

Review

Pd/C Catalysis under Microwave Dielectric Heating

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Abstract: Microwave-assisted organic synthesis (MAOS) provides a novel and efficient means of achieving heat organic reactions. Nevertheless, the potential arcing phenomena via microwave (MW) interaction with solid metal catalysts has limited its use by organic chemists. As arcing phenomena are now better understood, new applications of Pd/C-catalyzed reactions under MW dielectric heating are now possible. In this review, the state of the art, benefits, and challenges of coupling MW heating with heterogeneous Pd/C catalysis are discussed to inform organic chemists about their use with one of the most popular heterogeneous catalysts.

Keywords: microwaves; catalyst; Pd/C; heterogeneous catalysis; cross-coupling; hydrogen transfer; reduction

1. Introduction

Amongst noble metal heterogeneous catalysts, Pd/C can be considered as a versatile and convenient source of Pd for many reactions. It can be easily recovered by simple filtration, and the products obtained are usually not contaminated by traces of Pd. Pd/C is stable in open air, water, acids, and bases, often not requiring solvent degassing or an inert atmosphere [1]. The use of charcoal (or carbon) as the solid support ensures a higher surface area compared to the corresponding alumina and silica supported catalysts [2]. Furthermore, charcoal is one of the most active MW absorbing materials known so far. It is able to efficiently absorb MWs becoming an internal heat source by the very high surface temperatures generated [3]; as most of the heterogeneous catalyzed reactions occur on the active surface of the catalyst, Pd/C MW-assisted transformations are highly accelerated [4]. The electric discharge phenomena in metal–solvent mixtures have recently been reviewed [5], supporting the hypothesis that arcing is simply limited to large metal particles [6]. Nanometer-sized particles usually compose most of the commonly used supported catalysts (including Pd/C), ensuring safer reaction conditions under MWs irradiation. However, hot spots are frequently formed on the surface of the activated carbon surface under high electric field conditions; this effect is particularly frequent in the presence of solvents with low boiling points (i.e., THF and CH₂Cl₂), as recorded by experiments done with a high-speed camera [7,8].

Though the use of Pd/C in metal catalyzed reactions [9] and the use of MWs in heterogeneous catalyzed transformations have been recently reviewed [10], there are no reports covering the literature on the combination of Pd/C with MWs. We decided to fill this gap with this review. The subject is divided in chapters reporting different reactions catalyzed by Pd/C under MW dielectric heating. Different types of Pd/C catalysts are covered providing the heterogeneous nature of the catalyst.

2. Pd/C in Cross-Coupling Reactions under MW Heating

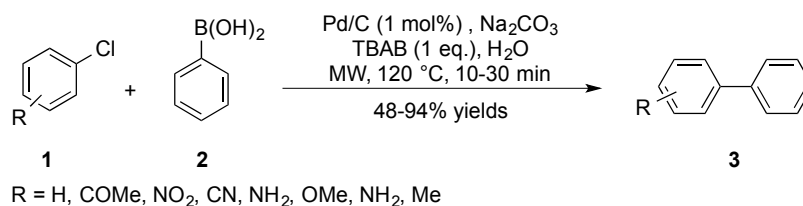
2.1. Suzuki–Miyaura Coupling

The central question concerning the mechanism of Suzuki–Miyaura coupling in the presence of Pd/C is whether the cross-coupling occurs through a heterogeneous or homogeneous catalytic pathway [11,12]. In heterogeneous conditions, the reaction occurs predominantly on the palladium surface and not in the solution phase and therefore with Pd/C inside the pores of the charcoal. This mechanism would lead to a complete recovery of Pd, as leaching into the solution phase would not occur.

In homogeneous catalysis with a heterogeneous catalyst, the reaction takes place in solution with metal species released by the support. To determine whether Pd/C is acting as a truly heterogeneous catalyst in Suzuki–Miyaura coupling, the reaction is usually stopped when the conversion is approximately 50%. Then, after filtration of the heterogeneous materials, the reaction mixture is maintained under the same reaction conditions. If the transformation occurs by a real heterogeneous catalysis, a complete stop of the transformation is observed after filtration, as no active catalytic palladium species should be present in solution. First, experiments showed behavior suggesting heterogeneous catalysis [13]. However, later on, different experimental evidence suggested a homogeneous pathway, as the presence of soluble palladium was observed during the reaction [14]. The problem of the heterogeneous or homogenous nature of the catalytically active species in a classic cross-coupling reaction has also been reviewed [15].

Water is the one of the best solvents for Pd/C-catalyzed reactions and has been extensively used in Suzuki couplings. The first example of the use of Pd/C for Suzuki coupling in aqueous media under conventional heating was reported in 1994 by scientists at Hoffmann–La Roche, carrying out standard couplings between arylboronic acids and aryl iodides or bromides in 2–15 h [13].

Later, Arvela and Leadbeater reported the coupling of aryl chlorides with phenylboronic acids using Pd/C in water under MW dielectric heating (Scheme 1) [16]. They observed that cooling while heating with MWs (simultaneous cooling) prolongs the lifetime of the aryl chloride substrates during the course of the reaction. In these conditions, biaryl derivatives, **3**, can be obtained in higher yields and an overall better recovery of unreacted materials is possible.



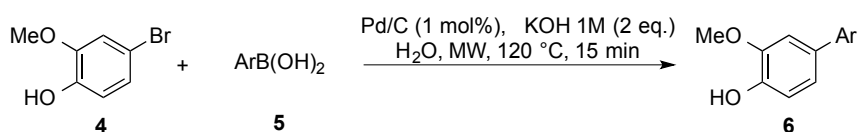
Scheme 1. Suzuki–Miyaura cross-coupling on aryl chlorides.

Under “simultaneous cooling” conditions, the external part of the reaction vessel is cooled by compressed air during the MW irradiation. This method generally allows for the furnishing of a higher level of MW power to the reaction mixture, enhancing any possible MW influence dependent on the electric field strength [17].

However, in 2009, Kappe and coworkers reproduced the Suzuki–Miyaura coupling reactions shown in Scheme 1 obtaining mostly identical results both in terms of conversion and selectivity with MW irradiation under simultaneous cooling and conventional heating at the same temperature and in the same reaction times [3]. This observations were later confirmed by Leadbeater’s group demonstrating how simultaneous cooling has no effect on large scale Suzuki couplings [18].

A novel Suzuki–Miyaura protocol in aqueous KOH proceeding with a complete chemoselectivity for arylbromides versus arylchlorides was reported by Freundlich and Landis in 2006. The method

seems to be complementary to Leadbeater's protocol, demonstrating also to be compatible with the presence of acid bromophenols as **4** (Scheme 2) [19].

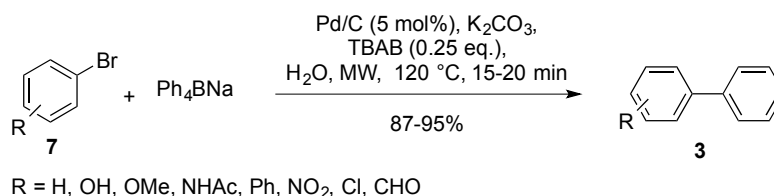


Entry	ArB(OH) ₂ 5	Yield
1	PhB(OH) ₂	83%
2	2-MeC ₆ H ₄ B(OH) ₂	91%
3	3-MeC ₆ H ₄ B(OH) ₂	90%
4	4-MeC ₆ H ₄ B(OH) ₂	89%
5	1-naphthyl B(OH) ₂	58%
6	2-naphthyl B(OH) ₂	48%
7	4-MeOC ₆ H ₄ B(OH) ₂	31%
8	4-ClC ₆ H ₄ B(OH) ₂	35%
9	4-MeO ₂ CC ₆ H ₄ B(OH) ₂	10%

Scheme 2. Suzuki–Miyaura protocol in aqueous KOH.

It is interesting to note that, while electron-neutral aryl-boronic acids (Entries 1–6 in Scheme 2) yielded acceptable yields, electron-rich (Entry 7) and electron-poor arylboronic acids (Entries 8 and 9) led to unsatisfactory isolated yields, probably because of the instability of boronic acids under these reaction conditions. When more stable potassium aryltrifluoroborate was used, the cross-coupling occurred in 30 min at the same temperature; however, the products were formed in lower yield (70% vs. 83% with PheB(OH)₂) [19].

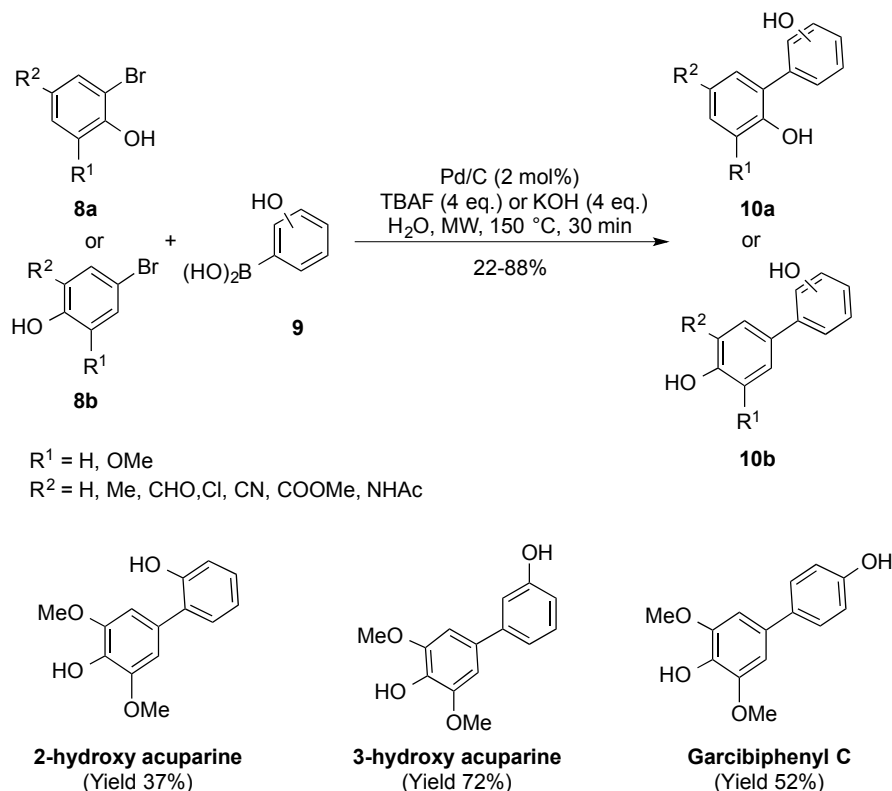
A protecting group free Pd/C-catalyzed, microwave-assisted cross-coupling reaction in water was also described by Bai in 2009 starting from tetraphenylborate and aryl bromides, **7** (Scheme 3) [20].



Scheme 3. Suzuki–Miyaura protocol with tetraphenylborate.

Under the optimized reaction conditions, various aryl bromides, including dibromobenzene, tribromobenzene, and some heterocycles yielded the cross-coupling products in excellent yields and with good atom economy. In this protocol, the waste was minimized as all four phenyl groups of the Ph₄BNa were coupled with arylbromides, **7**.

A protecting group free synthesis of biphenol aryl derivatives, **10**, can be accomplished through a MW-assisted Pd/C-catalyzed Suzuki–Miyaura coupling in water starting from *o*-bromophenols, **8**, and substituted boronophenols, **9** (Scheme 4) [21]. A careful evaluation on how the substituent position in **9** influenced the reaction efficiency was also reported: the *m*-boronophenol was the most reactive substrate, followed by the *p*-isomer. The optimized MW accelerated cross-coupling conditions were applied to the synthesis of nine naturally occurring phytoalexins with biaryl structures (Scheme 4) [22]. The cross-coupling occurred also under conventional heating (2.5 h at 80 °C vs. 30 min at 150 °C under MW irradiation) while, with the corresponding bromophenols, the products were obtained in acceptable yields only using MWs. It is noteworthy that, with iodophenols, conventional heating conditions are frequently sufficient to obtain the desired coupling products in good yields, while MW heating was indispensable only for the corresponding bromo derivatives.



Scheme 4. Suzuki–Miyaura based synthesis of naturally occurring phytoalexins.

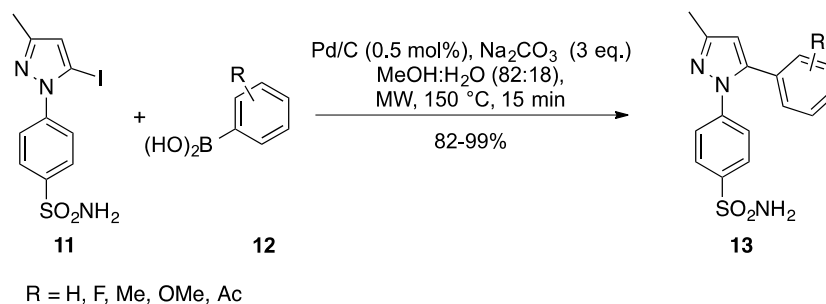
Some examples of Pd/C-catalyzed Suzuki coupling in organic solvents such as MeCN, MeCN/water [23], NMP/water [24], and EtOH/water [18] have also been reported. The introduction of the organic solvent is usually required to overcome the problem of low solubility of many aryl halides in water. Recently, a Suzuki–Miyaura cross-coupling between a thienylboronic acid and halopyridines has been described in water containing hexadecyltrimethylammonium bromide (CTAB) micelles. Best results under MW dielectric heating have been obtained with $\text{Pd}(\text{PPh}_3)_4$. However, in some cases, Pd/C (brand Degussa) yielded comparable results [25].

The Pd/C-catalyzed Suzuki reaction in toluene was also used as a model to

- evaluate the efficiency of a novel Dewar-like reactor for maintaining constant heat during MAOS [26]; and
- determine the mechanism of hot spot generation during MW dielectric heating through particle aggregation [27].

A parallel solution-phase synthesis of a library of pyrazoles, **13**, potentially active as COX-2 inhibitors has been developed via Suzuki coupling with Pd/C and MW dielectric heating in MeOH:H₂O containing Na₂CO₃ (Scheme 5). Although the substrates employed were different (aryl- and vinyl-boronic acids), this catalyst system provided good reproducibly and reliable results [28].

In 2005, Pd/C-catalyzed homo- and cross-couplings of boronic acids and aryl halides were successfully carried out both in aqueous media under high-intensity ultrasound (US) and in DME under MWs. In a trial series of 15 different iodo- and bromoaryls and 7 boronic acids, the use of both energy sources drastically reduced reaction times. The homo- and cross-couplings were also carried out in a new reactor featuring combined US and MW irradiation with further improvement of this potentially sustainable synthetic method (Table 1) [29].



Scheme 5. Solution-phase synthesis of potential COX-2 inhibitors.

Table 1. Compared yields of Suzuki reactions under US or MW alone and under combined US/MW.

Entry	Aryl Halide	Boronic Acid	US Yield %	MW Yield %	Comb.US/MW Yield, %
1	3-Br-anisole	Phenylboronic acid	54	64	88
2	2-I-thiophene	Phenylboronic acid	40	37	59
3	4-Cl-nitrobenzene	Phenylboronic acid	22	30	57
4	-	Thianthrene-1-boronic acid ^a	48	55	69
5	-	4- <i>t</i> -Buty-1-boronic acid ^a	68	74	86

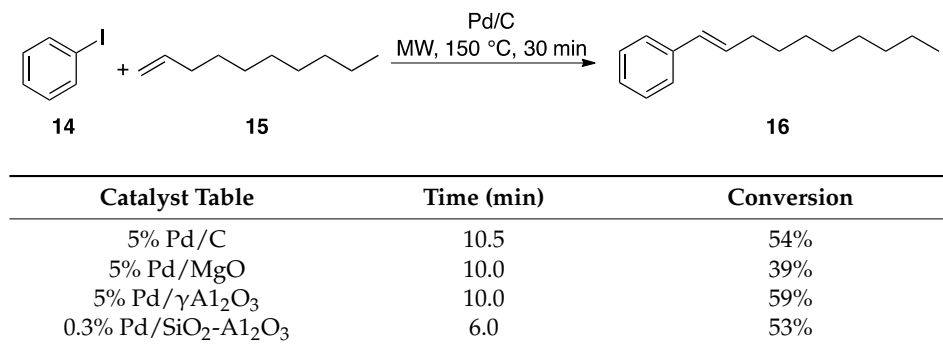
^a Suzuki homocoupling.

Carbon-supported Pd nanoparticles (NPs) are also suitable catalysts for MW-assisted Suzuki–Miyaura cross-coupling reaction. The use of carbon materials for the immobilization of Pd nanoparticles offers very interesting advantages such as good mechanical and chemical properties and an adequate pore size distribution. Furthermore, these materials have a rich surface chemistry allowing modifications by straightforward procedures to enhance both metal immobilization and stabilization. Three new hybrid nanocatalysts based on carbon-supported NPs showed excellent activities in short reaction times (5–10 min) reaching TOF values up to 3000 h^{−1} under MWs. Recycling studies showed that the nanocatalyst could be reused up to 5 times without any loss in catalytic activity. The reaction medium was found to have a strong influence on the recyclability of the nanocatalyst, which could be improved in the presence of polyethylene glycol [30]. Previously, Pd/Au NPs were also found to be very active in catalyzing the coupling between aryl bromide/aryl chloride and arylboronic acids [31].

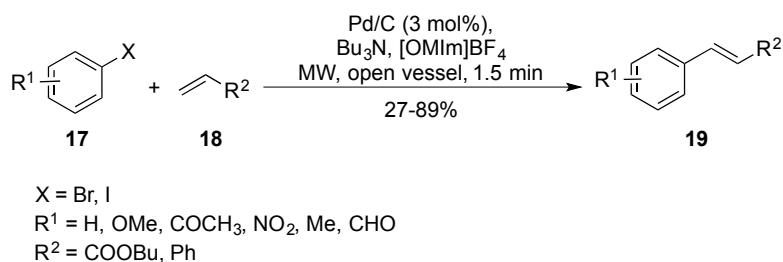
2.2. Pd/C for Mizoroki–Heck under MW Heating

The use of MW irradiation in Pd/C-catalyzed Mizoroki–Heck reactions was reported for the first time in 1997 by Wali [32], who initially screened several Pd catalysts in the reaction of acrylonitrile with iodobenzene under conventional heating. *E* and *Z* isomers of cinnamionitrile were obtained in a single step and the activity of the catalysts followed the series: Pd/CaCO₃ < Pd/C < Pd(acac)₂ < Pd/Al₂O₃ < Pd/MgO. Then, the influence of MW irradiation in the Heck reaction of iodobenzene and 1-decene was examined carrying out the reaction in a MW digester in the presence of the supported catalysts (Scheme 6).

A further improvement was obtained in 2004 by combining Pd/C, ionic liquid, and MW heating. Heck olefination of different aryl halides with butyl acrylates, **18**, was carried out simply treating a solution of the two starting materials, Bu₃N and Pd/C (3% mol), in ionic liquid [OMIm]BF₄ by irradiation with MWs for 90 s (Scheme 7) [33].



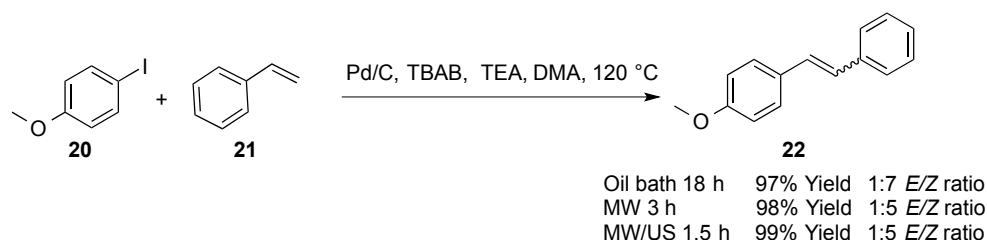
Scheme 6. Mizoroki–Heck reaction over heterogeneous Pd catalysis.



Scheme 7. Use of ionic liquids for Pd/C recycle in Mizoroki–Heck reaction.

A remarkable advantage of this protocol is the phase separation obtained with the ionic liquid. Pd/C remained completely in ionic liquid after the reaction and, after extraction of the product with an immiscible solvent, the catalyst could be easily recovered and reused several times. The catalyst phase was then irradiated with MWs for 30 s; another portion of iodobenzene, butyl acrylate, and Bu₃N was added and the procedure was repeated four times, observing only little loss in catalytic activity. However, this procedure lacked a precise indication of the temperature reached during reaction, suggesting that a domestic MW oven was probably employed.

Following the excellent results achieved with the Suzuki reaction (see above), the combination MW/US irradiations was also successfully applied to accelerate the Mizoroki–Heck reaction, comparing the single types of activation sources with conventional heating (Scheme 8) [34]. The reactor employed was a single reaction cell for simultaneous irradiation with both energy sources featuring a Pyrex US horn inserted in a professional multimode MW oven. All results showed that MW irradiation alone or, combined with high-intensity US, strongly promotes the reaction, generally decreasing reaction times to 1 h.



Scheme 8. Mizoroki–Heck reaction under combined MW/US irradiation.

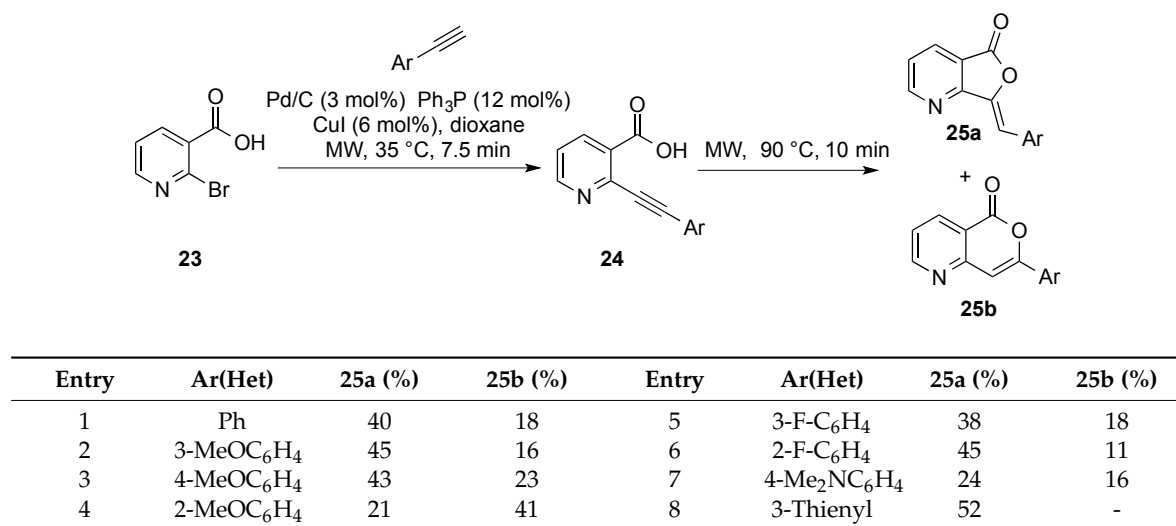
The currently accepted mechanistic theory for Mizoroki–Heck reactions catalyzed by Pd/C suggests that catalysis proceeds through dissolution and re-adsorption of Pd from the solid support. The Pd concentration in solution is highest at the beginning of the reaction. The presence of tetrabutylammonium bromide (TBAB, “Jeffrey conditions”) has been demonstrated to stabilize Pd

nanoparticles through electrostatic stabilization by the bromide anion and steric stabilization by the tetrabutylammonium cation [35]. Thus, the formation of Pd black that decreases the Pd/C efficiency is prevented [36]. However, although Pd/C itself is a strong MW-absorbing material when irradiated under suitable conditions, for some Mizoroki–Heck protocols containing several other MW-absorbing components such as ammonium cations, acetonitrile, triethylamine, and acrylic ester, a particularly strong heating of the Pd/C catalyst was not observed [36]. The crucial influence of the internal temperature and of the stirring in these reactions has been deeply studied by Kappe’s group, who concluded that (almost) all observed effects on reactivity under MW dielectric heating were purely thermal and not related to effects of the MW field [37].

One of the most recent improvements in Pd/C-catalyzed Mizoroki–Heck reaction under MW heating is the use of carbon nanotubes (CNTs) as support for palladium particles. Palladium supported on macroscopic pattern-vertically-aligned carbon nanotubes (Pd/VA-CNTs) catalyst exhibits higher activity if compared to Pd supported on simple activated charcoal under the same reaction conditions [38]. The catalyst demonstrated superior activity, particularly when styrene was used as the olefin source. MW dielectric heating allowed a significant acceleration of the C–C coupling reaction rate, shortening the reaction time from hours to minutes. The macroscopic shape of the catalyst remained unaltered after the catalytic tests cycling showing also a negligible Pd leaching. The cycling tests indicated the complete absence of deactivation of Pd/VA-CNT catalyst. In addition, the macroscopic patterned structure of the catalyst strongly facilitated the separation and the recycling of the catalyst after reaction, without filtration, which represents a major advantage for liquid-phase reactions from an economic and environmental point of view.

2.3. Pd/C for Sonogashira Coupling under MW Heating

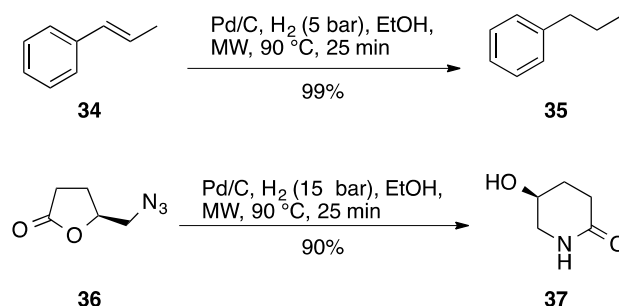
In 2011, the synthesis of 4-azaphthalides (**24**) and 5-azaisocoumarins (**25**) from 2-bromonicotinic acid and terminal alkynes by a MW-assisted tandem Pd/C–CuI–PPh₃–NEt₃-mediated Sonogashira followed by a 5-exo-dig or 6-endo-dig intramolecular cyclization (Scheme 9) was described [39].



Scheme 9. Pd/C mediated Sonogashira followed by a 5-exo-dig or 6-endo-dig intramolecular cyclization.

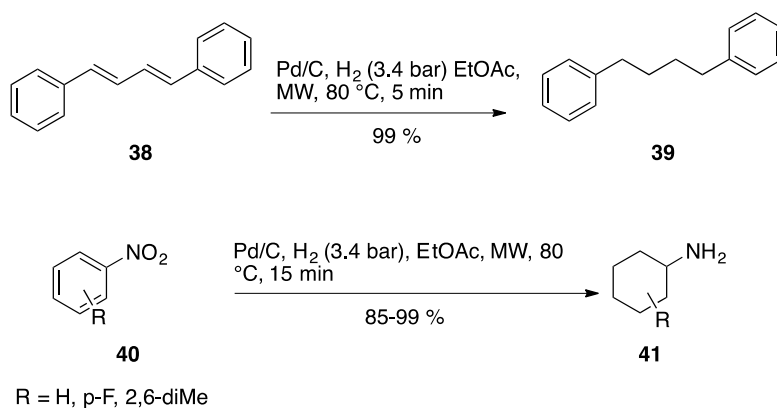
The first Sonogashira cross-coupling occurred at 35 °C requiring 1.5 h under conventional heating and 7.5 min under MWs. Further cyclization conducted at 90 °C for 10 min under MWs yielded Product **25a/25b**. A one-pot process could be set up modulating the temperature and the reaction time allowing the two consecutive reactions to occur. The authors found that results obtained by MWs or conventional heating were almost the same except for the reaction of 2-bromonicotinic acid with 4-ethynyl-N,N-dimethylaniline, which took place exclusively under MW heating.

MLS/Milestone [44]. Using this apparatus, several reactions including olefin reduction and azide hydrogenation were carried out in the presence of H₂ and Pd/C under MW irradiation (Scheme 12).



Scheme 12. Pd/C hydrogenation using a dedicated reactor constructed by MLS/Milestone.

Another generally applicable method for the introduction of gaseous hydrogen into a sealed reaction system for MAOS has been proposed by CEM [45]. Hydrogenation of different alkenes performed under MW heating resulted in complete conversion into the expected saturated product, while the same reactions performed in the oil bath at the same temperature, pressure, and time yielded no more than 55% conversion. These results indicate that MWs accelerate the reaction and have an influence on the outcome of the hydrogenation reaction. When simultaneous cooling was applied, aryl nitro derivatives **40** were also reduced into the corresponding amines **41** (Scheme 13). A similar approach was successfully employed for the hydrogenation of pyridines. While PtO₂ in AcOH enabled the best yield of the corresponding piperidines, Pd/C mediated reaction enabled no more than 35% yield [46].



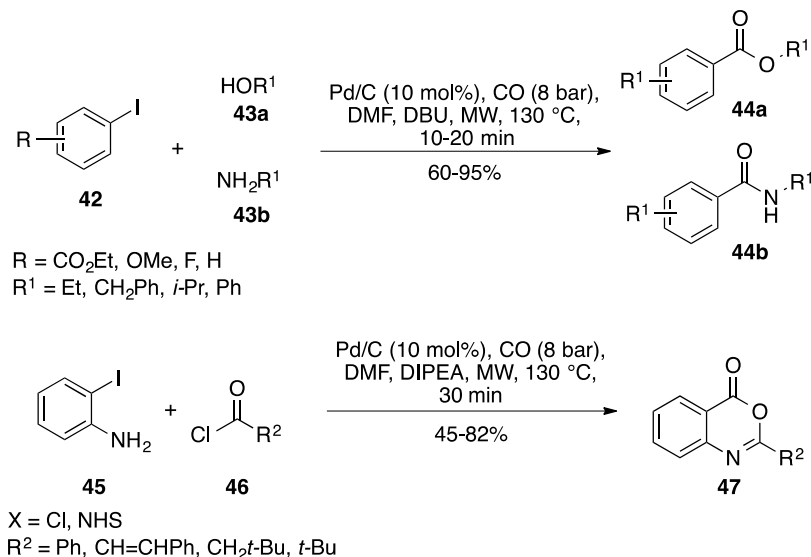
Scheme 13. Pd/C hydrogenation using the CEM gas device.

After testing many reactions conditions, Kappe understood that the stirring plays a critical role in the outcome of the hydrogenation processes. The previously observed differences between conventionally and microwave heated hydrogenations could be ascribed more to the efficient heating and the resulting higher H₂ dissolution into the solvent than to the selective MW heating of the catalyst [3,47].

3.2. Carbon Monoxide

Palladium catalyzed carbonylation of aryl halides in the presence of nucleophiles is an important reaction that can be applied to the synthesis of a wide range of aryl-carbonyl compounds. Most of the carbonylation procedures reported in the literature are based on the use of homogeneous Pd catalysts in the presence of phosphine ligands [48]. However, coupling the catalytic activity of Pd/C with MW

dielectric heating, esters or amides (**44ab**) were obtained from aryl iodides (**42**) and stoichiometric amounts of different alcohols and amines in the presence of DBU in DMF at 8.8 bar of CO, at 130 °C in 10–20 min depending on the substrate (Scheme 14) [49]. The set-up conditions allowed the efficient formation of arylamides **44b** even using barely nucleophilic amines such as anilines.

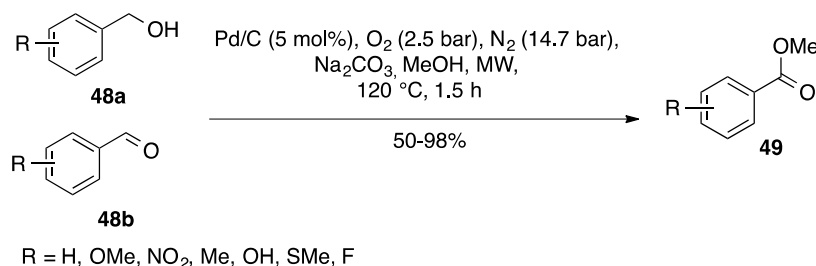


Scheme 14. Pd/C catalyzed carbonylation.

The versatility of this Pd/C-catalyzed carbonylation was confirmed by the cyclohydrocarbonylation of acyl chlorides **46** and *o*-iodoaniline **45** that yielded benzoxazinones **47** (Scheme 14). The catalyst was recycled at least three times without affecting the reaction yields.

3.3. Oxygen

Oxidation of alcohols (**48a**) or aldehydes (**48b**) has been described with Pd/C under MW dielectric heating in the presence of 2.5 bar of O₂ and 17.5 bar of N₂ in methanol as the solvent to yield the corresponding esters. Best results were obtained with benzyl alcohols and aromatic aldehydes (Scheme 15) [50]. Also in this case, the Pd/C can be regenerated by exposition to H₂ atmosphere under MW dielectric heating (60 °C).



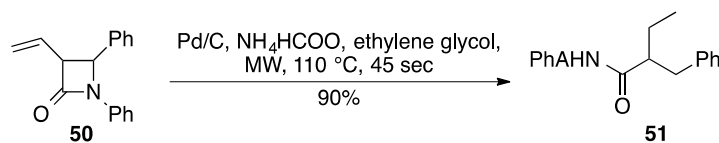
Scheme 15. Pd/C catalyzed oxidation with gaseous O₂.

4. Pd/C for Reductive Hydrogen Transfer Reactions

4.1. Formates as Hydrogen Source

Ammonium formate, sodium formate, and other formic acid salts can be used in Pd/C-catalyzed reduction of functional groups. In the presence of Pd/C, formates decompose to H₂, CO₂, and/or CO. The hydrogen gas is adsorbed onto the surface of the Pd metal, where it reacts with various functional

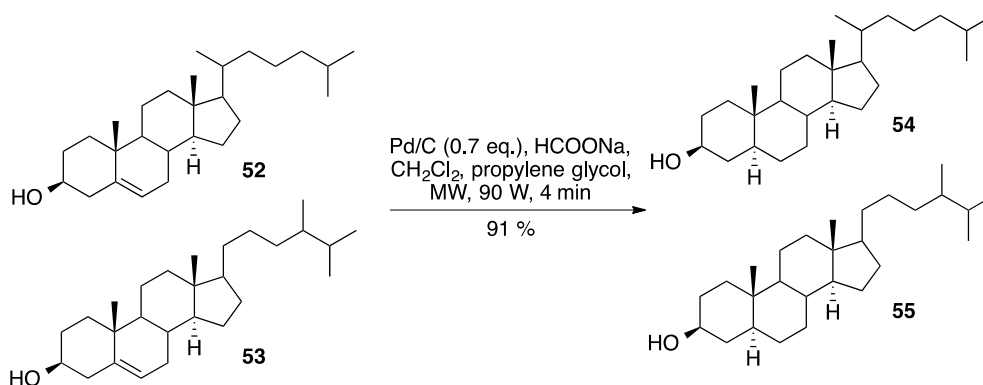
groups. The first examples of the use of ammonium formate and Pd/C under MWs assisted conditions (domestic oven) were reported by Bose and co-workers for standard hydrogenation and reductive transformation of β -lactams, **50** (Scheme 16) [51–53].



Scheme 16. Pd/C hydrogen transfer reaction with β -lactams.

Since this pioneering work, several reports on the application of MW irradiation to Pd/C-catalyzed hydrogen transfer reactions have been described.

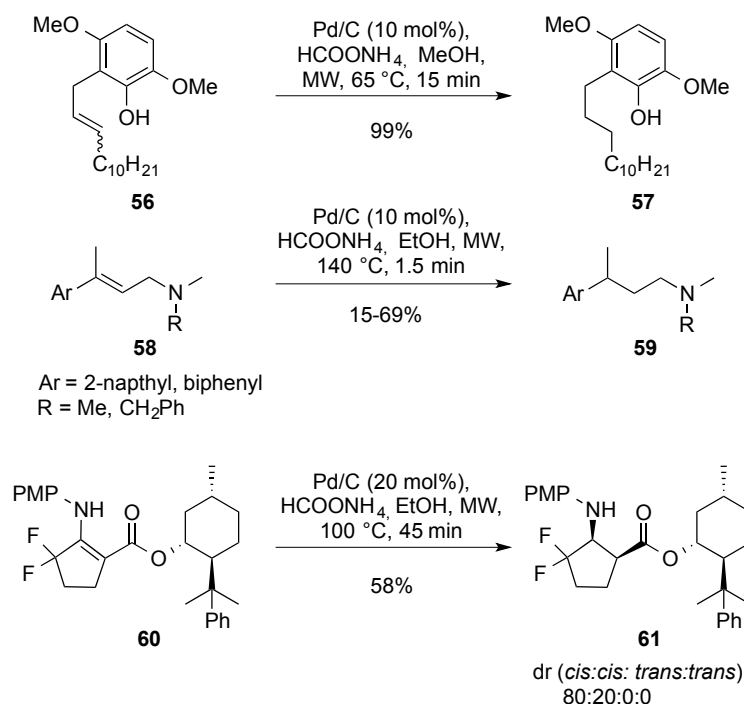
The kinetics of the hydrogen transfer of soybean oil with HCOONa was determined and compared with conventional heating, and it was found that the reaction rates were up to eight times greater using MWs compared to conventional heating [54]. A series of unsaturated sterols and bile alcohols (**52**, **53**) were stereoselectively reduced to the corresponding saturated derivatives (**54**, **55**) in the presence of Pd/C and HCOONH₄ under MWs in less than 10 min [55]. Compared with the conventional hydrogenation reaction using compressed hydrogen gas under high pressure, the MW-assisted version seems more convenient (Scheme 17).



Scheme 17. Pd/C hydrogen transfer reduction of steroids.

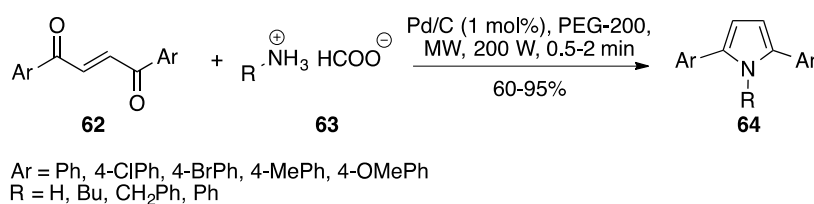
The double bond reduction using Pd/C and formic acid or formates under MW dielectric heating has been used also in the following processes:

- (i) some examples of a rapid cinnamate hydrogenation [56]
- (ii) the preparation of a key intermediate (**57**) for the first synthesis of the unusual nitrogen-containing N-(3-carboxylpropyl)-5-amino-2-hydroxy-3-tridecyl-1,4-benzoquinone isolated from *Embelia ribes* [57];
- (iii) the synthesis of novel selective σ_1 opioid ligands (**59**) [58];
- (iv) the preparation of an intermediate (**61**) for synthesis of fluorinated cyclic β -amino acid [59] (Scheme 18).



Scheme 18. Pd/C hydrogen transfer.

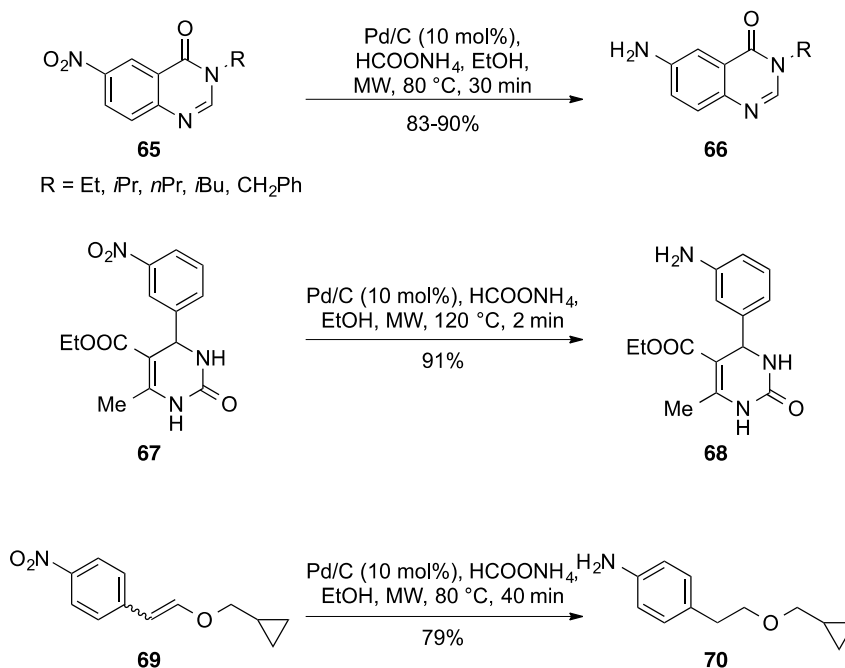
The use of Pd/C with formates under MWs also led to the double bond reduction of an intermediate for the synthesis of enantiopure 7-substituted azepane-2-carboxylic acids [60]. An interesting application of the formate hydrogen transfer process has been described in the synthesis of pyrrole derivatives with multiple aryl substituents (such as **64** in Scheme 19). Starting from but-2-ene-1,4-diones or but-2-yne-1,4-diones, after an initial hydrogenation of the carbon–carbon multiple bond, a MW-assisted Paal–Knorr cyclization worked to enable the corresponding pyrroles in good yields (Scheme 19).



Scheme 19. Tandem hydrogenation/Paal-Knorr reaction.

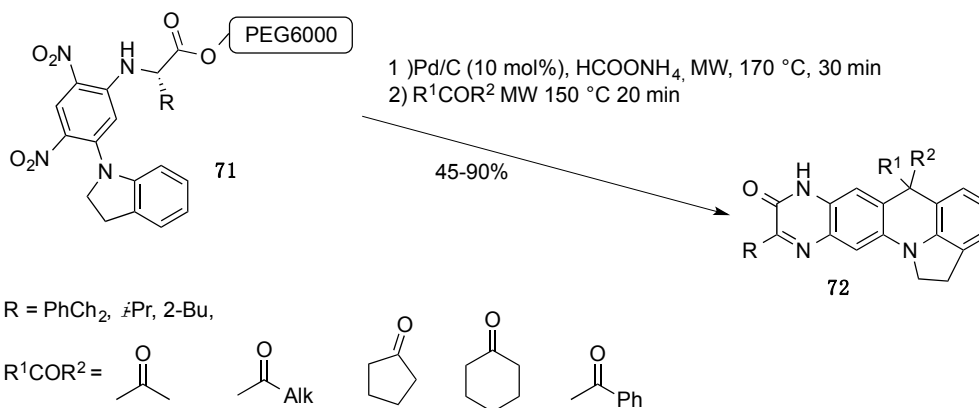
The reaction was performed under Pd/C catalysis in polyethylene glycol-200 (PEG-200) under MWs using ammonium formate or alkyl/arylammonium formates, as a joint source of reductant and nitrogen nucleophile for the ring closure (Scheme 19) [61].

Reduction of aromatic nitro derivatives has also been accomplished on different aromatic or heteroaromatic nitro derivatives (**65**, **67**, and **69**, Scheme 20) using ammonium formate and catalytic transfer hydrogenation in ethanol [62–65].



Scheme 20. Pd/C hydrogen transfer reduction of nitro derivatives.

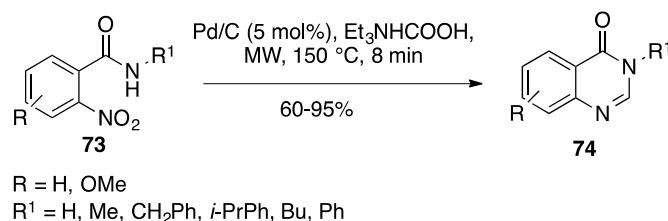
A Pd/C-catalyzed nitro reduction with ammonium formate was also applied to the synthesis of amino acids and indoline-substituted dinitrobenzenes supported on a soluble polymer (PEG6000) via a reductive double-ring closure, to yield the structurally diverse indolo fused pyrazino-/diazepino-quinoxalinones (**72** in Scheme 21). MW-assisted reduction of aryl nitro derivatives yielded the corresponding anilines that were submitted “in situ” to a Pictet–Spengler-type condensation with different ketones furnishing these novel heterocycle scaffolds [66].



Scheme 21. Synthesis of benzimidazole-alkyloxypyrrolo[1,2-a]quinoxalinones.

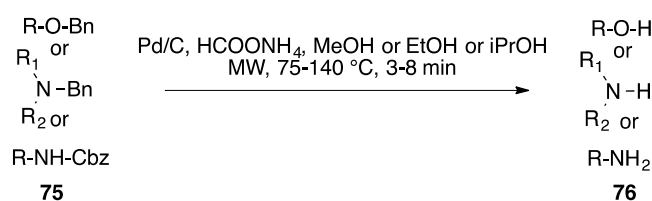
This reaction was also applied to the combinatorial synthesis of a library of benzimidazole-alkyloxypyrrolo[1,2-a]quinoxalinones [67].

Analogously, a Pd/C hydrogen transfer-cyclization in azeotropic triethylamine–formic acid mixture was described to occur under MW dielectric heating, to produce quinazolinones, **74**, in high yields (Scheme 22). In this case, the formic acid salt served either as a the hydrogen source and as a single-carbon source for the further cyclocondensation [68].



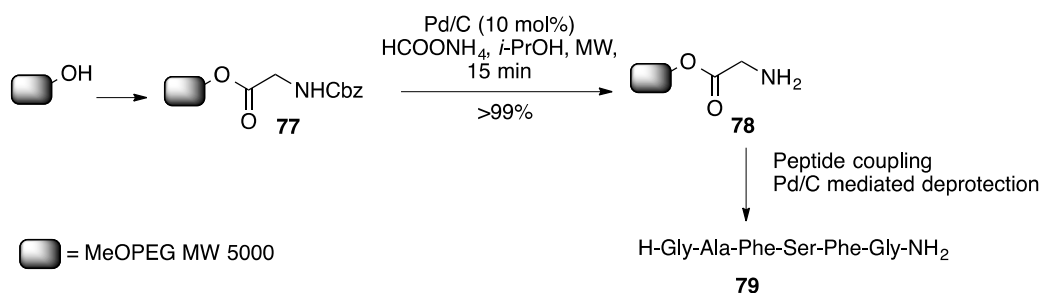
Scheme 22. Pd/C catalyzed tandem reduction/cyclocondensation.

The benzyl (Bn) and carboxybenzyl (Cbz) groups are largely utilized in masking functional groups such as alcohols, phenols, acids, and amines. To overcome the safety problems related to the use of gaseous hydrogen employed in the classical cleavage protocols, alternative procedures based on MW-assisted Pd/C-catalyzed transfer hydrogenation with ammonium formate and Pd/C have been developed (Scheme 23) [53,69–72].



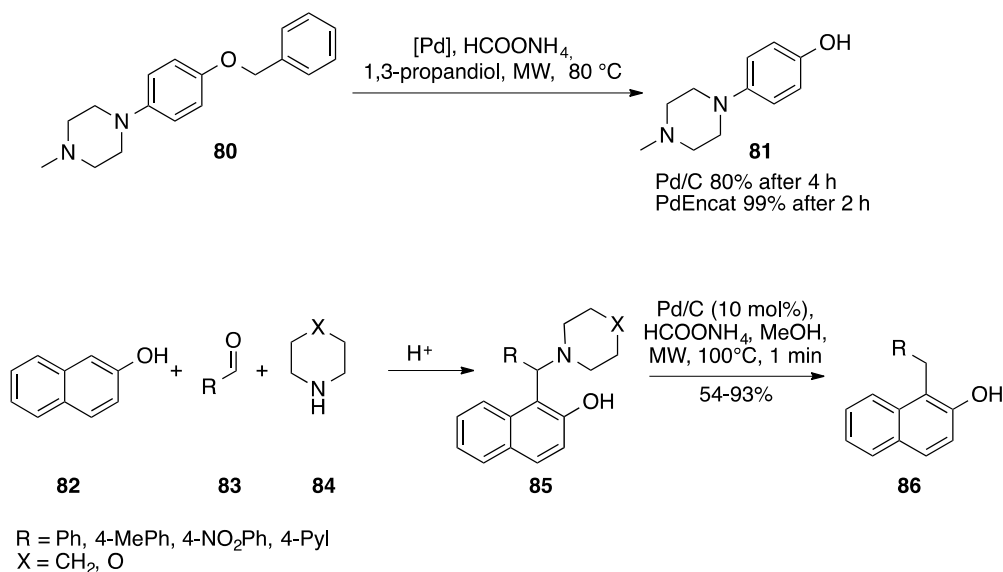
Scheme 23. Pd/C hydrogen transfer hydrogenolysis.

Deprotection of Cbz peptides supported on soluble supported MeOPEG 5000 was also accomplished in 10 min with HCOONH_4 and Pd/C in *i*-PrOH under MWs (Scheme 24). At the end, Pd/C was filtered off and the product was precipitated by cooling the reaction mixture. This strategy was applied to the synthesis of different oligopeptides as **79** in Scheme 24 [73].



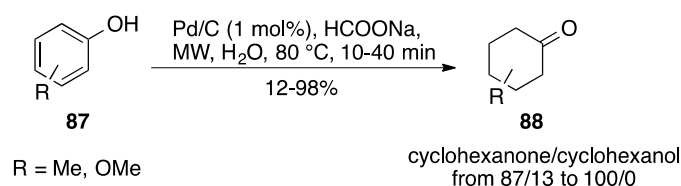
Scheme 24. Application of Pd/C catalyzed hydrogenolysis to peptide synthesis on soluble support.

In a comparative study, Pd/C and PdEncat were employed to deprotect phenoxybenzyl ethers, **80**, finding that the latter catalyst was superior in DMF at 80 °C (Scheme 25) [74]. Ammonium formate was also used for Pd/C-catalyzed reductive deamination of Mannich base in methanol under MW irradiation with excellent results after just 1 min of heating (Scheme 25) [75]. In this reaction, a first condensation between phenol and an aldehyde was carried out in the presence of piperidine or morpholine. The corresponding benzylamine **85** was then efficiently reduced with Pd/C under MW dielectric heating, yielding selectively 1-alkyl 2-naphthol **86**.



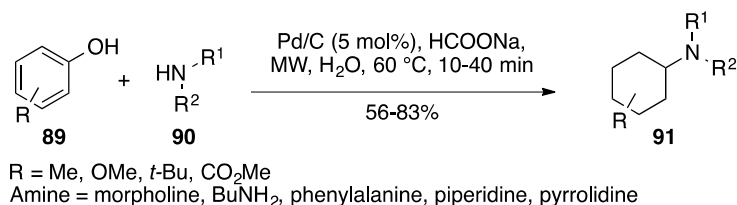
Scheme 25. Pd/C and PdEncat catalyzed deprotection of phenoxybenzyl ethers.

Selective reduction of phenols to cyclohexanones, **88**, catalyzed by Pd/C in the presence of HCOONa/H₂O has been studied. This MW-assisted reductive approach to cyclohexanone is highly efficient if compared to the standard oxidation of cyclohexane that generally requires high temperature. The conversion phenol/cyclohexanone was achieved in a 98% yield (Scheme 26) [76].



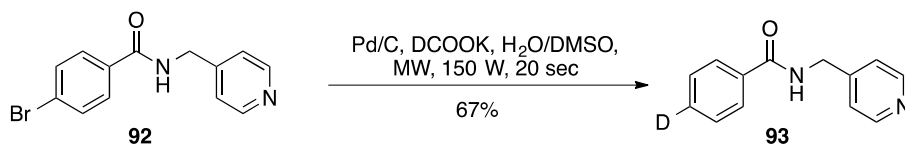
Scheme 26. Reduction of phenols.

More recently, a domino hydrogenation–reductive amination of phenols has been described for easy access to substituted cyclohexylamines (**91** in Scheme 27). Substituted phenols are reduced to cyclohexanones that are coupled in situ with different amines to yield, under the reductive condition, the corresponding substituted cyclohexylamines (Scheme 27). This protocol was also developed in continuous-flow for the production of cyclohexylamines in Gram scale (TON 32.7 and TOF 5.45 h^{−1}) [77].



Scheme 27. Reductive amination of phenols.

Pd/C has also been used for dehalogenation of aromatic compounds in the presence of deuterated formates inside a domestic MW oven. A rapid access (1 min) to deuterium-labeled compounds (**93** in Scheme 28) was possible but, in this case, better yields were obtained with Pd(OAc)₂ as catalyst [78].

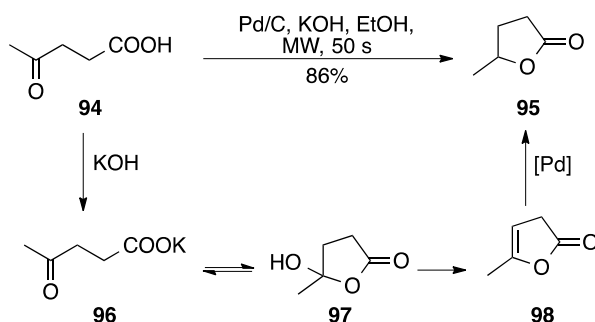


Scheme 28. Pd/C catalyzed D/Br exchange.

4.2. Other Hydrogen Sources

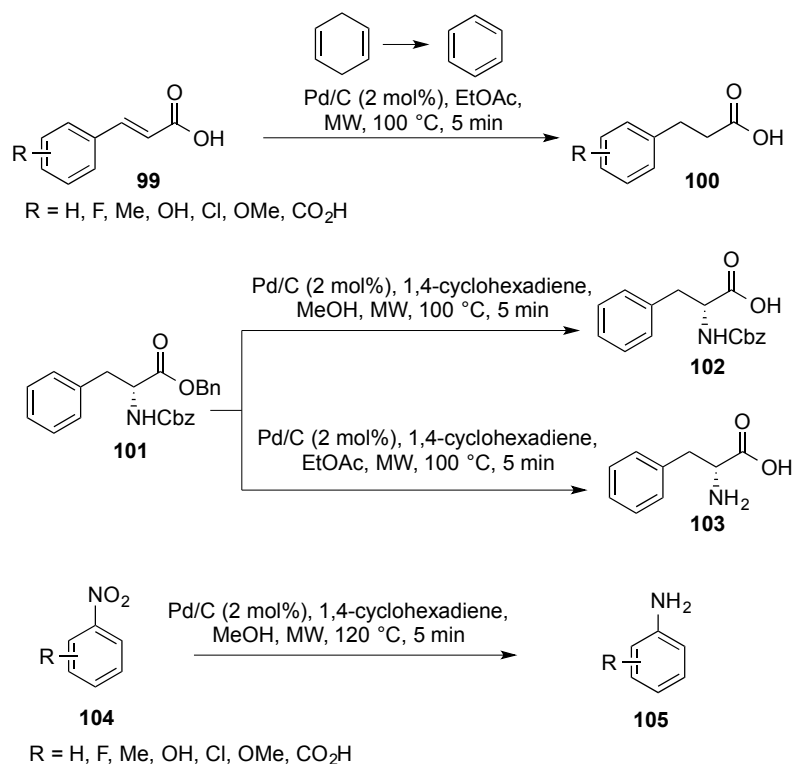
Although ammonium or sodium formates are easily available, inexpensive hydrogen donor sources, reaction by-products are gaseous (carbon dioxide and ammonia) and sometimes a considerable pressure build-up was observed at the end of the reaction. Additionally, when an excess of ammonium or sodium formate is used, an aqueous extraction is required as part of the reaction work-up. Thus, alternative hydrogen transfer sources have been investigated with the justification of finding a way to reduce the final pressure in the reaction vessel and to simplify the purification procedure.

Alcohols are cost-effective and environmentally friendly hydrogen sources and can represent attractive alternatives to hydrogen gas or formates. For example, glycerol can be used as a solvent and hydrogen donor in the catalytic transfer-hydrogenation of various unsaturated organic molecules. Glycerol was dehydrogenated with Pd/C under MW dielectric heating to yield dihydroxyacetone, a useful intermediate for organic synthesis and an important ingredient in sunless tanning products [79]. Alternatively, ethanol and isopropanol have each been used as a hydrogen source for Pd/C-catalyzed reduction of the ketone present in levulinic acid, **94**, (as potassium salt) with the formation of γ -valerolactone (GVL), **95** [80], a versatile solvent obtained from renewable sources [81] (Scheme 29). In this reaction, the temperature was not recorded as a domestic MW oven was employed.



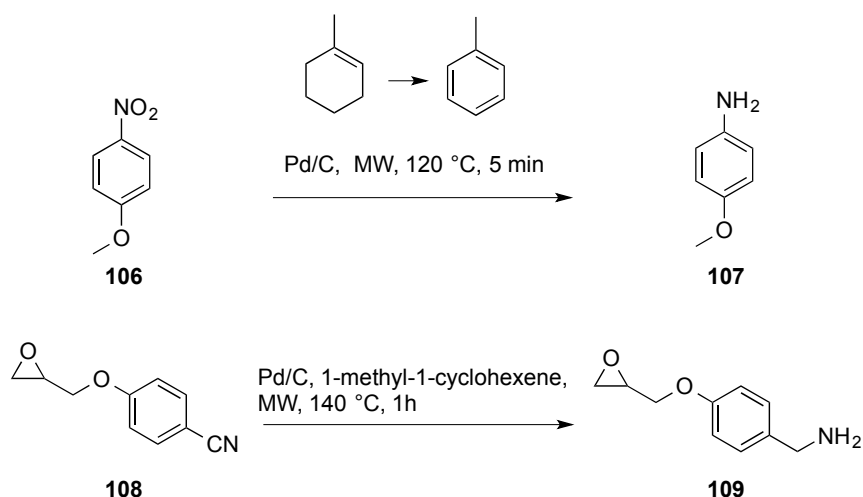
Scheme 29. Transformation of levulinic acid into GVL.

Cyclohexenes were also used as alternative hydrogen sources. Cyclohexadiene has several benefits as it generates volatile oxidized products that can be easily removed by standard evaporation techniques. The MW-assisted Pd/C-catalyzed procedure with cyclohexadiene was first optimized for a double bond reduction and rapid hydrogenolysis of benzyl (Bz) and carboxybenzyl (Cbz) groups [82]. While double bond hydrogenation occurred in EtOAc, the MW-assisted deprotection of CbzPheOBn, **101**, yielded the Cbz acid **102** with MeOH as the solvent. Alternatively, the fully deprotected H-Phe-OH **103** was obtained using EtOAc. The same authors reported later a general reduction of aryl nitro derivatives with Pd/C and 1,4-cyclohexadiene at 120 °C for 5 min (Scheme 30) [83].



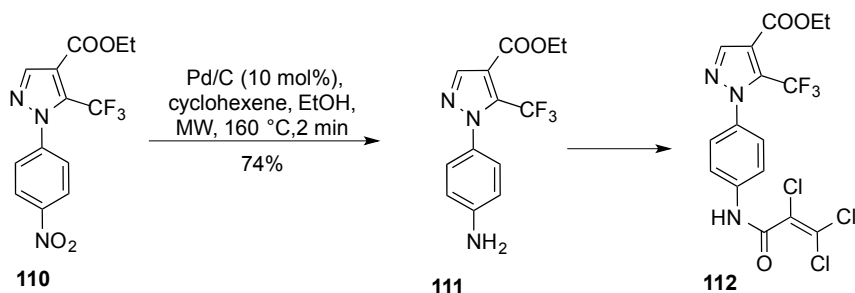
Scheme 30. Pd/C catalyzed hydrogen transfer with cyclohexenes.

Moreover, 1-methyl-1-cyclohexene has been used as a source of hydrogen with the obvious advantage of producing the safer toluene as the oxidized product. MW-assisted Pd/C-catalyzed reduction of aromatic nitro groups [84] and nitrile in 4-(2,3-epoxypropyl-1-oxy)benzonitrile, **108**, took place in good yields using 1-methyl-1-cyclohexene as a H_2 donor (Scheme 31) [85].



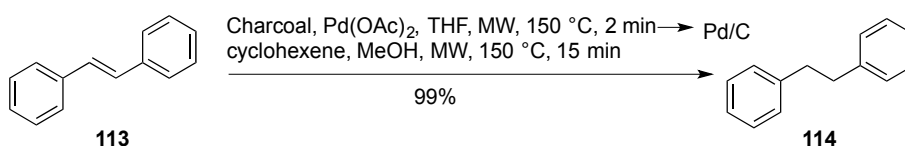
Scheme 31. Pd/C catalyzed hydrogen transfer with 1-methyl-1-cyclohexenes.

Cyclohexene has also been used as hydrogen donor in the reduction of the nitro derivative **110**, a key intermediate in the synthesis of the powerful canonical transient receptor potential channel (TRPC) inhibitor Pyr3, **112** (Scheme 32) [86].



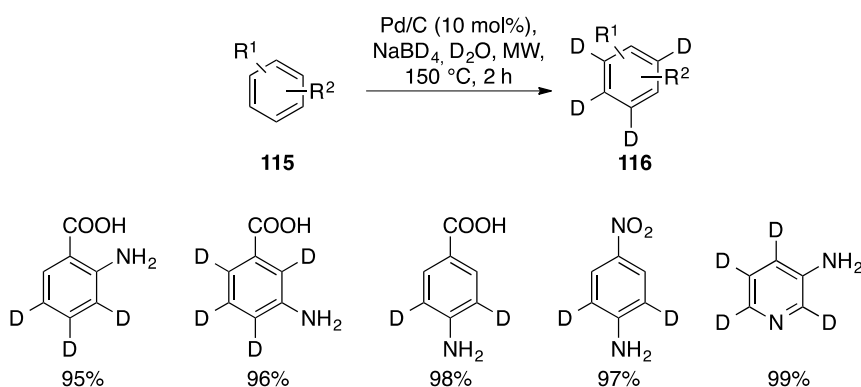
Scheme 32. Synthesis of the TRPC inhibitor Pyr3.

With the indubitable drawback of the benzene production, cyclohexene has also been used in a protocols developed to generate, in situ, the Pd/C catalyst from charcoal and Pd(OAc)₂ [87]. The protocol was applied to the hydrogenation of alkenes and alkynes and for the hydrogenolysis of O-benzyl ethers working with a remarkably low palladium loading (Scheme 33) and leaving products and solvents virtually free of palladium residues (<4 ppb).



Scheme 33. In situ Pd/C preparation and further hydrogen transfer.

Hydrogen–deuterium (H/D) exchange reactions of aminobenzoic acids and other aromatic and heteroaromatic compounds was catalyzed by Pd/C or other catalysts using NaBD₄ as the deuterium source (Scheme 34). A comparison between conventional heating and MW dielectric heating showed an increase of selectivity and yields when Pd/C was used under the most efficient MW dielectric heating [88].

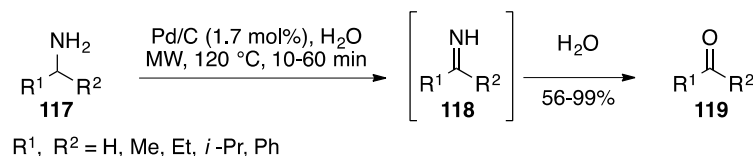


Scheme 34. Pd/C H/D exchange.

5. Pd/C in Oxidative Hydrogen Transfer Reactions

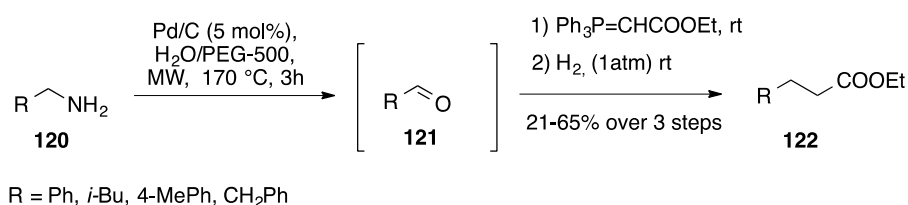
Pd/C in the presence of MWs is a good catalytic system for oxidizing amines to the corresponding imines. This reaction, originally observed by Murahashi in the 1990s [89], has been applied more recently to different organic transformations. The imine obtained through amine oxidation is a very reactive species that can further yield different products in a concerted domino process.

A very simple transformation of primary amines to ketones was described by Olah using Pd/C under MW dielectric heating. Water acted as the nucleophile, enabling this unusual transformation in good yield on different substrates (Scheme 35) [90].



Scheme 35. From amines to ketons.

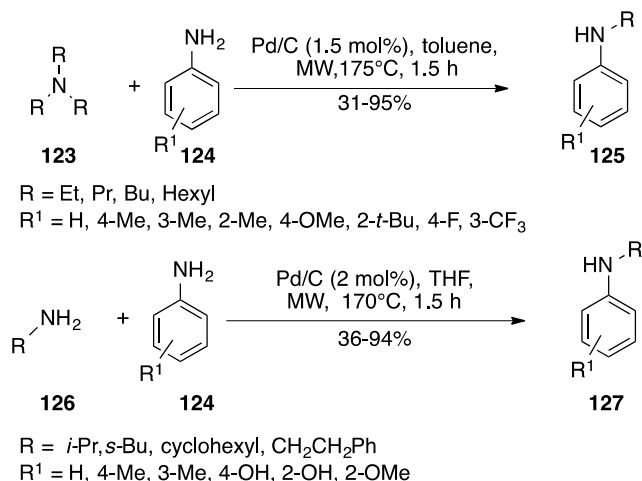
Following an analogous mechanism, Pt/C and Pd/C transformed primary amines into (symmetric) secondary amines. Oxidation of amine to imine occurred followed by the addition of a second molecule of amine to yield the disubstituted product. The reaction showed higher selectivity compared to the formed secondary amine when Pt/C is used, although in some cases, tertiary amine was observed as a by-product [91]. Pd/C in a mixture of water and PEG 500 oxidized, under MWs, a primary amine to the imine that was hydrolyzed into the corresponding aldehyde, which finally underwent a Wittig reaction in the same vessel where the oxidation took place. Exposure of the crude reaction mixture to H₂ gas, still in the same flask where the previous steps were carried out, yielded the deaminative homologation product (such as **122** in Scheme 36). Better results were obtained with benzyl amines, while aliphatic amines, enabling enolizable aldehydes, were converted into the Wittig product only with modest yields [92].



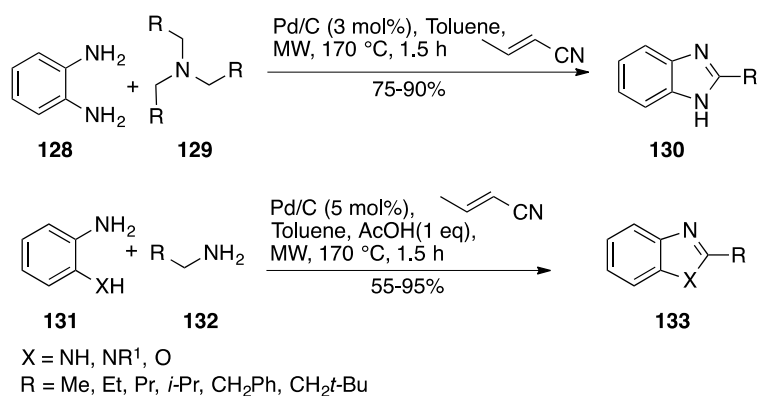
Scheme 36. Amine oxidation to aldehydes and in situ Wittig reaction and reduction.

The product of oxidation of secondary or tertiary (aliphatic) amines with Pd/C under MW dielectric heating can be used as the electrophile in reaction with aniline with the unusual result to alkylate an aniline with amines (Scheme 37). Non-symmetrical tertiary amines yielded a different ratio of alkyl transfer on aniline with the preference of the largest substituent transferred. For example, in the case of the reaction of aniline with N,N-dibutylmethylamine, N-butylaniline was always obtained as the major product, even if both the butyl and methyl groups were transferred. However, with the more hindered N,N-dimethylisopropylamine or N,N-diisopropylmethylamine, only the methyl group was transferred [93]. When the reaction was carried out in [bmim][PF₆] or THF at 170 °C for 90 min, even primary aliphatic amines could be used to alkylate anilines under higher atom economy. The use of the ionic liquid might be preferred to THF for safety reasons. However, with [bmim][PF₆], catalyst activity was lost, and the recycle was not possible [94].

The possibility of oxidizing amine to imines has also been exploited in the synthesis of heterocycles through an overall hydrogen transfer oxidative process. Porcheddu has described the synthesis of benzimidazoles (**132** in Scheme 38) through a Pd/C-catalyzed dehydrogenative amine activation, followed by cyclization with *o*-phenylenediamine, **130**, and final aromatization of the cyclization intermediate. The reaction occurred in toluene under MW dielectric heating with crotonitrile as a hydrogen acceptor, allowing the direct transformation of tertiary amines into benzimidazoles [95]. Primary amines (such as **131** in Scheme 38) can also be used in the presence of acetic acid as an additive in a synthesis of 1(H)-benzimidazoles, 1-substituted benzimidazoles, and benzoxazoles (such as **133** in Scheme 38) [96].

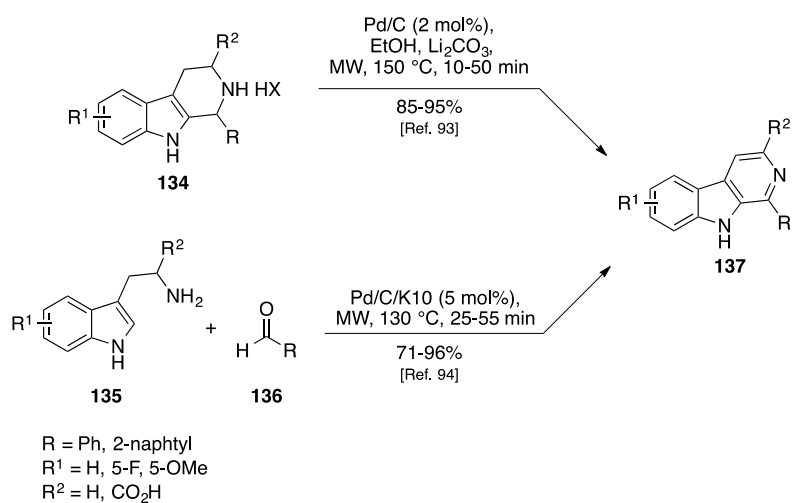


Scheme 37. Aniline alkylation with amines.



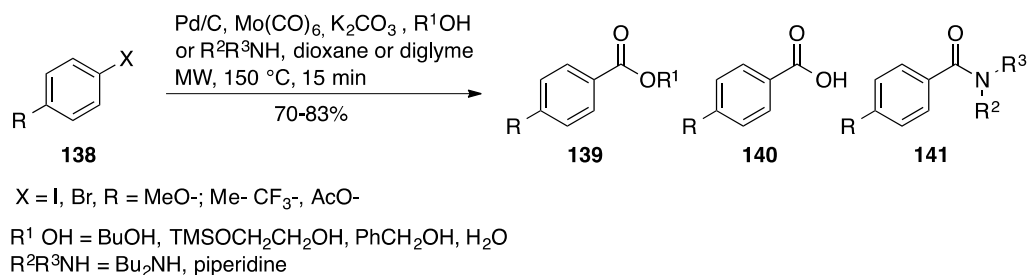
Scheme 38. Oxidative cyclisation of amines to give benzimidazoles.

Oxidative Pd/C-catalyzed oxidation was employed to aromatize tetrahydro- β -carboline salts in EtOH under MW irradiation (Scheme 39). Li₂CO₃ was required as an additive, and several substrates were submitted to the reaction with very good yields independently of substituents on the indole ring [97,98].

Scheme 39. Aromatization of tetrahydro- β -carbolines.

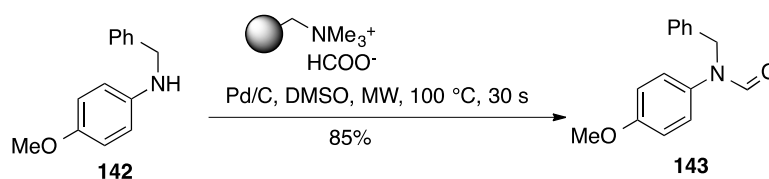
6. Other Pd/C-Catalyzed Transformations

Insertion of CO into aryl halides was obtained by heating under MW irradiation differently substituted bromides and iodides with solid molybdenum hexacarbonyl in the presence of Pd/C. Heating the molybdenum complex with MWs produced CO that could insert over the aryl–Pd bond and form esters, **139**, amides, **141**, or carboxylic acids, **140**, when alcohols [99], amines, or water was used as a nucleophile, respectively (Scheme 40) [100]. This approach prevents the use of toxic CO gas and the other typical drawbacks occurring with gas reagents.



Scheme 40. Mo(CO)₆ mediated carbonylation of aryl bromides and iodides.

A rapid and easy route to formamides by microwave-assisted *N*-formylation of primary and secondary amines was discovered. The reaction was based on a Pd/C-catalyzed reaction of a polymer-supported formate in DMSO and water. The solid-supported reagent under MW dielectric heating furnished the corresponding formamides in high yields, with reduced reaction time and solvent volume compared to the conventional heating approach (Scheme 41) [101].



Scheme 41. *N*-formylation of primary and secondary amines.

Pd/C and MWs have also been employed in depolymerization of lignin, a key step in the use of lignocellulosic biomass for the preparation of raw material in the chemical industry. After methylation of the benzyl alcohol of lignin with Fe₂(SO₄)₃ or Al₂(SO₄)₃, depolymerization was carried out over Pd/C under MW dielectric heating at 160 °C for 30 min. The pre-methylation allowed for a higher selectivity in depolymerization that yielded only 4 products instead of the 14–16 generally obtained on untreated lignin [102].

7. Conclusions

The use of Pd/C in MW-assisted reactions has proved to be a safe and advantageous process for organic synthesis. Many examples refer to cross-coupling reactions and with hydrogen transfer based on formate salts as hydrogen sources. The use of MWs, as expected, shortened the reaction time but, in some cases, was also crucial for the formation of the expected products. However, if compared with the variety of reaction catalyzed by Pd/C, the use of MWs is still limited, and many other possibilities may be explored soon, such as, for example, C–H activation, reductive alkylation, and aminative hydrogen transfer. We hope that this review will stimulate further exploration of new potential applications of this old but still important heterogeneous catalyst.

8. Addendum

During the revision period, a remarkable article was published [103] demonstrating a possible variation of the activation energy for NO conversion and H₂S decomposition due to MW irradiation. This phenomenon was rationalized elaborating a formula suitable for quantifying the effect. Although this is beyond the scope of this review, we want to highlight a report that may boost the development of novel MW catalytic reaction technology.

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Author Contributions: All the authors contributed equally to this work.

Conflicts of Interest: The authors declare no conflict of interest.

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