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HETEROGENEOUS CATALYSIS UNDER MICROWAVE HEATING

Microwave assisted organic synthesis emerged in the last years as an helpful technology. An overview on the large benefits recently observed coupling microwave dielectric heating with heterogeneous metal catalysts is reported.

Microwave irradiation emerged in the last years as an efficient and in some cases even green energy source [1, 2] widely applied in organic [1, 3], pharmaceutical [4] and peptide synthesis [5] as well as in biochemistry [6], nanotechnologies [7], pyrolysis of biomass feedstocks [8] and sintering processes [9]. Microwave-assisted organic synthesis (MAOS) has provided a new way to rapidly heat organic reactions remotely. Reduced reaction times, fast dielectric heating, and, in many cases, increased reaction yields are the strength of this technology. Despite the large application of MAOS in homogeneous catalysis transformations, and the strong rationale behind sintering processes, since the last years only few reports on the application of MAOS to heterogeneous catalyzed reactions have been described.

The combination of heterogeneous catalysts with microwaves has several advantages. Most of the solid catalysts highly absorb microwave irradiation and can be considered as an internal heat source. Most of the heterogeneous catalyzed reactions occur at the active surface of the catalyst and the direct coupling of the metal with microwaves is able to generate high (undetected) local temperatures on the surface let the reaction to completion in apparently less extreme conditions. As the catalyst itself can serve as a heat-

ing source the use of solvents can, in some cases, be avoided eliminating the adverse effects they can have on certain protocols [2c]. Heterogeneous catalyzed reactions usually require more extreme conditions than the corresponding homogeneous processes: this is not a problem as far as the stability of the catalysts is concerned and the somewhat lower catalytic activity can be compensated by using higher temperatures and catalyst loadings. Heterogeneous metal catalysts are commercially available in different forms.

As indicated above, despite the large application of microwave assisted sintering protocols [7], the use of solid catalysts in the presence of microwaves has been limited for several years in fear of the possible arcing phenomena generating hazardous conditions in the presence of flammable solvents and/or gas [10]. The electric discharge phenomena in metal-solvent mixtures has recently been reviewed by Kappe [11] and coworkers supporting the data reported by Hulshof [12] who observes that arcing is basically linked to large metal particles and that most of the commonly used supported catalysts have nanometer sized particles ensuring safety reaction conditions under microwave irradiation even in organic solvents.

The major groups of heterogeneous metal catalysts are: *i*) unsupported metals, *ii*) supported metal catalysts, *iii*) heterogenized metals

Tab. 1 - Temperature of different solvents reached after microwave irradiation in the presence and absence of homogeneous and heterogeneous palladium catalysts

Solvent	bp (C°)	tan δ	T (pure solvent)	T with Pd(OAc) ₂ ^b	T with Pd/C ^b	ΔT
DMF	153	0.161	139 °C	140 °C	183 °C	44 °C
THF	66	0.047	89 °C	97 °C	132 °C	43 °C
toluene	111	0.040	66 °C	70 °C	118 °C	52 °C
CCl ₄	76	n.d.	62 °C	67 °C	93 °C	31 °C

^aSingle-mode sealed vessel microwave irradiation, 150 W constant magnetron output power, 1 mL solvent, sealed 10 mL Pyrex reaction vessel, magnetic stirring, external sensor. Temperature was monitored by an external IR sensor; starting temperature 30 °C.
^b0.05 mmol.

and iv) nanoparticle-based complexes. Each group has different interactions with microwaves and has been successfully applied to the synthesis of different compounds. Here some applications in microwave assisted organic synthesis of Pd/C, one of the most common heterogeneous metal catalyst, are briefly analyzed on the base of our experience. In comparison to other expensive and air-sensitive catalysts, Pd/C is more easily handled being reused after recovery from the reaction mixture by simple filtration. Differently from a common perception, Pd is not very expensive: its 2008 price is about 12 €/g, much less of Au (35 €/g), Pt (51 €/g), Ir (216 €/g) or Rh (230 €/g) [13]. Pd/C is very stable under acid and basic conditions and has much higher surface area than alumina and silica supported ones. Moreover, it efficiently couples with microwaves because its strong absorbing support charcoal generating high temperatures on the catalyst surface and, by conduction, in the reaction medium.

A qualitative evaluation of the efficiency of heating of Pd/C with respect to homogenous Pd catalysts (*i.e.* Pd(OAc)₂) under microwave dielectric heating in different solvents (DMF, CCl₄, toluene and THF) at 150 W for 1 minute indicated that the presence of the palladium salt itself has no effect on the temperature increase. On the contrary, adding the same amount of Pd/C to the solvents, a temperature rising (from 31 to 52 °C in 1 minute depending on the solvent) occurred (Tab. 1).

Pd/C has been efficiently applied to the microwave-assisted carbonylation of aryl iodides with stoichiometric amount of the nucleophile [14]. 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 [15]. Ketones, carboxylic acids, esters, or amides that can be easily obtained either in solution [15b, 16] and in solid phase [15e] under conditions compatible with the atom economy principles.

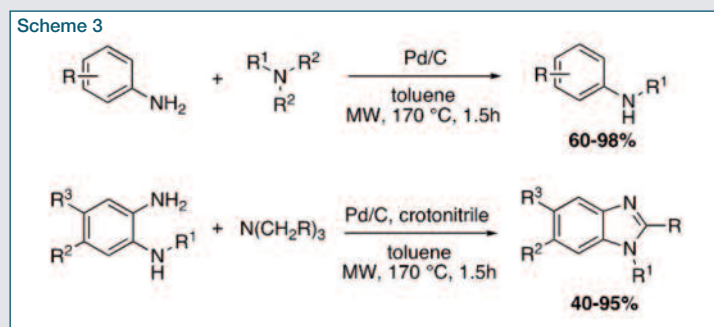
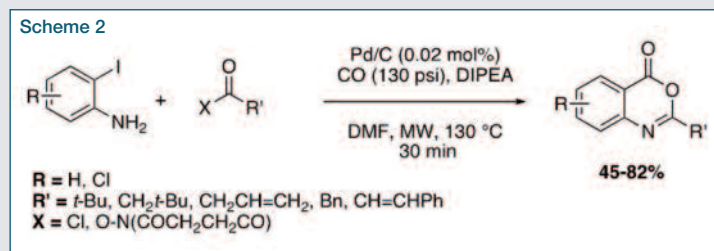
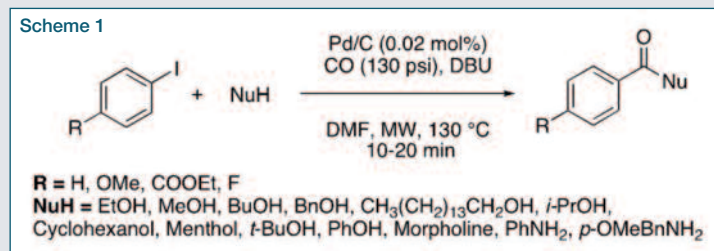
Most of the carbonylation procedures reported in the literature are based on the use of homogeneous Pd catalysts in the presence of phosphine ligands. However, an excess of phosphine is often required to avoid catalyst deactivation, and its separation from the reaction products and regeneration is usually difficult limiting the

applicability of carbonylation procedures [17].

When Pd/C is employed as the catalyst to alkoxycarbonylation reactions, high pressures of CO (70-300 psi) as well as high temperatures (>130 °C) and a large excess of nucleophiles (up to 10 equivalents) are requested to obtain acceptable yields. However, coupling the catalytic activity of Pd/C with microwave irradiation, it is possible to obtain esters or amides from aryl iodides using stoichiometric amounts of different alcohols and amines in the presence of DBU in DMF at 130 psi (8.8 atm) of CO, irradiating the reaction mixture at 130 °C for 10-20 minutes depending on the substrate (Scheme 1). The versatility of Pd/C for this carbonylation reaction is also confirmed by the possibility to carry out cyclohydrocarbonylation producing benzoxazinones, recycling the catalyst at least three times without changes in the reaction yields (Scheme 2).

Recently the application of Pd/C under microwave irradiation has been applied to the synthesis of both substituted anilines [18] and benzimidazole [19] derivatives (Scheme 3).

The monoalkylation of anilines can be possible using a tertiary amine as the alkylation source using Pd/C in toluene and irradiating with microwaves at 170 °C for 1.5 h. It is interesting to note that the solvent plays a key role on this transformation and that running the reaction in solvent-free conditions a rapid increase of the pressure inside the microwave tube was observed because of a possible arching phenomena.



Heating a tertiary amine in the presence of Pd/C under microwave irradiation generates dehydrogenation of the tertiary amine with formation of the iminium ion. If the reaction is carried out in the presence of 1,2-phenylenediamine, the synthesis of benzimidazoles is possible. The reaction seems to occur in het-

erogeneous phase as demonstrated by the possibility to reuse the catalyst recovered several times without significant lowering in the reaction yields; good to excellent yields taking advantages from the efficient coupling of Pd/C with microwaves can be obtained in short reaction times (Scheme 3). Running the reaction in the same conditions but in a preheated oil bath at 175 °C a conversion is observed as well but, as expected, longer reaction times (24-48 h) are needed to obtain in any case worst yields.

An interesting example of microwave-assisted heterogeneous Pd catalyzed reaction is the hydrogenation of pyridine derivatives. Typically, metal catalysts such as Pt, Rh, Ru, or Ni are necessary to effect the reduction of pyridines. Using microwave irradiation as the heating source at 120 psi of H₂ in AcOH at 80 °C, it is possible to fully hydrogenate nicotinic acid in 98% yield [20].

Even if arching phenomena have never been observed, PtO₂ was used as heterogeneous catalyst for the microwave-assisted hydrogenation of substituted pyridines giving piperidines in optimal yields and good diastereoselectivities.

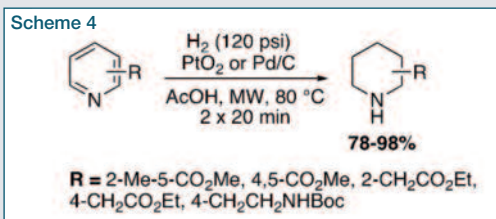
It is interesting to note that the optimized microwave-assisted procedure allows to directly transfer the hydrogenation protocol in continuous flow obtaining even better yields [21].

It has to be emphasized that one of the key differences between the catalytic hydrogenations performed by microwave batch and continuous flow methods lies in the fact that the amount of the heterogeneous catalyst is significantly higher in flow processing than in a typical batch experiment (*i.e.* 150 vs. 2 mg in the experiments reported in Scheme 4).

Microwave irradiation is frequently used not only in the optimization of reaction conditions to be transferred in continuous flow, but even as an efficient heating source in flow processes [22, 23]. Focusing on heterogeneous process several metal coated capillaries (*i.e.* Pd, Au, Ag, Cu) can be used in microwave-assisted continuous flow synthesis. A gold film was successfully used in benzannulation of aryl aldehydes with alkynes (Scheme 5) [24].

In this example because of adhesion problems, the gold film needs to be precipitated on a transparently-thin silver layer inside the capillary. The film acts as an internal heating source as well as the catalytically active species. The same film or a copper film can be used in the synthesis of propargylic amines [25].

In this study, Organ and co-workers reported the first and so far more accurate temperature control on the film surface indicating that the revealed 180 °C temperature inside the reaction mixture corresponds to a 950 °C on the surface of the metal (Scheme 6). These

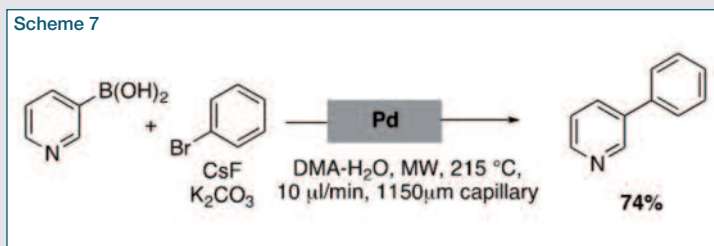
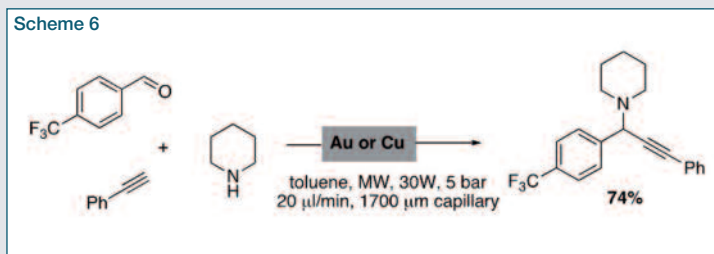
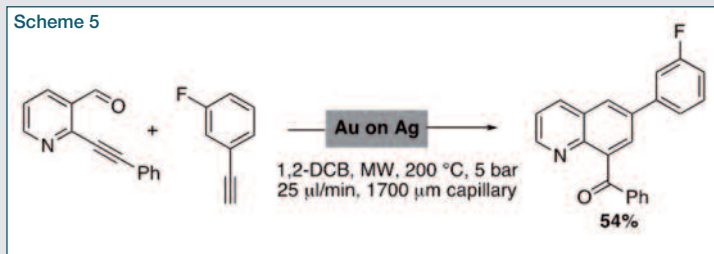


data provide a very good rationale for the tremendous reaction rate enhancement of metal film-catalyzed microwave-assisted continuous-flow reactions.

The advantages of this technology are well exemplified by the Suzuki cross-coupling reaction on a small film of Pd deposited in the

proper capillary: better yields and higher temperature are observed using microwave irradiation with respect to traditional heating flow protocols [26].

The previous reported examples are just an overview on the possible applications of heterogeneous catalysts in MAOS and continuous-flow synthesis. The direct coupling of microwaves with metals, or their solid supports obtaining high temperatures on the active surface of the catalyst consents to run reactions in a very fast and efficient way. Despite the large application of microwave heating on material science and the rational understanding on how this energy source can efficiently activate metals and metal oxides particles interacting with them, only in the last few years the use of heterogeneous catalysts and microwave irradiation started to be appreciated. As very recent reports and applications demonstrate and rationalize how to work in a healthy way coupling the advantages of heterogeneous catalysis in terms of catalyst recovery and recyclability, and microwave irradiation as an efficient energy source, we can expect that in the near future more and more studies will combine these approaches. The microwave assisted reactions can even be con-



sidered as an efficient tool for the batch optimization of transformations that have to be transferred in continuous flow.

Besides flow processes can benefit from the use of microwaves as heating source especially when heterogeneous catalysts are used. It is interesting to note that microwaves once coupled with flow conditions can be efficiently applied on large scale synthesis avoiding the problems of penetration depths.

Even if it is far from being completely understood and foreseen, the application of different heterogeneous catalysts in microwave assist-

ed reactions starting from the data reported in the literature, and from the very good results obtained will hopefully have an increasing application because of the possible benefits in term of waste and energy saving especially on large scale processes.

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RIASSUNTO

Catalisi eterogenea per riscaldamento con microonde

Negli ultimi anni le microonde hanno dimostrato di essere un'efficiente fonte di riscaldamento da utilizzare in chimica organica per condurre reazioni in condizioni spesso meno drastiche e con tempi più brevi rispetto a quelle richieste con fonti di riscaldamento tradizionali. Qui vengono brevemente analizzati i vantaggi legati all'impiego simultaneo di catalizzatori eterogenei e riscaldamento con microonde.