-mediated C–N bond formation by amination protocols, 5) C–N bond-forming reactions using click chemistry and 6) miscellaneous. We decided not to incorporate ring-closing metathesis and related topics as we judged this deserves a separate review.

1. Microwave-Assisted Suzuki–Miyaura and Stille Reactions

The Suzuki–Miyaura and Stille protocols are two of the most versatile and well-investigated microwave-assisted cross-coupling reactions in modern organic synthesis. Carrying out these high-speed cross-couplings under controlled microwave irradiation can be considered today as an almost routine synthetic procedure. A large number of scientific manuscripts have been published dealing with the development of microwave-assisted Suzuki–Miyaura and Stille reactions as convenient C–C bond-forming tools.[4] A substantial amount of work has been performed to improve the existing cross-coupling protocols, to introduce novel and more active catalytic systems or ligands for achieving cleaner conversions and higher rates, and to invent versatile methods for monitoring the reactions more closely to gain

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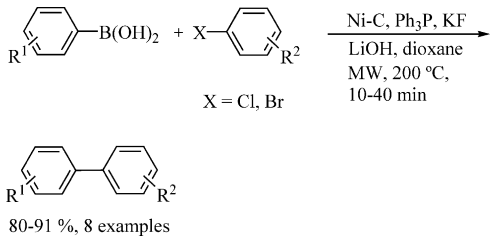
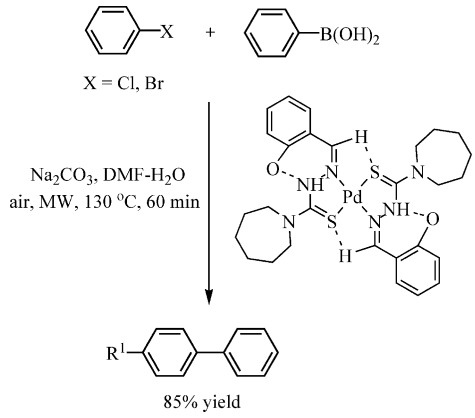
new insights into the reaction mechanisms. Furthermore, a plethora of manuscripts dealing with the application of microwave-assisted Suzuki–Miyaura and Stille reactions for the generation of biologically interesting target molecules as well as synthetically useful building blocks can also be found in the recent literature. Only a very limited selection of these new endeavours will be represented in this review.

To improve the catalysts used in Suzuki–Miyaura reactions under both conventional and microwave-assisted conditions, Lipshutz et al. have performed extensive research to find novel and cheaper catalytic systems for carrying out heterogeneous cross-coupling reactions. In order to establish novel parallels to the Pd-based catalysts used in cross-coupling reactions, they investigated Ni on charcoal as a cheap and highly effective alternative (Scheme 1).[5] The conventional drawback of long reaction times for Ni/C heterogeneous catalysis was circumvented by the use of microwave irradiation. A large number of Suzuki–Miyaura reactions were successfully carried out in a mere 10–40 min under focused microwave irradiation, and the products were isolated in good-to-excellent yields (80–91%).



Scheme 1. Microwave-assisted, Ni-mediated Suzuki–Miyaura reactions.

Loupy and co-workers have designed a novel palladium complex based on a thiosemicarbazone ligand as a catalyst for microwave-assisted Suzuki–Miyaura reactions under aerobic conditions (Scheme 2).[6] The advantageous nature of this new catalytic system is revealed by the very low catalyst loading of the reaction; the ratio of aryl halide to the palladium catalyst was as high as 1000. The reactions proceeded with high conversions as well as yields and in most cases, the TONs were found to be high.

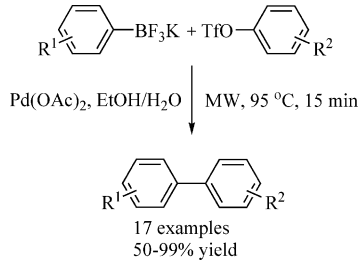


Scheme 2. Suzuki–Miyaura reactions using a Pd–thiosemicarbazone complex.

Kabalka et al. have recently published[7] the results of an interesting investigation into the microwave-assisted Suzuki–Miyaura reaction of potassium organotrifluoroborate salts with a variety of aryl triflates (Scheme 3). Such cross-coupling reactions have been well documented in the literature by Molander and co-workers[8] and are particularly interesting due to increased reactivity and high tolerance to air and moisture.

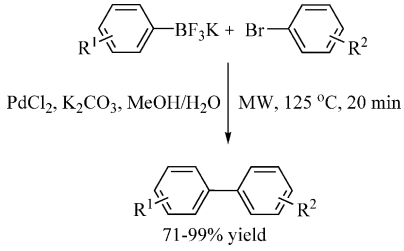
Dr. Prasad Appukkuttan was born in 1977 at Vaikom, Kerala, India. He completed his Masters in Organic Chemistry in 2000 at the School of Chemical Sciences, Mahatma Gandhi University, Kerala, and at JNCASR, Bangalore, with Prof. C. N. R. Rao, FRS. He then joined the group of Prof. Dr. Erik Van der Eycken at the University of Leuven, Belgium, for his doctoral studies and completed his Ph. D. in 2004. After carrying out post-doctoral research stays at the University of Leuven with Prof. Dr. Erik Van der Eycken and at the Uppsala University, Sweden, with Prof. Dr. Mats Larhed, he is currently engaged in his third post-doctoral stay in the group of Prof. Dr. Paul Knochel at the Ludwig-Maximilians-Universität, München, Germany, as an Alexander von Humboldt fellow.

Erik Van der Eycken is Professor of Organic Chemistry and head of the Laboratory for Organic & Microwave-Assisted Chemistry (LOMAC) at the University of Leuven (K. U. Leuven), Belgium. He received his Masters diploma (1982) and his Ph. D. degree (1987) in organic chemistry from the University of Ghent, Belgium, with Prof. Maurits Vandewalle on the total synthesis and structural elucidation of Specionin, an iridoid insect antifeedant. From 1988 to 1992 he worked as a scientific researcher at the R&D laboratories of AGFA-Gevaert, Mortsel, Belgium. He moved back to the University of Ghent as a scientific collaborator on photoinduced reactions of HIV-active drugs with Prof. Denis De Keukeleire and Prof. Piet Herdewijn (1992–1995). From 1995–1997 he worked to the Flemish Inter-University Institute for Biotechnology (VIB), Ghent, with Prof. Marc Van Montagu where he was involved in the synthesis of intermediates for the elucidation of biological reaction pathways. In 1997 he became Doctor Assistant at the K. U. Leuven, Belgium, in the group of Prof. Georges Hoornaert where he was involved in heterocyclic chemistry. He was appointed part-time professor in 2004 at the same university and started his independent academic career. After short periods of postdoctoral work at the University of Graz (2002) with Prof. C. O. Kappe on microwave-assisted hetero-Diels–Alder reactions, at The Scripps Research Institute (La Jolla, USA) (2003) in the group of K. B. Sharpless on microwave-assisted click chemistry and at Uppsala University (2004) with Prof. M. Larhed and Prof. A. Hallberg on microwave-assisted carbonylations, he was appointed full-time professor in 2007 at the K. U. Leuven. The main focus of his research is the investigation of the application of microwave irradiation in different domains of organic synthesis, that is, the synthesis of bioactive natural product analogues and heterocyclic molecules applying transition-metal-catalysed reactions and solid-phase organic synthesis. His laboratory is also active in the field of microwave-assisted synthesis of (cyclic) peptides and peptidomimetics.



Scheme 3. Suzuki–Miyaura reactions of organotrifluoroborates with aryl triflates.

Harker and Crouch have recently described an interesting parallel to the Kabalka protocol, investigating the microwave-assisted Suzuki–Miyaura reactions of various aryl halides with potassium organotrifluoroborates (Scheme 4).[9] The authors carried out the reaction by using $PdCl_2$ as the catalyst and K_2CO_3 as the base in aqueous methanol, while no ligands were used in this investigation. The reactions proceeded at 125 °C in 20 min with high yields and purity.



Scheme 4. Suzuki–Miyaura reactions of organotrifluoroborates with aryl halides.

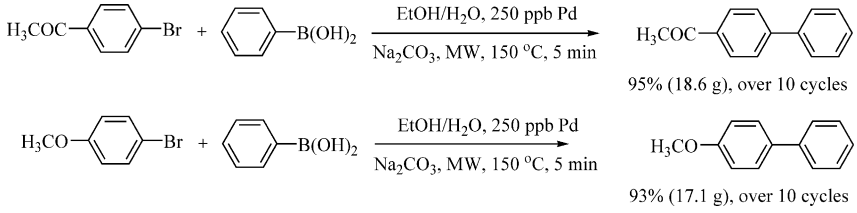
Leadbeater and co-workers have recently described a number of interesting developments in the field of microwave-assisted Suzuki–Miyaura cross-coupling reactions. As a part of their ongoing investigation of microwave-assisted cross-couplings in neat water,[10] the authors carried out the reactions by using ultra-low concentrations of the Pd catalyst, often ranging between 50 ppb and 5 ppm (Scheme 5).[11] The reactions were performed in water using Na_2CO_3 as base at 150 °C for 5 min at 300 W of maximum irradiation power and a phase-transfer catalyst like *n*-tetrabutylammonium bromide (TBAB) was often needed for a smooth reaction. The authors also investigated the scale-up of the reaction by applying an automated set-up. The reaction was performed in 10 mmol batches over 10 cycles and resulted in very high yields and purities.

The Leadbeater group also described open-vessel, microwave-assisted Suzuki–Miyaura biaryl couplings in neat water using ultra-low amounts of the Pd catalyst (Scheme 6).[12] This is particularly noteworthy as an open-vessel reaction is a much safer option for scale-up purposes. This protocol is also an effective substitute for reactions running in continuous flow format when the handling of solids as well as viscous or volatile liquids is often problematic. The authors demonstrated the usefulness of the protocol by conducting a series of reactions at a 1.0 mol scale which resulted in very high conversions and yields of up to 99%.

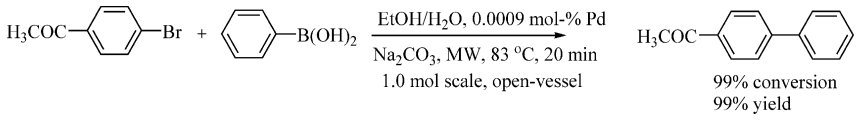
A significant problem with microwave-assisted reactions is their monitoring. Leadbeater and Smith described the use of a dedicated monomode microwave apparatus in combination with a commercially available Raman module for in situ monitoring of Suzuki–Miyaura reactions.[13] As it is important for Raman spectroscopy that the reaction mixture is homogeneous, water/ethanol mixtures were chosen as the solvent and DBU as the base. The authors have demonstrated that for an array of Suzuki–Miyaura reactions, although the product yield cannot be quantified by using this technique, it is possible to determine if the reaction occurs and when it has reached completion.

Arvela and Leadbeater have recently described microwave-assisted Suzuki–Miyaura reactions with simultaneous cooling as an effective method for achieving higher yields (Scheme 7).[14] This technique allows for higher levels of microwave energy to be introduced into the reaction mixture while maintaining the bulk of the material at a relatively low temperature by passing a stream of compressed air over the reaction vessel. They demonstrated that the cooling significantly increased the product yield for Suzuki couplings of aryl chlorides bearing electron-neutral or electron-donating substituents using simple Pd sources.

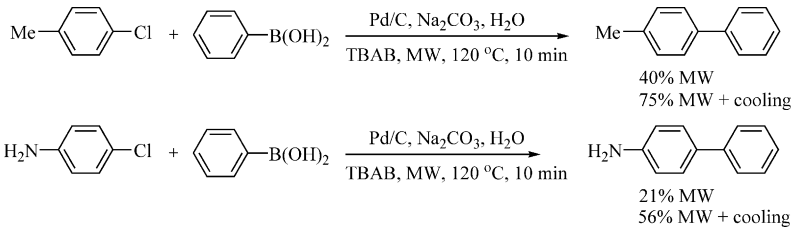
Ley and co-workers investigated the synthesis of encapsulated Pd-based catalytic systems (Pd EnCat™) and their



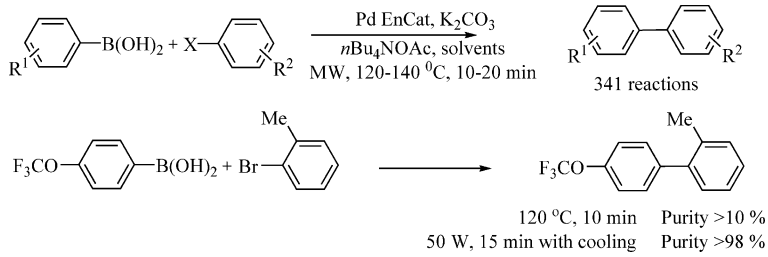
Scheme 5. Suzuki–Miyaura reactions using ultra-low catalyst loadings.



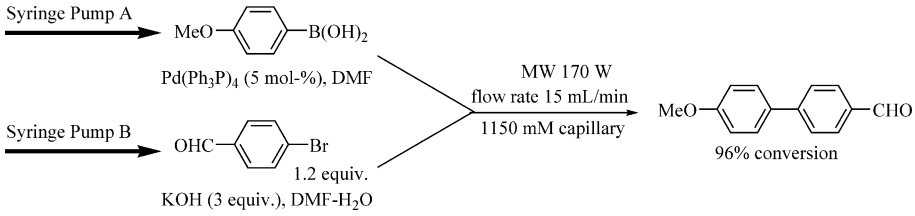
Scheme 6. Suzuki–Miyaura reactions in open vessels with ultra-low catalyst loadings.



Scheme 7. Microwave-assisted Suzuki reactions under simultaneous cooling.



Scheme 8. Suzuki–Miyaura reactions using encapsulated Pd catalysts.

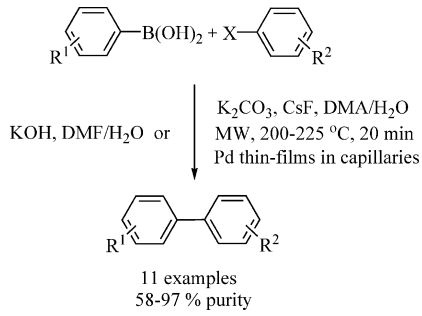


Scheme 9. Microwave-assisted Suzuki–Miyaura reactions under flow format.

use in Suzuki–Miyaura reactions (Scheme 8).[15] They have successfully demonstrated the application of this methodology both in batch mode for classical library generation as well as under continuous-flow conditions for scale-up purposes. Furthermore, the authors investigated these microwave-assisted protocols under simultaneous cooling with compressed air and they observed significantly improved yields and purities in comparison with the uncooled cases. These protocols were also investigated in a continuous-flow system to generate several grams of the target biaryl compounds without the need of regenerating the Pd EnCat catalyst.

Comer and Organ have reported an interesting investigation of Suzuki–Miyaura reactions based on the concept of performing the reactions in a flow format (Scheme 9).[16] This so-called "microreactor" was developed in an effort to circumvent the difficulties of freshly preparing reaction mixtures for each microwave-assisted run. The device contained a large stainless-steel mixing chamber with multiple inlet tubes through which the reagents can be fed to the reactor. After mixing, they merge into a single outlet which allows the mixture to pass through the cavity of the microwave reactor for irradiation. The authors were successful in generating a small library of biaryl compounds in very high yields and purity by applying this novel technique.

They have also reported a detailed study of Suzuki–Miyaura reactions that may also be described under the label of microwave-assisted continuous-flow organic synthesis (MACOS).[17] They developed a novel catalytic concept by generating highly porous palladium thin films in capillaries (Scheme 10). In order to carry out the Suzuki–Miyaura reactions, stock solutions containing the boronic acids, halides, bases and solvents were premixed and subsequently passed through these Pd-coated capillaries[18] under microwave irradiation in such a way that the temperature was maintained consistently at 200 °C. The reactions proceeded very smoothly, furnishing the biaryl products in high yields and purity (11 examples, 58–97% purity).



Scheme 10. Microwave-assisted Suzuki–Miyaura reactions under continuous-flow conditions.

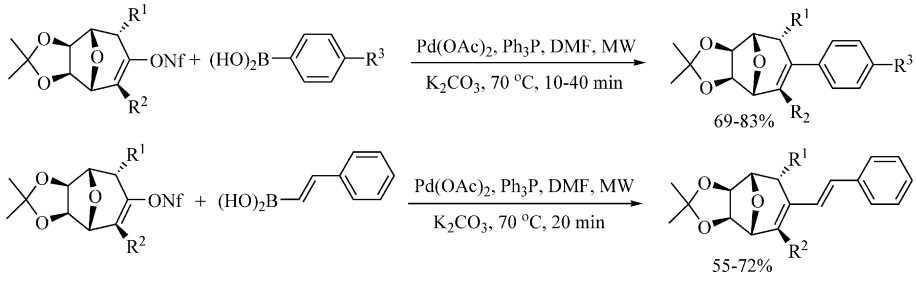
Högermeier and Reißig have recently reported the microwave-assisted Suzuki–Miyaura reactions of alkenyl nonaflates with aryl and alkenyl boronic acid derivatives (Scheme 11).[19] This investigation is particularly interesting as alkenyl nonaflates (nonafluorobutane sulfonates) are excellent substrates in a variety of palladium-catalysed coupling reactions, exhibiting a slightly higher reactivity compared with the corresponding triflates. The authors used nonaflates prepared from 8-oxabicyclo[3.2.1]oct-6-en-3-one and its derivatives as these richly decorated oxabicyclic ketones have proved to be remarkably valuable building blocks in numerous syntheses.

Microwave irradiation dramatically shortened the reaction times and gave superior results in comparison with analogous reactions carried out under conventional heating conditions. Even in the case of highly hindered nonaflates superior yields were obtained.

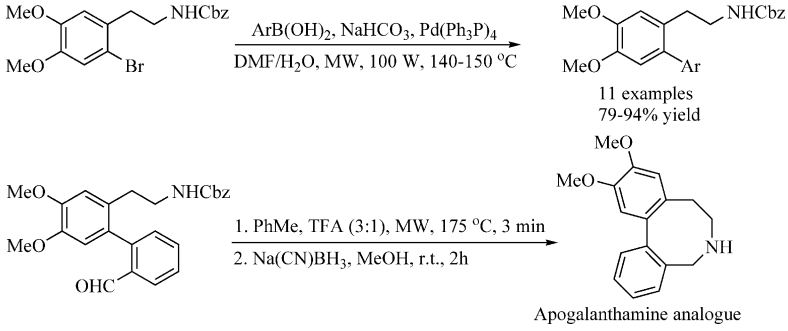
Van der Eycken and co-workers have successfully developed a microwave-assisted Suzuki–Miyaura protocol of highly electron-rich (2-bromo-4,5-dimethoxyphenyl)-ethylamine, deemed as a difficult substrate for cross-coupling reactions under conventional heating conditions (Scheme 12).[20] A variety of aryl rings were successfully introduced in high yields at the 2-position under microwave irradiation. The authors further demonstrated the usefulness of the methodology by studying the cross-coupling of electron-withdrawing and hindered (2-formylphenyl)boronic acid, successfully extending the synthesis towards the generation of the 10,11-dimethoxy-5,6,7,8-tetrahydrodibenzo[*c*,*e*]-azocine skeleton of the apogalanthamine analogues.

Van der Eycken and co-workers have further reported the microwave-assisted Suzuki–Miyaura reactions of electron-withdrawing and hindered 2-nitrophenylboronic acid with a variety of aryl and heteroaryl halides which generate useful 2-nitrobiaryl intermediates (Scheme 13).[21] Microwave irradiation was critical in promoting the cross-couplings with very high yields and purity, as well as in minimizing the proto-deboronations. The authors used this protocol in combination with a microwave-assisted Cadogan cyclization to generate a variety of carbazole analogues that are difficult to obtain in a swift and easy manner, clearly outlining the usefulness of the microwave-assisted protocol.

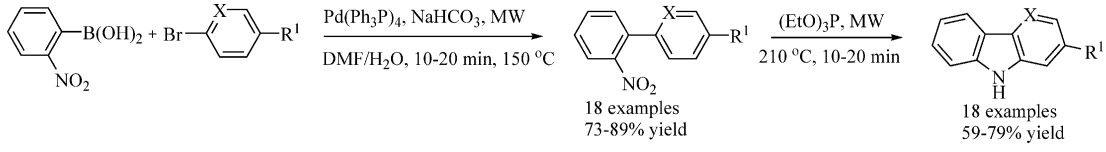
Van der Eycken and co-workers have described an interesting microwave-assisted Suzuki–Miyaura protocol for the decoration of the valuable 2(1*H*)-pyrazinone scaffold in solution and on a solid-support (Scheme 14).[22] The authors reported the first solid-phase synthesis of 2(1*H*)-pyrazinones based on the Strecker reaction of a resin-bound amine with an appropriate aldehyde in the presence of a cyanide, providing a wide diversity of substituents at the C6 position of the pyrazinone ring. Different substituents were introduced at the C3 position by microwave-assisted transi-



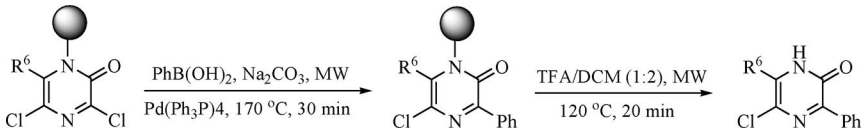
Scheme 11. Microwave-assisted Suzuki–Miyaura reactions of alkenyl nonaflates.



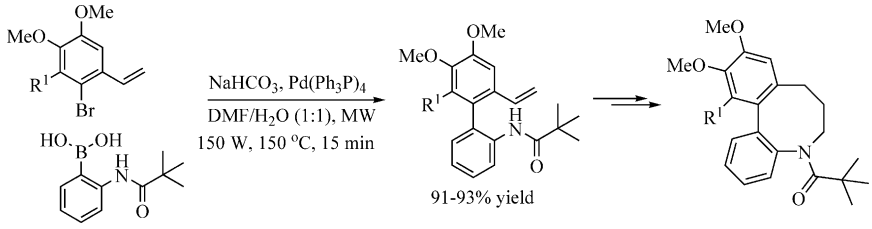
Scheme 12. Microwave-assisted synthesis of apogalanthamine analogues.



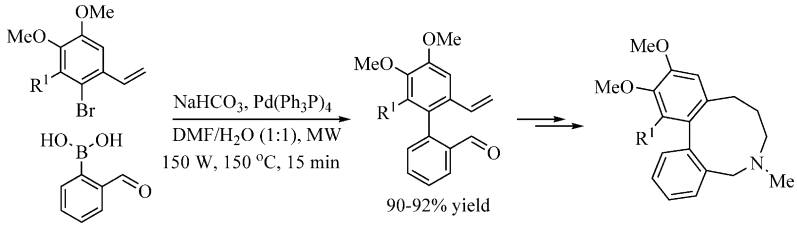
Scheme 13. Microwave-assisted synthesis of carbazole analogues.



Scheme 14. Microwave-assisted decoration of the pyrazinone scaffold on a solid support.



Scheme 15. Microwave-assisted synthesis of *N*-shifted buflavine analogues.



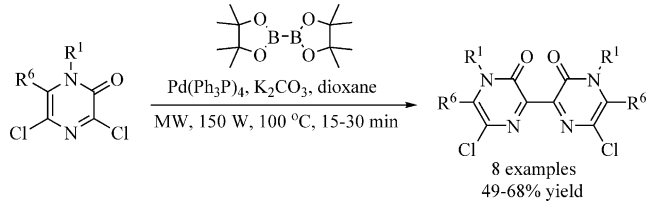
Scheme 16. Microwave-assisted synthesis of ring-expanded buflavine analogues.

tion-metal-catalysed reactions, taking advantage of the sensitive imidoyl chloride moiety.

The Van der Eycken group has also reported the synthesis of *N*-shifted buflavine analogues as part of their research on the microwave-assisted transition-metal-catalysed synthesis of medium-sized ring natural product analogues that are difficult to obtain.[23] This novel protocol comprised a microwave-assisted Suzuki–Miyaura cross-coupling reaction followed by a microwave-assisted ring-closing metathesis (RCM) reaction[24] (Scheme 15). The key biaryl intermediates were generated by using [$Pd(Ph_3P)_4$] as the catalyst at 150 °C for 15 min, and the products were isolated in excellent yields of 91–93%.

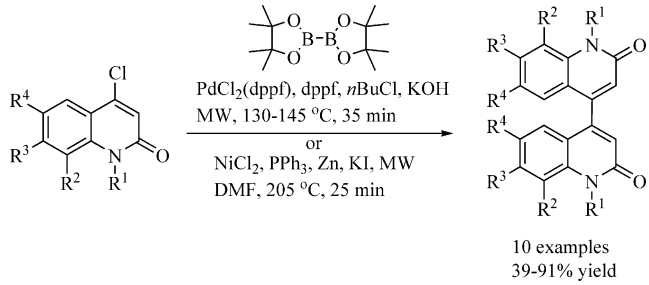
By using a similar strategy based on the combination of microwave-assisted Suzuki–Miyaura and RCM reactions, Van der Eycken and co-workers have reported the synthesis of ring-expanded buflavine analogues possessing a nine-membered medium-sized ring system (Scheme 16).[25] For the generation of the key biaryl intermediates required for the RCM reaction, a microwave-assisted cross-coupling of 2-formylphenylboronic acid with highly electron-rich *o*-bromostyrenes was used by applying [$Pd(Ph_3P)_4$] as the catalyst at 150 °C for 15 min, and the products were isolated in excellent yields of 90–92%. Microwave irradiation was found to be critical in this investigation to minimize the protodeboronation caused by the electron-withdrawing formyl group at the position *ortho* to the boronic acid functional group.

Hoornaert and co-workers reported the synthesis of novel, highly-functionalized bi[2-(1*H*)-pyrazinone] systems[26] from cheap and easily available starting materials based on a microwave-assisted Suzuki–Miyaura-type homodimerization protocol (Scheme 17). The authors found that the use of microwave irradiation was helpful in considerably accelerating the reaction as well as in substantially improving the yields in some cases.

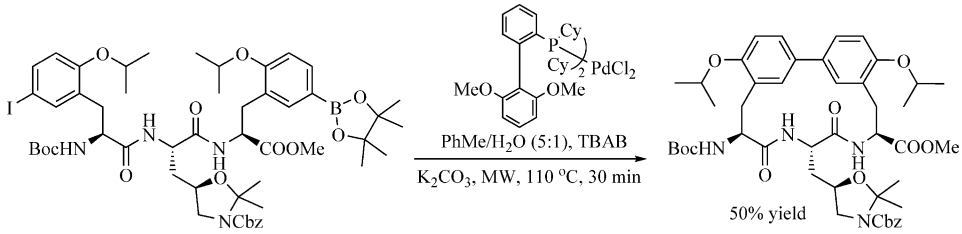


Scheme 17. Microwave-assisted synthesis of bi[2-(1*H*)-pyrazinone] systems.

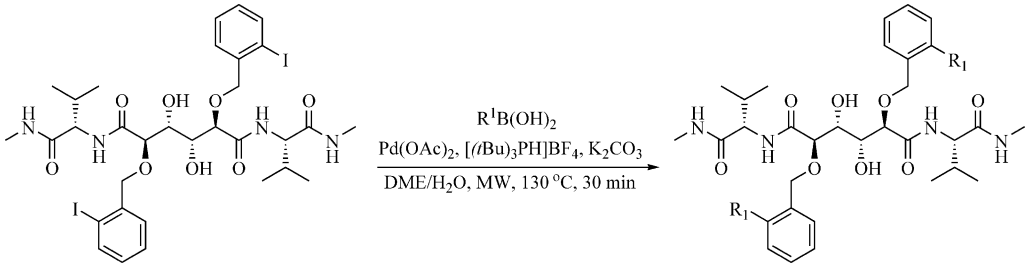
Kappe and co-workers have reported a similar strategy for the synthesis of highly functionalized 4,4′-biquinolones[27] by the microwave-assisted, one-pot borylation–Suzuki–Miyaura reaction of 4-chloroquinolin-2(1*H*)-ones (Scheme 18). The authors reported two efficient procedures



Scheme 18. Microwave-assisted synthesis of functionalized 4,4′-biquinolones.



Scheme 19. Microwave-assisted synthesis of Biphenomycin B.



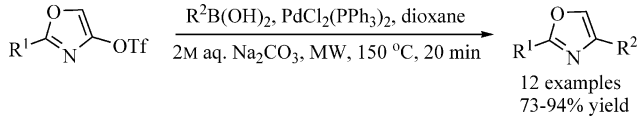
Scheme 20. Microwave-assisted synthesis of HIV-1 protease inhibitors.

for the purpose, based either on a microwave-assisted Pd^0-catalysed one-pot borylation–Suzuki–Miyaura reaction or on a Ni^0-mediated homocoupling of a 4-chloroquinolin-2(1*H*)-one precursor. Both protocols were effective in carrying out the homodimerizations, generating the targets in good-to-excellent yields of 39–91%.

Another interesting application of the microwave-assisted Suzuki–Miyaura reaction was recently described by Lépine and Zhu.[28] The authors investigated the total synthesis of Biphenomycin B (Scheme 19), a cyclic tripeptide showing activity against Gram-positive, β-lactam-resistant bacteria, such as *Streptococcus aureus*, *Enterococcus faecalis* or *Streptococcus*. The authors performed the macrocyclization to furnish the 15-membered ring system of the title molecule in a yield of 50% by a microwave-assisted, intramolecular Suzuki–Miyaura reaction. It is particularly noteworthy that the microwave-assisted procedure gave a rewarding 33% yield when simple $Pd(OAc)_2$ was used in the absence of ligands, whereas the use of much more specific catalytic systems met with failure or furnished very low yields of the target biaryl compound when performed under conventional heating conditions.

One of the ingenious applications of microwave-assisted Suzuki–Miyaura reactions in the synthesis of drug-like molecules was recently reported by Larhed and co-workers by which the authors developed a small library of 24 novel C_2-symmetric HIV-1 protease inhibitors (Scheme 20).[29] The Larhed group has successfully used a carbohydrate-based scaffold with the intention of optimizing the binding of the P1/P1′ and P2/P2′ side-chains to the C_2-symmetric HIV-1 protease. The authors investigated a variety of Pd-catalysed reactions under microwave-assisted conditions for the decoration of the scaffold including the Suzuki–Miyaura reaction, in which the catalytic combination of $Pd(OAc)_2$ and $[(t\mathrm{Bu})_3\mathrm{PH}]BF_4$ was successfully used in the presence of K_2CO_3 as base.

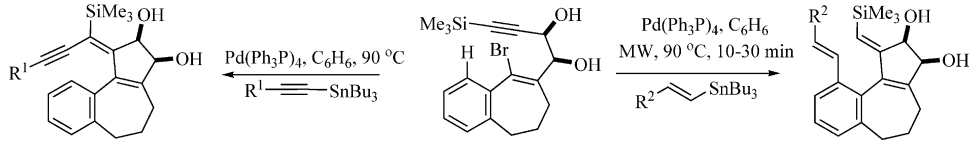
Greaney and co-workers have described an interesting protocol for the functionalization of the 2- and 4-positions of the oxazole using Suzuki–Miyaura reactions.[30] 2-Aryl-4-trifloyloxazoles were investigated as reagents in microwave-assisted cross-couplings with a range of aryl and heteroaryl boronic acids resulting in good-to-excellent yields of 73–94% (Scheme 21). It is noteworthy that the best conditions using $[PdCl_2(PPh_3)_2]$ as catalyst and 2 M aqueous Na_2CO_3 as base under microwave irradiation furnished an excellent yield of 94% whereas the reaction using the same reagents under conventional heating conditions yielded a mere 16% of the product.



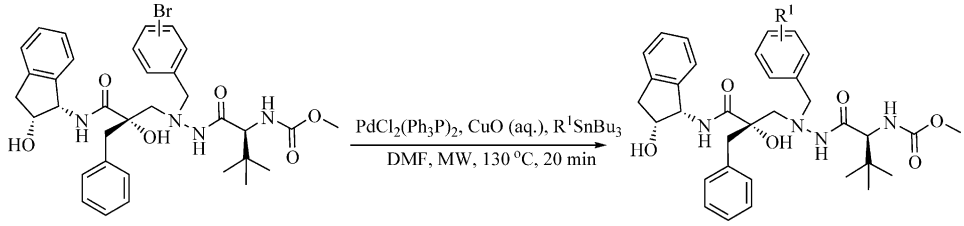
Scheme 21. Suzuki–Miyaura reactions of 2-aryl-4-trifloyloxazoles.

Bour and Suffert have reported[31] a novel, microwave-assisted cyclization–C–H activation–Stille cross-coupling protocol for inactivated aromatic moieties (Scheme 22). Based on previous results that the 4- and 5-*exo*-*dig* cyclocarbopalladation can be used for the elaboration of highly functionalized bicyclic systems and that this multistep reaction terminates with a Stille cross-coupling, the authors used vinyl, allyl and heteroaromatic tributylstannanes as the final coupling partners. While trying to carry out the Stille reaction across the triple bond in the benzosuberone starting materials, the authors found a C–H activation product instead of the expected direct Stille-coupling product. Microwave irradiation was investigated and dramatic accelerations were found compared with the experiments carried out under conventional heating conditions.

Hallberg and co-workers have reported[32] the synthesis of two series of P1′-extended HIV-1 protease inhibitors



Scheme 22. Microwave-assisted Stille reactions on functionalized bicyclic systems.



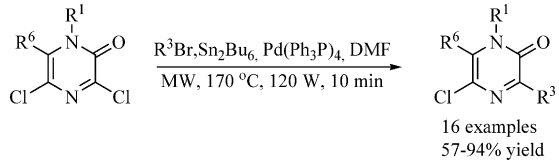
Scheme 23. Stille reactions in the synthesis of HIV-1 protease inhibitors.

comprising a tertiary alcohol in the transition-state mimic (Scheme 23). Microwave-accelerated Stille cross-couplings were utilized to rapidly optimize the P1′ side-chain using $[PdCl_2(Ph_3P)_2]$ as the catalyst in the presence of CuO. As expected, the authors described lower yields for the Stille cross-couplings in comparison with the Suzuki–Miyaura cross-couplings.

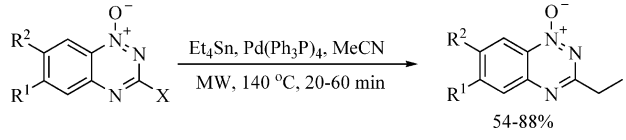
Van der Eycken and co-workers described[33] a chemoselective, one-pot cross-Stille reaction of benzylic halides with 3,5-dichloro-2(1*H*)-pyrazinones in order to decorate the C3 position of the pyrazinone scaffold (Scheme 24). This novel protocol avoids the purification and handling of toxic stannylated intermediates. This investigation is particularly interesting as the authors tried to elaborate an easy and flexible protocol for the incorporation of various alkyl and benzyl moieties at the C3 position of the 2(1*H*)-pyrazinone scaffold in order to generate aminopiperidine carboxylate (APC) systems incorporating unnatural amino acids at the *i*+1 position as potent β-turn mimetics. The reactions were carried out in a one-pot fashion between the pyrazinone and benzyl bromide in the presence of Sn_2Bu_6 and $[Pd(Ph_3P)_4]$ as the catalyst for 10 min at 170 °C. The products were isolated in good-to-excellent yields of 57–94%. It is noteworthy that significant improvements in yields were established when these microwave-assisted Stille reactions were performed with simultaneous cooling using compressed air.

Dehlinger et al. have recently reported a microwave-assisted arylstannane synthesis applying a Stille coupling protocol. This was used in the synthesis of complex pyridin-3-ylphenyl biaryl systems as part of an investigation into the design and synthesis of novel ligands for β4 nicotinic acetylcholine receptors (Scheme 25).[34] The corresponding aryl bromide was initially converted into the corresponding trimethylstannyl derivative by a microwave-assisted, Pd-catalysed reaction in a mere 3 min (in comparison with the 20 h under conventional heating) in a good yield of 79%. The authors then used a variety of functionalized 3-bromopyridines as microwave-assisted Stille reaction partners, furnishing the target pyridin-3-ylphenyl systems in good yields of 33–61%.

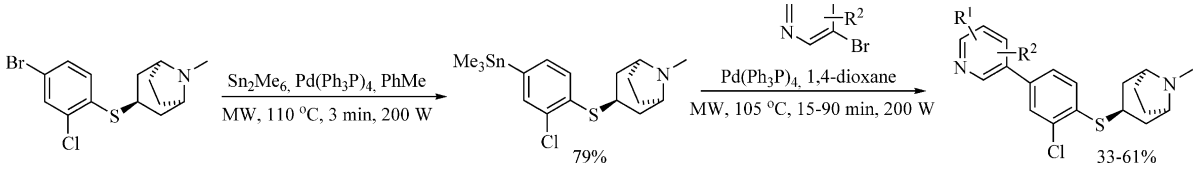
Pchalek and Hay described microwave-assisted Stille coupling reactions as convenient tools in the synthesis of hypoxia-selective 3-alkyl-1,2,4-benzotriazine 1,4-dioxide anticancer agents such as SN29751 (Scheme 26).[35] The introduction of a 3-alkyl substituent is a key step in their synthesis. The authors performed the microwave-assisted Stille reaction by using $[Pd(PPh_3)_4]$ in MeCN at 140 °C, furnishing the targets within 20–60 min with good yields ranging between 54 and 88%.



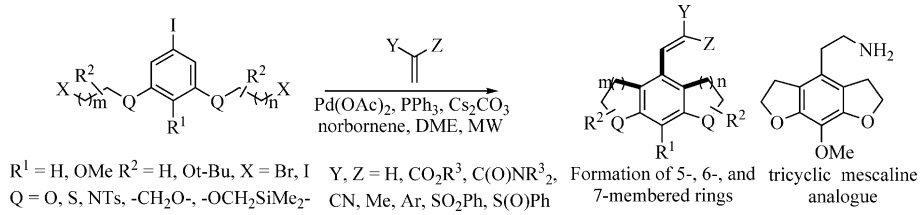
Scheme 24. Microwave-assisted, one-pot cross-Stille reactions.



Scheme 26. Stille reactions in the synthesis of hypoxia-selective anticancer agents.



Scheme 25. Stille reactions in the synthesis of pyridin-3-ylphenyl systems.



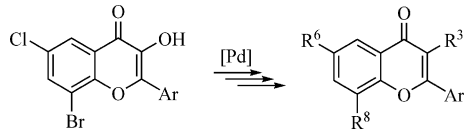
Scheme 27. Norbornene-mediated palladium-catalysed synthesis of tricyclic heterocycles.

2. Microwave-Assisted Heck and Sonogashira Reactions

The Heck reaction,[36] generally conducted with alkenes and organohalides or pseudo-halides as reactants, is one of the most widely investigated transition-metal-mediated C–C bond-forming reactions. Heck reactions are often employed in present-day academic and industrial procedures and are much more popular than their alkyne counterpart, the Sonogashira reaction.[37] Numerous elegant synthetic transformations based on C–C bond-forming Heck and Sonogashira reactions have been developed both in classical organic synthesis and in microwave-assisted organic synthesis (MAOS). In recent years, the development of "ligand-free" palladium-catalysed protocols for carrying out these reactions in a more efficient manner has also gained much interest. The earlier examples of microwave-assisted Heck and Sonogashira reactions have been extensively reviewed.[38] Only a very narrow selection of the vast array of manuscripts that have appeared during recent years will be summarized in this contribution.

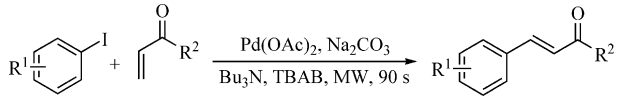
Lautens and co-workers have described an interesting synthesis of tricyclic heterocycles by a microwave-assisted tandem aryl alkylation/Heck coupling sequence.[39] The reaction involves a palladium-catalysed norbornene-mediated tandem process in which the alkylation of an *ortho*-C–H bond is followed by a Heck reaction at the *ipso* carbon of the aryl iodide (Scheme 27). The direct functionalization of aromatic C–H bonds avoids the need for activating groups. A number of tricyclic oxygen-, nitrogen-, silicon- and sulfur-containing heterocycles were generated as well as a tricyclic mescaline analogue. The products were rapidly accessed within minutes with the use of microwave irradiation.

A diversity-oriented approach to the decoration of the chromone scaffold, which can be regarded as a privileged structure for drug development, has been developed by Luthman and co-workers.[40] 2-Aryl/styryl-8-bromo-6-chloro-3-hydroxychromone derivatives were synthesized and it has been demonstrated that excellent regioselectivity could be obtained by performing reactions at the 8-position first, with the Stille, Heck, Suzuki and Sonogashira reactions giving good-to-excellent yields (63–98%) (Scheme 28). Stille and Heck reactions at the 6-position also gave the desired products in good yields (64–86%). The hydroxy group in the 3-position was activated as a triflate and used in Stille reactions (63–94%). Several of these reactions were performed under microwave irradiation conditions.



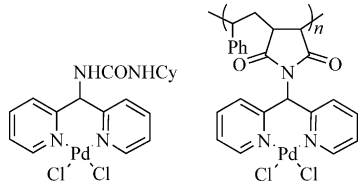
Scheme 28. Synthesis of 2,3,6,8-tetrasubstituted chromone scaffolds.

It has been demonstrated by Leadbeater et al. that microwave-assisted Heck coupling reactions of aryl iodides in open reaction vessels[41] could be scaled up from the mmol to the mol scale. The reactions were performed by using 0.1 mol-% palladium acetate as the catalyst, sodium carbonate and tributylamine as bases and tetra-*n*-butylammonium bromide as an additive (Scheme 29). Yields range from 15 to 98%. The same author has shown that microwave-assisted Suzuki and Heck coupling reactions using ultra-low catalyst loadings can be easily scaled up from the 1 to 10 mmol level and adapted to an automated stop-flow apparatus.[42] This is of interest for the chemical industry for the preparation of, for example, pharmaceuticals, as lengthy metal extracting steps for product purification are not required.



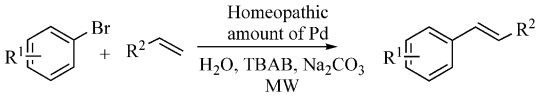
Scheme 29. Solvent-free, open-vessel microwave-assisted Heck couplings.

The use of the bis(2-pyridyl)methylamine–palladium dichloride complex, which is eventually anchored covalently to a styrene–maleic anhydride copolymer, is described by Nájera and co-workers for microwave-assisted Heck, Suzuki and Sonogashira cross-coupling reactions in water resulting in high TONs (Scheme 30).[43]



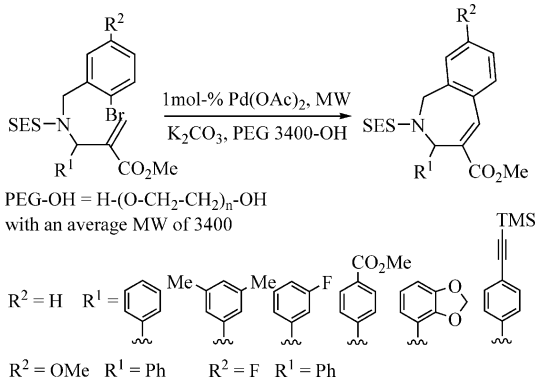
Scheme 30. Bis(2-pyridyl)methylamine–palladium dichloride complexes for C–C cross-coupling reactions in water.

As a result of their finding that Suzuki reactions could be run efficiently with catalyst concentrations as low as 50 ppb, Arvela and Leadbeater have shown that Heck couplings can be performed in water using microwave irradiation and Pd catalyst concentrations as low as 500 ppb (Scheme 31).[44]



Scheme 31. Microwave-assisted Heck coupling using homeopathic quantities of Pd.

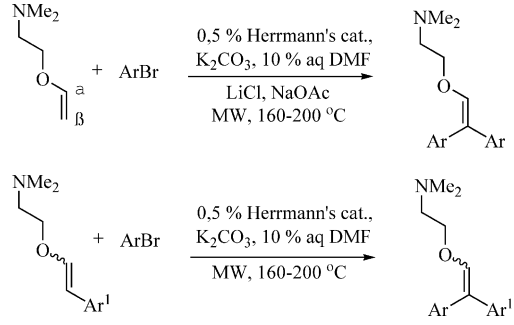
Lamaty and co-workers obtained[45] a set of novel benzazepines by the palladium-catalysed Heck reaction of alkylated 2-(trimethylsilyl)ethanesulfonyl (SES)-protected β-amino esters in poly(ethylene glycol) (PEG-3400) as the solvent under microwave irradiation (Scheme 32). According to the authors this represents the first preparation and characterization of PEG-stabilized palladium nanoparticles obtained under microwave irradiation. A slightly modified procedure using copper iodide, potassium carbonate and PEG-3400 had been previously developed by the same author to synthesize various substituted *t*Bu-cinnamates by microwave-assisted Heck arylation.



Scheme 32. Preparation of diverse benzazepines by microwave-assisted Heck reaction in poly(ethylene glycol).

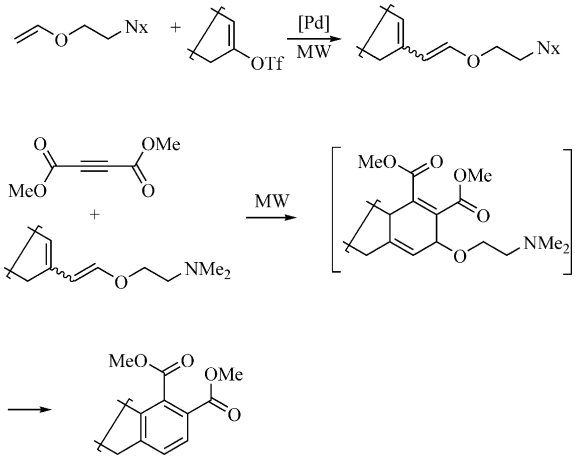
Over the years, extensive work on (microwave-assisted) Heck reactions has been carried out by Hallberg and Larhed and co-workers. A detailed study of the arylation of the vinyl ether bond using inexpensive aryl chlorides has been performed,[46] which showed that the Heck reaction took place selectively on the less substituted β position when the reaction was run in air using P(*t*Bu)$_3$, liberating [(*t*Bu)$_3$PH]BF$_4$, and high-density microwave processing (Scheme 33). The selectivity for the linear β-product in PEG-200 is slightly higher than in aqueous DMF. DFT calculations support a ligand-driven selectivity rationale.

Larhed and co-workers also developed a rapid protocol for microwave-assisted regioselective double β-arylations[47] of the chelating vinyl ether *N*,*N*-dimethyl-2-ethenyloxyethanamine using Herrmann's Pd^{II}-phosphapalladacycle as the palladium source (Scheme 34). They demonstrated that by proper selection of the experimental parameters, it is possible to achieve symmetrical and non-symmetrical terminal β,β-diarylations with both electron-rich and electron-poor aryl bromides. According to the authors, the good terminal regioselectivity suggests that the palladacycle serves as a source of weakly coordinated palladium(0) in this high-temperature process.

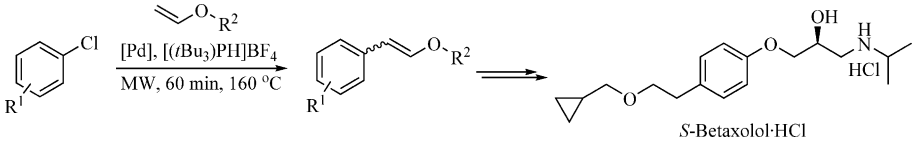


Scheme 34. Chelation-controlled microwave-assisted β-arylation and β,β-diarylation of *N*,*N*-dimethyl-2-ethenyloxyethanamine.

The same principle of chelation control was applied by Larhed and co-workers to the synthesis of a set of 1-alkoxy-1,3-butadienes by microwave-assisted Heck vinylation of electron-rich amino-functionalized vinyl ethers (Scheme 35).[48] The reactions were performed with high regioselectivity. The resulting dimethylaminoethoxy-1,3-buta-



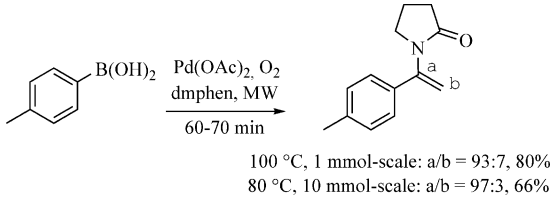
Scheme 35. Regioselective terminal vinylations and subsequent Diels–Alder/amino alcohol elimination reactions.



Scheme 33. Selective terminal Heck arylation of vinyl ethers with aryl chlorides.

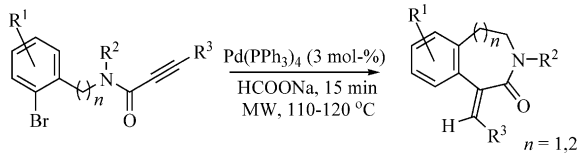
dienes were investigated as substrates in microwave-assisted Diels–Alder reactions.

Larhed and co-workers expanded the scope of the relatively slow oxidative Heck arylation of electron-rich olefins using oxygen under controlled microwave irradiation.[49] The reaction was performed on a multigram scale in a multimode autoclave reactor applying a continuous flow of oxygen (Scheme 36). An excellent α/β selectivity of 97:3 was obtained and a yield of 66%. This is an interesting finding as the use of reactive gases under microwave irradiation has not been thoroughly investigated.



Scheme 36. Use of oxygen under microwave irradiation for the oxidative Heck arylation of an electron-rich olefin.

Donets and Van der Eycken described an interesting approach to the generation of the 3-benzazepine framework by intramolecular Heck reductive cyclization (Scheme 37).[50] As a result of the reaction mechanism, the formation of the medium-sized ring occurred with full regio- and stereoselectivity.

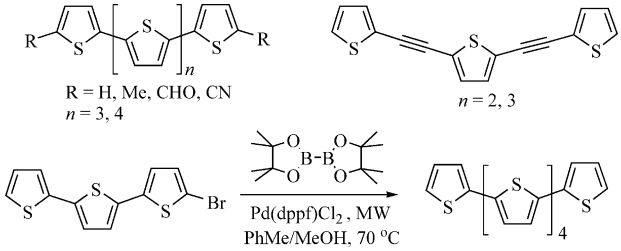


Scheme 37. Synthesis of the 3-benzazepine framework by intramolecular Heck reductive cyclization.

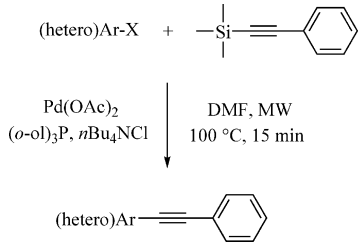
The 4-hydroxycyclohexa-2,5-dien-1-one ("quinol") fragment represents a new pharmacophore in anticancer drug development. Stevens and co-workers have developed[51] a novel procedure, based on a microwave-assisted Sonogashira coupling with concomitant cyclization, leading to 4-[1-(arylsulfonyl-1*H*-indol-2-yl)]-4-hydroxycyclohexa-2,5-dien-1-ones in moderate yields (Scheme 38).

Phenylethynylene compounds containing the 6-methylpyran-2-one group were synthesized by Marder and co-workers via classic or microwave-assisted Sonogashira cross-coupling reactions[52] to explore the optical properties of such donor–acceptor systems. By using 0.5 mol-% $[(PPh_3)_2PdCl_2]$ and 0.5 mol-% CuI in a CH_3CN/Et_3N solvent mixture (5:3) containing 1.05 equiv. of the terminal alkyne at 120 °C ceiling temperature, the desired compounds were obtained in 92 and 38% yields (Scheme 39).

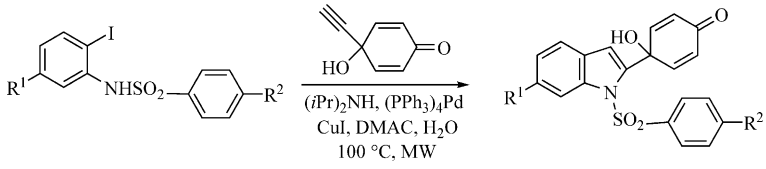
Oligothiophenes bearing five and six thiophene units are important electroactive materials that are capable of self-assembly in the solid state and giving high-performance organic thin-film transistors (FET). The facile synthesis of poorly soluble unsubstituted as well as modified α-quinque- and -sexithiophenes under microwave irradiation in the liquid phase by Suzuki cross-coupling has been described by Barbarella and co-workers (Scheme 40).[53] Interestingly, unsubstituted sexithiophene was obtained in 84% yield by applying a microwave-assisted one-pot borylation/Suzuki



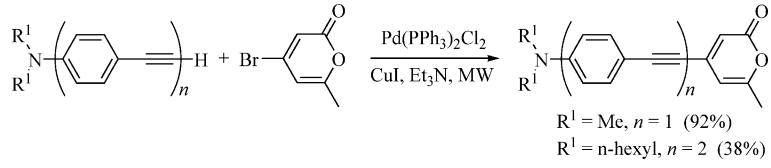
Scheme 40. Solution-phase microwave-assisted synthesis of unsubstituted and modified α-quinque- and sexithiophenes.



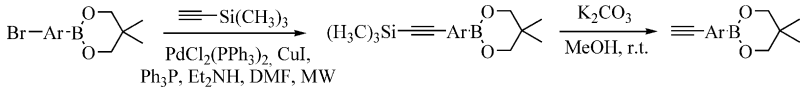
Scheme 41. Copper-free palladium-catalysed Sonogashira-type coupling of aryl halides and 1-aryl-2-(trimethylsilyl)acetylenes.



Scheme 38. Synthesis of indol-2-yl-substituted 4-hydroxycyclohexa-2,5-dien-1-ones.



Scheme 39. Synthesis of 4-ethynylpyran-2-ones containing the 6-methylpyran-2-one group.



Scheme 42. Synthesis of ethynylaryl boronates.

reaction. As an extension, oligothiophenes containing acetylenic spacers were synthesized by microwave-assisted Sonogashira coupling reactions.

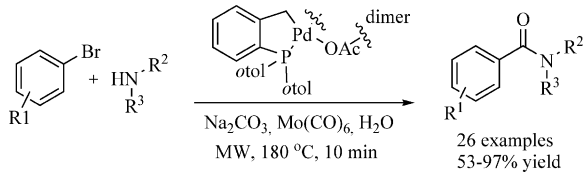
Sørensen and Pombo-Villar have elaborated a procedure for the direct coupling of trimethylsilylacetylenes with a number of activated aryl and heteroaryl halides to give 1,2-diarylacetylenes in a palladium-catalysed Sonogashira-type coupling without the use of a copper co-catalyst (Scheme 41).[54] It was demonstrated that the reactions could be dramatically speeded up upon microwave irradiation. As could be expected, iodides afforded better results than the corresponding bromides.

Wang and co-workers have developed a facile method for the synthesis of protected ethynylaryl boronates by the selective Sonogashira reactions of the corresponding bromoaryl boronates with trimethylsilylacetylene and subsequent desilylation (Scheme 42).[55] The use of microwave irradiation was found to significantly improve the reaction yields and shorten the reaction time of the cross-coupling. The reaction is tolerant to the presence of chloro substituents. The resulting compounds can be used in the construction of diboronic acid libraries through [2+3] Huisgen cycloaddition for carbohydrate fluorescent sensor development.

3. Microwave-Assisted Carbonylation Reactions

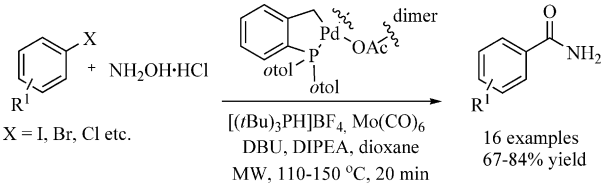
Transition-metal-mediated carbonylation protocols[56] are a relatively under-explored area of research in comparison with other transition-metal-mediated protocols like cross-couplings and Heck reactions. Gas-free carbonylative protocols using solid CO sources like $[Mo(CO)_6]$ have paved a safe way for performing these reactions under high-density microwave irradiation.[57] Several interesting investigations of microwave-assisted carbonylative protocols have been reported in recent years relating to the development of novel carbonylative procedures encompassing a variety of nucleophiles for the in situ synthesis of, for example, amides, esters and sulfonamides and the application of these methodologies to the generation of biologically interesting target molecules.

Larhed and co-workers have reported an interesting investigation of microwave-assisted aminocarbonylations of various aryl halides in pure water[58] using a variety of structurally different amines as nucleophiles for the in situ generation of the aryl amides (Scheme 43). The carbonylations were carried out under microwave-assisted conditions at 180 °C for 10 min in water by using $[Mo(CO)_6]$ as the solid CO-liberating source and Herrmann's palladacycle as the catalyst. A small library of 26 amides was generated in high yields of 53–97%, completely avoiding the formation of competing hydroxycarbonylation products, clearly outlining the potential of the protocol.



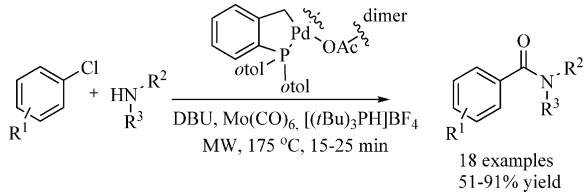
Scheme 43. Microwave-assisted aminocarbonylation of aryl bromides in water.

Wu and Larhed have described another interesting investigation of microwave-assisted aminocarbonylations in which hydroxylamine was used as an ammonia equivalent[59] for the in situ generation of primary amides, avoiding the use of toxic ammonia gas (Scheme 44). The reactions were performed at 150 °C for 20 min using an excess of DBU and DIPEA as bases for the smooth release of free NH_2OH which was in situ reduced to ammonia in the presence of excess $[Mo(CO)_6]$. Together with a combination of Herrmann's palladacycle and $[(tBu)_3PH]BF_4$ as a preligand, the aryl halides were treated with $[Mo(CO)_6]$, delivering the benzamide products in good yields of 67–84% in 10–30 min.

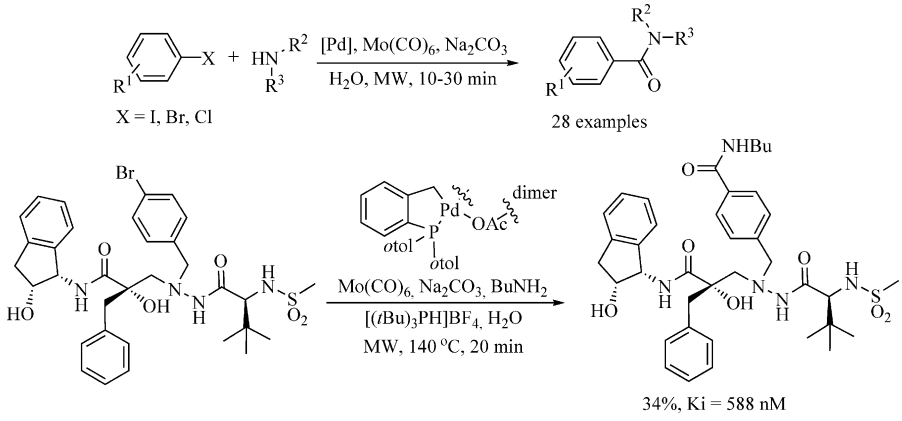


Scheme 44. Microwave-assisted synthesis of primary benzamides.

The same authors have reported another interesting case study of microwave-assisted aminocarbonylations of sluggishly reacting aryl chlorides[60] for the in situ generation of the corresponding benzamides (Scheme 45). The carbonylations were carried out under microwave-assisted conditions at 175 °C for 15–25 min using $[Mo(CO)_6]$ as the solid CO-liberating source. The use of Herrmann's palladacycle as the catalyst, together with $[(tBu)_3PH]BF_4$ as an additional ligand, was found to be the best conditions, and a small library of 18 benzamides was generated in high yields of 51–91%.



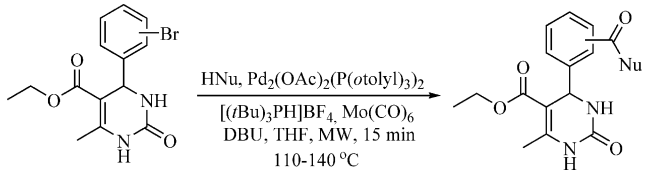
Scheme 45. Microwave-assisted aminocarbonylation of aryl chlorides.



Scheme 46. Microwave-assisted aminocarbonylation of aryl halides in water.

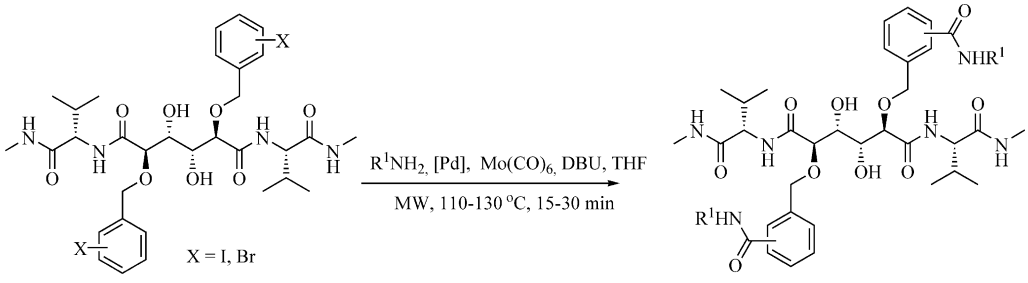
Lagerlund and Larhed have also reported microwave-assisted aminocarbonylations of a variety of aryl iodides, bromides and chlorides in pure water[61] using a diverse array of organic amines as nucleophiles for the in situ generation of the corresponding benzamides (Scheme 46). The authors found that although the aryl iodides and bromides gave smooth aminocarbonylation reactions using $Pd(OAc)_2$ and Herrmann's palladacycle as catalysts, the more sluggish aryl chlorides demanded the use of the preligand $[(t\mathrm{Bu})_3\mathrm{PH}]\mathrm{BF}_4$ for the conversions. They reported the development of a small library of benzamides in high yields and purity under microwave-assisted conditions at 110–180 °C in 10–30 min. This successful protocol was later used in the synthesis of a novel HIV-1 protease inhibitor, albeit the compound was formed in a moderate yield of 34%.

The Larhed and Kappe groups have, together, reported an interesting microwave-assisted aminocarbonylation protocol for the orthogonal decoration of each position of dihydropyrimidones (DHPMs)[62,63] owing to the usefulness of this scaffold for drug synthesis. They explored the use of *ortho*-, *meta*- and *para*-substituted 4-bromoaryl-DHPMs in the aminocarbonylation reaction (Scheme 47), in addition to a variety of Suzuki–Miyaura, Heck and amination reactions. Although the standard aminocarbonylation protocol for aryl bromides using Herrmann's palladacycle performed well with this scaffold, addition of Fu's salt $[(t\mathrm{Bu})_3\mathrm{PH}]\mathrm{BF}_4$ allowed a reduction of the ceiling temperature from 150 to 130 °C. The reactions were carried out for 15 min and good yields of amides were isolated with both the *para*- and *meta*-substituted DHPMs (56–87%), although the *ortho*-substituted DHPMs furnished lower yields. The authors also explored the alkoxycarbonylation of the DHPMs in methanol as a combined nucleophile and solvent in the presence of $\{[(t\mathrm{Bu})_3\mathrm{PH}]\mathrm{BF}_4\}$, and the *para*- and *meta*-methyl esters were obtained in good yields (71–77%) at temperatures as low as 110 °C.



Scheme 47. Microwave-assisted decoration of the dihydropyrimidine scaffold.

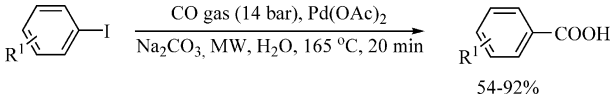
Encouraged by the smoothness and chemoselectivity of the microwave-assisted protocol, the Hallberg group investigated the aminocarbonylations of more complex medicinally related substrates and employed aminocarbonylations to achieve bis-functionalizations of the benzyloxy P1/P1′ side-chains of the C_2-symmetric dihydroxyethylene-based HIV-1 protease inhibitor scaffold.[64] The aminocarbonylations were conducted in the absence of ligands in the case of the aryl iodide substrate with $Pd(OAc)_2$ as precatalyst using 14 different primary and secondary amines (Scheme 48). In all cases, 15 or 30 min of microwave irradiation at 110 °C and a quick filtration and subsequent purification furnished all but one of the 14 bis-amides in moderate-to-good yields and over 95% purity. Similarly, the *meta*-substituted aryl bromide substrate was investigated using



Scheme 48. Microwave-assisted synthesis of novel HIV-1 protease inhibitors.

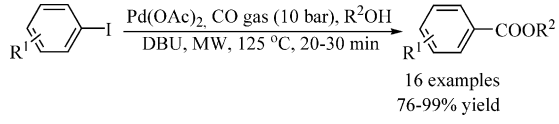
Herrmann's palladacycle and $[(t\mathrm{Bu})_3\mathrm{PH}]\mathrm{BF}_4$ at 130 °C and the desired amide products were isolated within 15 min.

Kormos and Leadbeater have recently reported another interesting case study[65] of microwave-assisted carbonylation reactions in which they investigated the hydroxycarbonylations of various aryl iodides in water using gaseous carbon monoxide in prepressurized reaction vessels (Scheme 49). The authors applied a newly developed dedicated multimode microwave reactor (Anton Paar Synthos 3000, equipped with a gas-loading interface) for the reactions, in which it is possible to perform reactions in heavy-walled quartz reaction vessels operating at 80 bar. The hydroxycarbonylation reactions were performed in a sealed tube preloaded with 14 bar CO using Na_2CO_3 as base in water at 165 °C for 20 min using either 1 mol-% of $Pd(OAc)_2$ or 0.01 mol-% of commercially available Pd solutions and the corresponding carboxylic acid products were isolated in good yields.



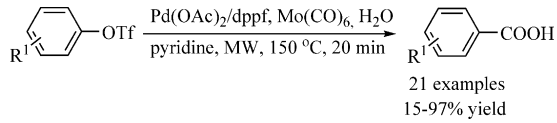
Scheme 49. Microwave-assisted hydroxycarbonylations using CO.

The same authors have recently described an interesting investigation of microwave-assisted carbonylation reactions in which they investigated the alkoxycarbonylations[66] of various aryl iodides using an alcohol as solvent and nucleophile (Scheme 50). Reactions were run in a sealed tube in an Anton Paar Synthos 3000 apparatus pre-loaded with 10 bar CO pressure using 0.1 mol-% $Pd(OAc)_2$ as catalyst and 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) as base at 125 °C for 20–30 min. An excess of the corresponding alcohol was used as solvent and nucleophile and the corresponding benzoates were isolated in good yields of 76–99%.



Scheme 50. Microwave-assisted alkoxycarbonylations of aryl iodides.

Silvani and co-workers have reported a Pd-catalysed hydroxycarbonylation of aryl and vinyl triflates[67] using in situ generated carbon monoxide under microwave irradiation. The reactions were performed in water using $[Mo(CO)_6]$ as the solid CO-liberating source and a combination of $Pd(OAc)_2$ and pyridine as base (Scheme 51). The reactions were carried out at 150 °C for 20 min and the corresponding carboxylic acids were isolated in good yields and purities in most of the cases.



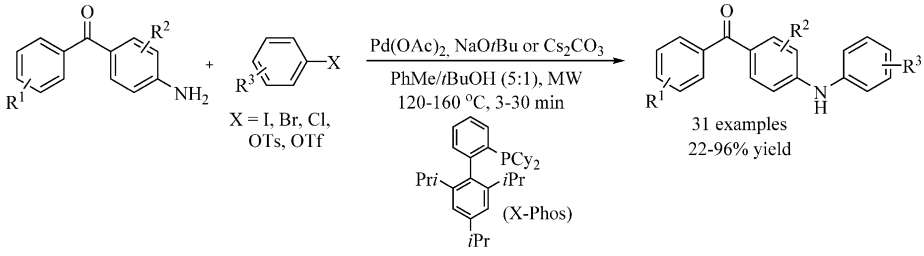
Scheme 51. Microwave-assisted hydroxycarbonylations of aryl and vinyl triflates.

4. Transition-Metal-Mediated C–N Bond Formation by Amination-Type Reactions

C–N bond-forming reactions have always attracted considerable interest from synthetic chemists because of their precious applications in the synthesis of drug-like molecules, natural product analogues and heterocyclic molecules.[68] The development of novel catalytic systems, ligands and novel synthetic protocols has revolutionized this area of research, both in academia as well as in industry.[69] However, the application of microwave irradiation in promoting C–N bond-forming reactions is still a relatively under-explored area of research in comparison with other transition-metal-mediated protocols like cross-couplings and Heck reactions. One of the reasons behind this limitation is probably the fact that the modern C–N bond-forming reaction uses a variety of bulky ligands and catalysts which often demands sensitive and/or inert reaction conditions. In this chapter only a rather small selection of the available literature regarding the application of microwave irradiation for C–N bond formation is presented.

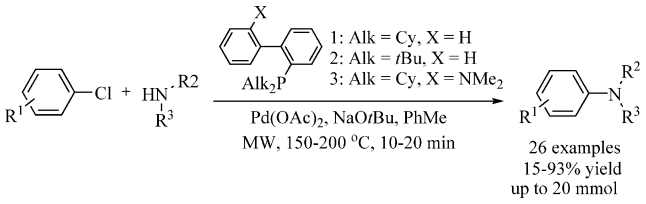
Skjaerbaek and co-workers have reported an efficient microwave-assisted amination protocol[70] in which they generated substituted arylaminobenzophenone p38 MAP kinase inhibitors using a Pd-catalysed aryl amination protocol (Scheme 52). The reactions were carried out using a variety of aryl halides, tosylates and triflates with various aminobenzophenones with $Pd(OAc)_2$ as the catalyst and $NaOt\mathrm{Bu}$ or Cs_2CO_3 as the base in the presence of X-Phos as an external phosphane ligand. A large number of aminations were successfully performed under microwave-assisted conditions at 120–160 °C in a mere 3–30 min and the products were isolated in very good yields and purity.

Maes et al. have reported[71] a rapid Buchwald–Hartwig amination of electron-rich and neutral aryl chlorides and



Scheme 52. Microwave-assisted arylations of aminobenzophenones.

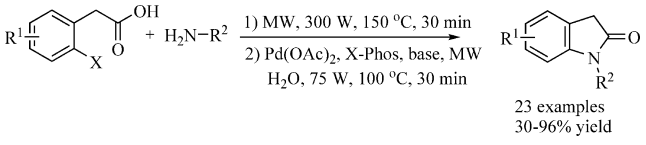
bromides under microwave-assisted conditions[72] in which a variety of primary and secondary aliphatic amines were coupled with these substrates (Scheme 53). The reactions were carried out by applying a combination of $Pd(OAc)_2$ with three different 2-(dicyclohexylphosphanyl)biphenyl ligands using NaO*t*Bu as the base at 150–200 °C for 10–20 min and the target amines were isolated in good yields.



Scheme 53. Microwave-assisted aminations of aryl chlorides.

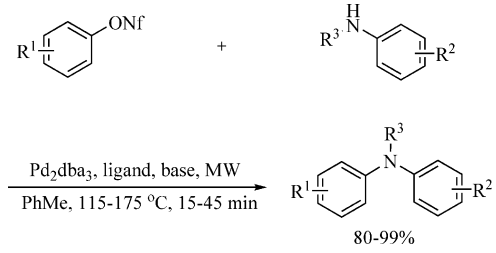
Maes and co-workers have also described a microwave-assisted scale up of the Buchwald–Hartwig amination protocol in which the authors used similar reactions in up to 20 mmol scale.[73]

Poondra and Turner have reported a microwave-assisted sequential amide bond formation and intramolecular amidation[74] to develop a small library of functionalized oxindoles. This occurs a two-step process involving an initial microwave-assisted amide bond formation between a 2-haloarylacetic acid and various alkylamines or anilines followed by a palladium-catalysed intramolecular amidation under aqueous conditions (Scheme 54). The reactions were successfully performed at 100 °C in 30 min using a combination of $Pd(OAc)_2$ and X-Phos, delivering the target oxindoles in good yields.



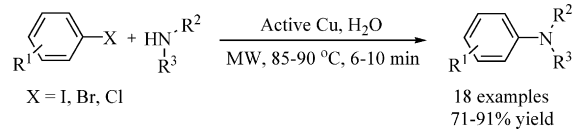
Scheme 54. Microwave-assisted one-pot synthesis of oxindoles.

Buchwald and co-workers have described a microwave-assisted Pd-catalysed amination of aryl nonaflates[75] using the soluble organic amines DBU or MTBD (7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene) as bases (Scheme 55). The authors applied a catalytic combination of $[Pd_2(dba)_3]$, together with bulky phosphane ligands like X-Phos, to effect the transformation under microwave-assisted conditions at 115–175 °C in 15–45 min. The corresponding aminated products were isolated in yields of 80–99%.



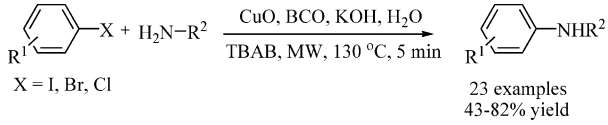
Scheme 55. Microwave-assisted aminations of aryl nonaflates.

Yadav et al. have recently reported active Cu-promoted mild *N*-arylations of a variety of amines, amides, imides and β-lactams with aryl halides[76] under microwave-assisted conditions (Scheme 56). The authors used a curious repetitive intermittent irradiation of a mixture of an aryl halide, an amine, amide, imide or β-lactam and an active copper catalyst in an aqueous suspension for 2 min at 100 W followed by thorough mixing for 2 min outside the microwave cavity. The reactions proceeded smoothly in 6–10 min at 85–90 °C and a small library of *N*-arylated compounds was isolated in good yield and purity.



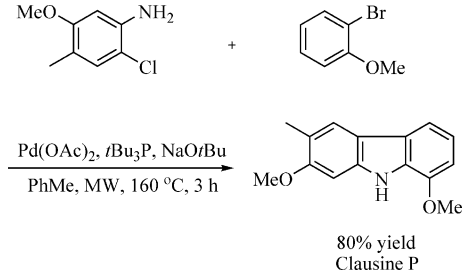
Scheme 56. Microwave-assisted, active Cu-promoted aminations.

Wan and co-workers have recently described a microwave-assisted amination of aryl halides under aqueous conditions (Scheme 57).[77] The reactions were conducted using a combination of CuO and bis(cyclohexanone) oxalyldihydrazone (BCO) at 130 °C for 5 min in the presence of KOH as base and TBAB as the phase-transfer catalyst in water as the solvent. Both electron-rich and -deficient aryl halides were aminated with various amines to provide the corresponding anilines in good yields of 43–82%.



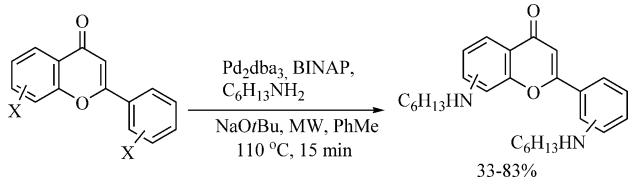
Scheme 57. Microwave-assisted Cu^{II}-promoted aminations of aryl halides.

Bedford and Betham have recently developed a novel protocol for the synthesis of *N*-H carbazoles from 2-chloroanilines and aryl bromides by consecutive catalytic Buchwald–Hartwig amination and C–H activation in a one-pot manner (Scheme 58).[78] A range of carbazoles, including the natural product Clausine P, were synthesized. The authors used a combination of $Pd(OAc)_2$ and tBu_3P in the presence of NaO*t*Bu as base at 160 °C for 3 h under microwave irradiation. The carbazole analogues were isolated in high yields and purity.



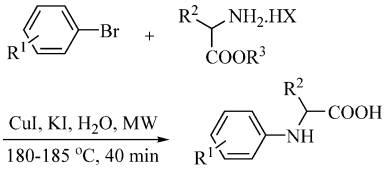
Scheme 58. Microwave-assisted one-pot synthesis of *N*-H carbazoles.

Caddick and co-workers reported a microwave-assisted diversity-oriented synthesis (MEDOS)[79] using a number of Pd-catalysed procedures for the generation of functionalized flavones (Scheme 59). The authors performed a number of Buchwald–Hartwig aminations on diversely functionalized dihaloflavones with hexylamine in the presence of NaO*t*Bu as base using a $[Pd_2(dba)_3]$/BINAP catalytic system. The reactions were performed at 110 °C for 15 min under microwave irradiation in toluene and the corresponding aminated flavones were isolated in 33–83% yields.



Scheme 59. Microwave-assisted decoration of flavones.

An ingenious protocol was reported by Larhed and co-workers for the microwave-assisted copper-catalysed *N*-arylation of functionalized aryl bromides using water as the solvent.[80] The authors explored the amination by using various amino acids or amino acid esters and a diverse set of substituted aryl bromides which furnished non-protected *N*-arylated amino acids with only minor racemization (Scheme 60). The reactions were carried out with K_2CO_3 as base and 10 mol-% of CuI in pure water containing small amounts of KI solution under microwave irradiation at 180–185 °C for 40 min and the corresponding *N*-arylated amino acids were isolated in good yields and purities. This novel *N*-arylation protocol was applied to the synthesis of interesting target molecules in the field of angiotensin AT1 and AT2 receptor ligands.

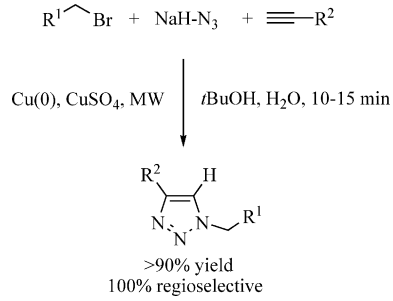


Scheme 60. Microwave-assisted *N*-arylation of amino acids.

5. C–N Bond Formations by Click Chemistry

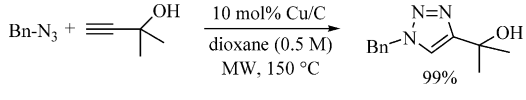
The term "click chemistry",[81] originally coined in 2001 by Kolb, Finn and Sharpless at The Scripps Research Institute, relates to a set of powerful, highly reliable, selective reactions that enable the rapid synthesis of useful new compounds and combinatorial libraries, usually through heteroatom links. The process must meet a set of stringent criteria to be applicable in this context. The reaction must be modular, wide in scope, give very high yields, only generate inoffensive byproducts that can be removed by non-chromatographic methods (such as crystallization or distillation), and be stereospecific (but not necessarily enantioselective). The process characteristics required include simple reaction conditions (ideally, the process should be insensitive to oxygen and water), readily available starting materials and reagents, the use of no solvent or a solvent that is benign (such as water) or easily removed and simple product isolation. Among the most useful click reactions are 1,3-dipolar cycloadditions, with the cream of the crop being the reaction of organic azides with alkynes, known for over 100 years and studied most extensively by Huisgen[82] in the early sixties. The Cu^I-catalysed stepwise variant was independently discovered in 2002 by the groups of Fokin and Sharpless (La Jolla) and Meldal (Denmark) to be a reliable catalytic process resulting in an unprecedented level of regioselectivity.[83] In the few years since its discovery, the Cu-catalysed azide–alkyne **c**ycloaddition (CuAAC) reaction has been established as one of the most valuable means for the covalent assembly of complex molecules.

Van der Eycken and co-workers were the first to investigate the effect of microwave irradiation on the Cu^I-catalysed Huisgen [2+3] dipolar cycloaddition reaction (Scheme 61).[84] A three-component reaction was developed in which the required azide is generated in situ from the corresponding halide. Microwave irradiation dramatically decreases the reaction times from hours to minutes without affecting the 1,4-regioselectivity of the reaction. The 1,2,3-triazole products generated often crystallize from the reaction mixture rendering the process an ideal multicomponent click reaction.



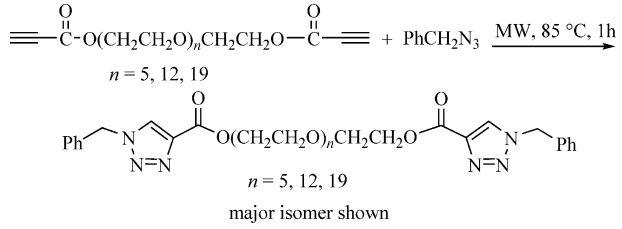
Scheme 61. Microwave-assisted three-component synthesis of 1,4-disubstituted 1,2,3-triazoles.

Examples of click chemistry mediated by a source of heterogeneous copper(I) are rare. Lipshutz and co-workers described the virtues of copper-in-charcoal (Cu/C) as a simple, inexpensive, general and efficient heterogeneous catalyst for the 1,3-dipolar cycloaddition reaction of an azide with a terminal acetylene.[85] It was demonstrated that microwave irradiation could dramatically speed up this heterogeneous procedure (Scheme 62).



Scheme 62. Heterogeneous microwave-assisted copper-in-charcoal-catalysed click chemistry.

It has been found that 1,3-dipolar cycloaddition reactions of azides with alkynes substituted with electron-withdrawing groups are fast and take place at low temperatures under microwave or conventional conditions. Katritzky and co-workers have developed strategies[86] for the synthesis of a set of oligo-triazoles by using mono-, di-, tri-, tetra- and hexa-alkynes (Scheme 63).

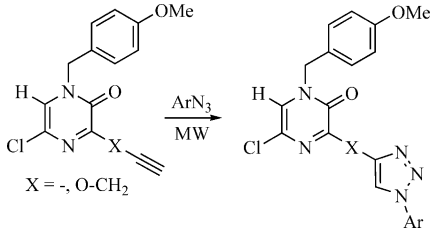


Scheme 63. Regioselective formation of bis-triazoles from long chain di-alkynes and benzyl azide.

Van der Eycken and co-workers described[87] the indirect coupling of various 3-ethynyl-2(1*H*)-pyrazinones with different glycosyl β-azides en route to the synthesis of glycopeptidomimetics (Scheme 64). A microwave-assisted Cu^I-catalysed Huisgen [2+3] dipolar cycloaddition reaction was used.

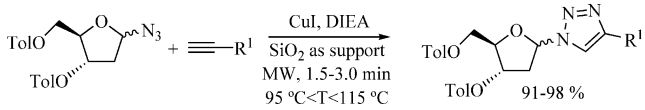
The same authors evaluated the coupling of a set of newly generated furo[2,3-*b*]pyrazines with five-membered sugars[88] using a microwave-assisted regioselective Cu^I-catalysed [2+3] dipolar cycloaddition reaction. A small library of hitherto unknown nucleoside analogues was generated (Scheme 65).

They also explored the application of click chemistry to the 2(1*H*)-pyrazinone scaffold for the generation of hitherto unknown skeletons.[89] Two different pathways have been successfully evaluated: (1) through a C–C or C–O linkage of the acetylenic part to the C3 position of the 2(1*H*)-pyrazinone scaffold and (2) by the introduction of an azide into the C3 position (Scheme 66). The heterodiene system of the pyrazinone was subsequently used in a Diels–Alder reaction.



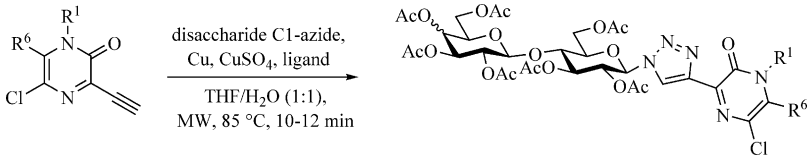
Scheme 66. Microwave-assisted 1,3-dipolar cycloaddition of acetylene-derived 2(1*H*)-pyrazinones with various azides.

Various α- and β-2′-deoxy-1,2,3-triazolyl nucleosides were synthesized by Benhida and co-workers using a Cu^I-catalysed, microwave-assisted protocol.[90] The reactions were carried out in open vials, without any solvent and by using silica gel as a support (Scheme 67). The temperature, ranging between 95–115 °C, was measured digitally.

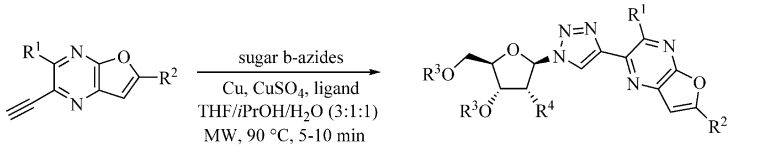


Scheme 67. 1,3-Dipolar cycloaddition for the generation of nucleoside analogues by using microwave irradiation under atmospheric pressure and solvent-free conditions.

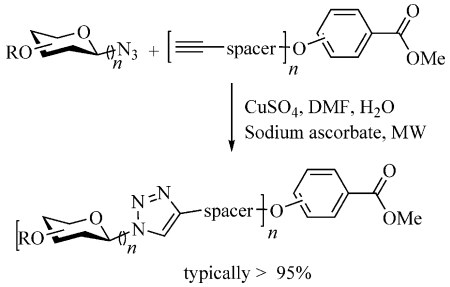
A multivalent display of carbohydrates is frequently used as a method to increase affinities in various contexts. Several azido carbohydrates were used by Liskamp, Pieters and co-workers in microwave-assisted regioselective Cu^I-catalysed [3+2] cycloaddition reactions[91] with different kinds of alkyne-bearing dendrimers leading to triazole glycodendrimers, up to the nonavalent level (Scheme 68).



Scheme 64. Synthesis of glycopeptidomimetics utilizing the 2(1*H*)-pyazinone scaffold.



Scheme 65. Furo[2,3-*b*]pyrazine nucleoside analogues with a 1,2,3-triazole linkage.



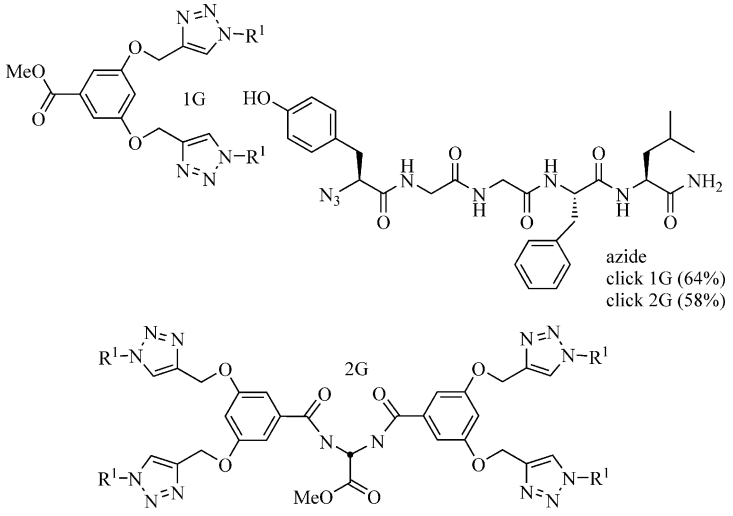
Scheme 68. Microwave-assisted Cu^{I}-mediated synthesis of triazole glycodendrimers under microwave irradiation.

Liskamp and co-workers have also shown that (cyclic) peptides can be efficiently attached to suitably functionalized dendrimers by a 1,3-dipolar cycloaddition reaction which was conveniently assisted by microwave irradiation to ensure complete modification of the alkyne end-groups (Scheme 69).[92] Di-, tetra-, octa- and hexadecavalent dendrimeric peptides were synthesized in this way.

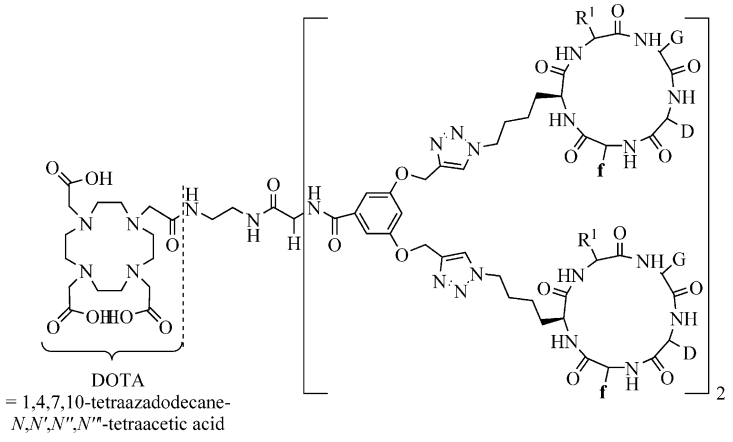
Analogously they also synthesized DOTA-conjugated multivalent cyclic-RGD peptide dendrimers by microwave-assisted 1,3-dipolar cycloaddition reactions (Scheme 70).[93] Multivalency is a well-accepted approach to increasing the interaction of weakly interacting individual ligands with their respective receptors. These analogues were radiolabelled with In^{III} to evaluate the in vitro receptor binding characteristics and in vivo tumour targeting properties.

A simple and robust strategy for anchoring one or several carbohydrate derivative(s) to a solid-supported oligonucleotide has been described by Morvan and co-workers[94] Click chemistry was applied to attach the carbohydrate residues to the oligonucleotide backbone (Scheme 71). It was demonstrated that microwave irradiation significantly improved the reaction kinetics.

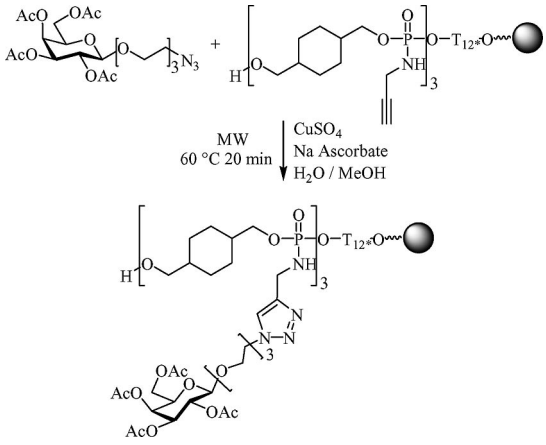
An alternative regioselective solid-phase procedure for the synthesis of di- and tri-substituted 1,2,3-triazoles has been described by Gao and Lam[95] The sequence starts from a poly(styrene-divinylbenzene) (1%) sodium sulfinate resin from which the vinyl sulfone dipolarophile is generated. This dipolarophile serves to direct the regiochemistry of the cycloaddition and, as it is eliminated during the process, it is a traceless linker in the solid-phase synthesis (Scheme 72). By using microwave irradiation the total reaction time could be shortened from 1 d to 1 h. When the last



Scheme 69. Azide and the corresponding peptide dendrimers.

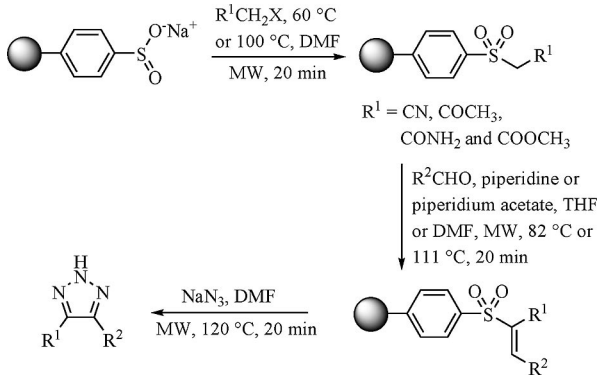


Scheme 70. Synthesis of a DOTA-conjugated tetravalent *cyclo*[RGDfK]peptide dendrimer using click chemistry.



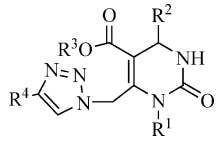
Scheme 71. Synthesis of multiply labelled carbohydrate oligonucleotides on a solid support by microwave-assisted click chemistry.

step was run with the addition of a suitable alkyl halide, various tri-substituted 1,2,3-triazoles could be generated in a one-pot fashion.



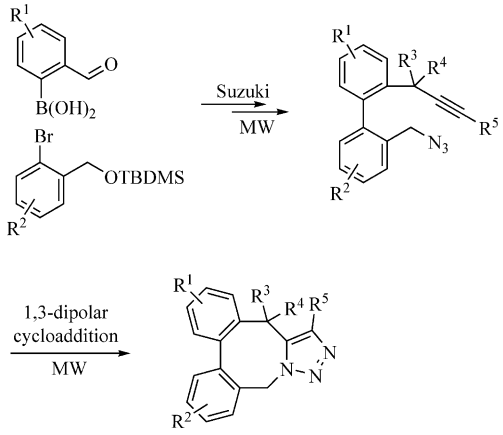
Scheme 72. Regioselective sulfinate solid-phase synthesis of 1,2,3-triazoles.

A small combinatorial library of 27 compounds with four points of diversity was generated by Kappe and co-workers, merging the Biginelli three-component dihydropyrimidone (DHPM) synthesis with click chemistry.[96] The privileged DHPM scaffold was decorated at C6 with a 1,2,3-triazole pharmacophore (Scheme 73).



Scheme 73. Combining a Biginelli multicomponent reaction with click chemistry.

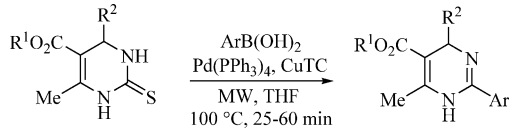
An example of click chemistry used for the synthesis of natural product analogues was described by Van der Eycken and co-workers.[97] Hitherto unknown 7-aza analogues of steganacin and steganone containing a 1,2,3-triazole ring were synthesized by a 1,3-dipolar cycloaddition reaction to generate the highly strained medium-sized ring system (Scheme 74). It was found that microwave irradiation was highly beneficial in promoting these click reactions.



Scheme 74. Generation of hitherto unknown steganacin and steganone aza analogues.

6. Miscellaneous

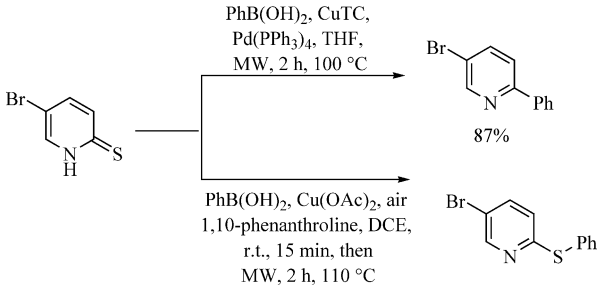
A few interesting microwave-assisted procedures dealing with comparatively under-explored metal-mediated protocols, such as the Liebeskind–Srogl-type couplings and Chan–Lam reactions, can be found in recent literature. An interesting example is the protocol described by Lengar and Kappe;[98] the authors demonstrated that microwave irradiation can tremendously speed up the sluggish thioether-boronic acid Liebeskind–Srogl-type couplings. Moreover an unprecedented novel carbon–carbon cross-coupling reaction was discovered involving thioamides and boronic acids. A combinatorial library of 2-aryl-1,4-dihydropyrimidines was generated starting from 3,4-dihydropyrimidine-2-thiones by direct microwave-assisted Pd^0-catalysed/Cu^I-mediated cross-coupling (Scheme 75).



Scheme 75. Carbon–carbon cross-coupling of boronic acids with 3,4-dihydropyrimidine-2-thiones under Liebeskind–Srogl conditions.

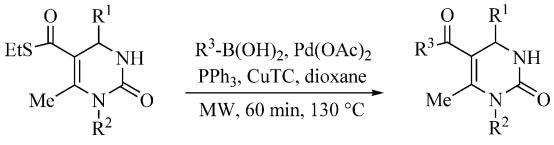
As an extension, Prokopcová and Kappe described the dethionylation carbon–carbon cross-coupling of a range of aromatic and non-aromatic six- and five-membered cyclic thioamides with boronic acids.[99] According to the authors, the reaction is independent of ring size, aromaticity/non-aromaticity and the presence of additional heteroatoms or other functional groups in the starting thioamide.[100] Interestingly, it was demonstrated that although the catalytic Pd^0/Cu^I system resulted solely in carbon–carbon bond formation, the use of stoichiometric amounts of Cu^{II} under an air atmosphere resulted in carbon–sulfur bond formation

(Scheme 76).[98,99] It has been shown that both types of thioamide cross-couplings are orthogonal to the traditional base-catalysed Suzuki–Miyaura cross-coupling of aryl halides with boronic acids.



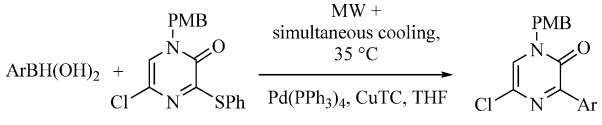
Scheme 76. Orthogonal reactivity between carbon–carbon and carbon–sulfur cross-couplings in 5-bromopyridine-2(1*H*)-thione.

The same authors reported the efficient solution-phase synthesis of a 30-membered library of 5-aroyldihydropyrimidinones by an automated sequential and parallel microwave-assisted synthesis (Scheme 77).[101] The thiol esters, resulting from a Bignelli reaction, serve as starting materials for a Pd^0-catalysed, Cu^I-mediated, Liebeskind–Srogl cross-coupling with boronic acids, providing rarely described 5-aroyl-3,4-dihydropyrimidin-2-ones.



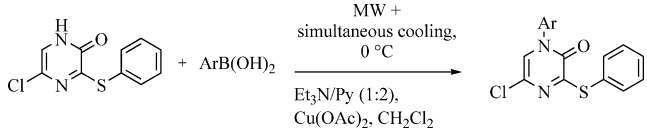
Scheme 77. 5-Aroyl-3,4-dihydropyrimidin-2-one library generation by Liebeskind–Srogl cross-coupling.

Van der Eycken and co-workers have developed an optimized protocol for the C3-arylation of 2(1*H*)-pyrazinones by using Liebeskind–Srogl conditions under microwave irradiation with simultaneous cooling at 35 °C (Scheme 78).[102] When the reactions were performed under microwave irradiation at an elevated temperature (65 °C), only moderate yields were observed. Although the couplings could be performed under conventional conditions, this required rather long reaction times and resulted in noticeably lower yields. The authors conclude that the reactions clearly benefit from simultaneous cooling during microwave irradiation, most probably due to the high and sustained power input, resulting in efficient catalysis, with cooling of the bulk of the material ensuring stabilization of the thermally labile compounds.



Scheme 78. Pd-catalysed Cu^I-mediated cross-coupling of arylboronic acids and 2(1*H*)-pyrazinones facilitated by microwave irradiation with simultaneous cooling.

Van der Eycken and co-workers have demonstrated that simultaneous pronounced cooling during microwave irradiation might have a profound impact on the yield of the reaction. They utilized the Chan–Lam protocol, a Cu^{II}-mediated cross-coupling reaction using an arylboronic acid to decorate the N1 position of the 2(1*H*)-pyrazinone scaffold (Scheme 79).[103] It was demonstrated that this cross-coupling resulted in significantly improved yields (sometimes an increase in yield of >100% was observed) when performed under microwave irradiation with simultaneous cooling at 0 °C. The authors argued that maintaining the bulk of the material at a relatively low temperature is beneficial for the stability of the thermally labile compounds formed, with the significantly higher level of microwave energy introduced into the system resulting in a more efficient catalysis.



Scheme 79. Cu^{II}-mediated cross-coupling of arylboronic acids and 2(1*H*)-pyrazinones facilitated by microwave irradiation with simultaneous cooling.

Summary and Outlook

The examples cited in this review clearly demonstrate that many transition-metal-mediated protocols greatly benefit from microwave irradiation. This non-classical method of transferring energy to a reaction medium has developed in the last decade as a standard tool not only in the academic laboratory but also in an industrial research environment. The success of microwave-assisted transformations has made microwave irradiation a first choice for the synthetic chemist instead of considering the technique as a desperate last resort for an unsatisfying classical heating experiment. The development of dedicated mono- and multimode microwave instruments, allowing full control of the experimental parameters, as well as the possibility of in situ monitoring of the reaction progress, have tremendously increased its applicability. Microwave irradiation not only accelerates reactions, but most often also furnishes cleaner reaction mixtures. Sometimes different reaction pathways compared with those observed under conventional heating conditions are detected. The development of the novel technique of simultaneous cooling has attracted interest as it has been demonstrated that pronounced cooling during microwave irradiation might have a profound impact on the yield of the reaction. Currently a variety of transition-metal-mediated protocols are performed under microwave irradiation, even on a large scale. It can, therefore, be expected that this fast and efficient technology will become the energy-transfer methodology of choice in transition-metal-mediated chemistry.

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