## Microwave-Assisted Cross-Coupling and Hydrogenation Chemistry by Using Heterogeneous Transition-Metal Catalysts: An Evaluation of the Role of Selective Catalyst Heating

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Abstract: The concept of specific microwave effects in solid/liquid catalytic processes resulting from the selective heating of a microwave-absorbing heterogeneous transition-metal catalyst by using 2.45 GHz microwave irradiation was evaluated. As model transformations Ni/C-, Cu/C-, Pd/C-, and Pd/ Al<sub>2</sub>O<sub>3</sub>-catalyzed carbon-carbon/ carbon-heteroatom cross-couplings and hydrogenation reactions were investigated. To probe the existence of specific microwave effects by means of selective catalyst heating in these transformations, control experiments compar-

### Introduction

The use of microwave heating to perform chemical reactions involving heterogeneous transition-metal catalysts is becoming increasingly popular in the scientific community.<sup>[1-3]</sup> For these transformations, the use of microwave heating appears to be particularly attractive since heterogeneous supported metal catalysts are generally strongly microwave absorbing.<sup>[4]</sup> Therefore, selective heating of the heterogeneous catalyst by microwave irradiation will occur under certain conditions, which may result in differences in reaction rates and selectivity relative to control experiments performed by using conventional conductive heating at the same bulk temperature ("specific microwave effects").<sup>[5–18]</sup> Literature ex-

**Keywords:** cross-coupling • heterogeneous catalysis • hydrogenations • mass transfer • microwave chemistry conventional heating experiments under carefully controlled conditions were observed. This was true also for reactions that use low-absorbing or microwave transparent solvents, and was independent of the microwave absorbtivity of the catalyst support material. In the case of hydrogenation reactions, the stirring speed was found to be a critical factor on the mass transfer between gas and liquid phase, influencing the rate of the hydrogenation in both microwave and conventionally heated experiments.

amples include the utilization of Pd/C,<sup>[5-7]</sup> Pd/SiO<sub>2</sub>,<sup>[8]</sup> PdEn-Cat,<sup>[9]</sup> Pd/glass,<sup>[10,11]</sup> supported/stabilized Pd nanoparticles,<sup>[12]</sup> Ni/C,<sup>[13]</sup> Ni/graphite,<sup>[14]</sup> Cu/C,<sup>[15]</sup> and other supported metal species<sup>[16]</sup> in combination with microwave dielectric heating for achieving highly efficient carbon–carbon and carbon–heteroatom bond formation reactions. In addition, several cases of microwave-enhanced hydrogenation reactions involving Pd/C and related supported metal species have been reported.<sup>[17,18]</sup>

However, the selective heating of metal (or other strongly microwave absorbing) particles under microwave conditions is a rather complex phenomenon depending strongly on the type of support, particle size (surface-to-volume ratio), electromagnetic field strength (power density), and a variety of other factors.<sup>[4,19]</sup> In heterogeneous gas-phase catalysis, the rationale and advantages of using microwave irradiation to selectively heat the often very strongly microwave absorbing catalyst bed while the reactive gas—being inherently microwave transparent—remains at a lower temperature are reasonably well established.<sup>[20]</sup> In the case of solid/liquid transformations, the genuine selective heating characteristics of catalyst particles compared to the bulk reaction mixture and the resulting influence on reaction rate and selectivity often



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ing microwave dielectric heating and conventional thermal heating at the same reaction temperature were performed. Although the supported metal catalysts were experimentally found to be strongly microwave absorbing, for all chemistry examples investigated herein no differences in reaction rate or selectivity between microwave and

remain unclear.<sup>[5–18]</sup> In the present manuscript, we present a critical reinvestigation of microwave-heated transitionmetal-catalyzed carbon–carbon/carbon–heteroatom crosscoupling reactions and hydrogenation protocols, to elucidate the role that microwave irradiation in conjunction with the use of heterogeneous catalysts plays in these transformations.

### **Results and Discussion**

Negishi and Ullmann-type cross-couplings by using Ni/C and Cu/C catalysts: Our initial model transformations focused on cross-couplings that utilized Nickel-in-Charcoal (Ni/C) and Copper-in-Charcoal (Cu/C) as heterogeneous catalysts. In recent years, Lipshutz and co-workers have published extensively on the use of these (and related) inexpensive base metal heterogeneous catalysts to perform very efficient microwave-assisted, for example, Ni-catalyzed Suzuki, Negishi, and Kumada carbon-carbon cross-couplings,<sup>[13]</sup> Cucatalyzed azide-alkyne cycloadditions<sup>[21]</sup>, and Ullmann-type diarylether formations,<sup>[15]</sup> in addition to Ni-catalyzed amination, and reduction processes.<sup>[13]</sup> Importantly, compared to previous studies by the same group employing conventional heating in an oil bath dating back to the late 1990s,<sup>[22]</sup> the reaction times for most of these transformations could be reduced from several hours to a few minutes by using sealedvessel microwave processing.<sup>[13-15,21]</sup> Choosing the Negishi cross-coupling of aryl chloride 1 with organozinc reagent 2 as our first model reaction (Scheme 1a) we wanted to see if the dramatic rate enhancement on going from 16 h employing oil-bath heating at 60°C,<sup>[23]</sup> to 15 min under microwave conditions at 150°C<sup>[13]</sup> was due to selective heating of the strongly microwave-absorbing Ni/C catalyst (see below), or could be rationalized by a simple thermal effect as a result of the significantly higher reaction temperature.<sup>[24]</sup> As a second example, we have selected the Cu/C-promoted Ullmann-type diaryl ether formation involving aryl bromide 4 and phenol 5 (Scheme 1b). According to Lipshutz and coworkers, full conversion and a 86% yield of diaryl ether 6 can be obtained under microwave conditions at 180°C for 30 min (no data for conventional heating were provided).<sup>[15]</sup> Since both cross-couplings were performed by using micro-



Scheme 1. The Negishi and Ullmann-type cross-coupling as a model reaction.[13,15]

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wave-transparent dioxane<sup>[24]</sup> as the solvent, the chances to observe selective heating of the metal catalyst appeared to be high in these cases.

The starting point for the investigation of both transformations was to evaluate the microwave absorbtivity of the involved catalysts. Both Ni/C and Cu/C were prepared according to the detailed protocols reported by the Lipshutz group starting from activated charcoal Darco KB-G and the corresponding metal nitrate salts.<sup>[13,21]</sup> The loading of Ni and Cu within the catalyst preparations was determined by ICP-MS (inductively coupled plasma mass spectroscopy) analysis to be 3.6% (w/w) for Ni and 8.1% (w/w) for Cu, respectively. Similar to our recent studies involving Pd/C,<sup>[25]</sup> the microwave absorbtivity of both catalysts in comparison to the non-impregnated charcoal support was determined by suspending samples of the solid materials in carbon tetrachloride as the microwave-transparent solvent and observing bulk temperature changes on irradiation with constant microwave power. As can be seen in Figure 1, the Ni/C catalyst



Figure 1. Microwave heating profiles for 100 mg samples of Ni/C, Cu/C, and charcoal (C) suspended in  $CCl_4$  (2.0 mL) in a 10 mL quartz reaction vessel at constant 150 W magnetron output power (single-mode reactor, fiber-optic temperature measurement).

proved to be a significantly stronger microwave absorber than untreated charcoal, whereas the Cu/C catalyst surprisingly showed reduced microwave absorbtivity. It can be as-

> sumed that the temperature of the metal catalysts under these conditions, at least for Ni/C, must, therefore, be significantly higher than the monitored bulk mixture temperature.<sup>[25]</sup>

> At this point, it needs to be emphasized that the species initially present in the charcoal matrix in both catalysts prepared by impregnation of Ni- $(NO_3)_2$  or Cu $(NO_3)_2$  and subsequent thermal treatment likely involve Ni<sup>II</sup> and Cu<sup>II</sup> oxides, re-

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spectively.<sup>[21,22]</sup> For many of the subsequent cross-coupling transformations, in particular for reactions involving Ni/C, a reduction step to a zero-valent metal prior to coupling is required.<sup>[13,21,22,26,27]</sup>

To accurately compare the results obtained by direct microwave heating with the outcome of a conventionally heated reaction at the same temperature we have used a reactor system that allows us to perform both types of transformations in an identical reaction vessel and to monitor the internal reaction temperature in both experiments directly with a fiber-optic probe device.<sup>[28]</sup> This system has the advantage that the same reaction vessel and the same method of temperature measurement is used. In this way, all parameters apart from the mode of heating are identical and, therefore, a fair comparison between microwave heating and thermal heating can be made. For the Negishi cross-coupling reaction shown in Scheme 1a, the literature protocol published by Lipshutz and co-workers was followed as closely as possible.<sup>[13]</sup> In the event, 8.1 mol% of the Ni/C catalyst and 30 mol% of triphenylphosphine ligand were suspended in anhydrous dioxane. The Ni<sup>II</sup>/C precatalyst was subsequently activated by addition of excess *n*BuLi in hexane, followed by addition of the two coupling partners 1 and 2. For the preparation of the organozinc reagent 2 we have developed a microwave modification of a recent general zincation protocol reported by the Knochel group describing the insertion of Zn dust into 4-iodotoluene in the presence of anhvdrous LiCl in THF.<sup>[29,30]</sup> Applying sealed-vessel microwave heating at 150°C, a reaction time of 30 min was sufficient to achieve full conversion as monitored by GC-FID analysis.

The subsequent microwave-assisted Negishi cross-coupling (Scheme 1a) was performed at 150°C (internal temperature measurement) within 15 min hold time (~5 bar pressure). This protocol consistently (three repetitions) led to GC-FID conversions of ~96% ( $\pm 1\%$ ) and provided a 93% isolated product yield of biphenyl 3, in good agreement with the results published by Lipshutz (94%).<sup>[13]</sup> For the control experiments involving conventional heat transfer, the reactor setup was immersed into an oil bath preheated to an appropriate temperature to ensure an internal reaction temperature of ~150°C. As already previously noted,<sup>[31]</sup> it has to be emphasized that comparison studies between microwave and conventional heating experiments must not only take the final reaction temperature into account, but must also provide for similar heating and cooling profiles. In particular, for short overall reaction times, the ramp time will become important. In the present case, appropriate adjustment of the utilized microwave power (27 W for 1 min and 10 W for 4 min initial microwave power) led to a ramp time of  $\sim 5$  min in the microwave run, which was comparable to the heating profile experienced in the oil-bath experiment (see Figure S1 in the Supporting Information). Interestingly, the results for the conventionally heated Negishi cross-couplings displayed no significant differences compared to the microwave runs performed at the same temperature of 150 °C. Conversions of 93% ( $\pm 4\%$ , three repetitions) with an isolated yield of 87% of biphenyl product 3 from one of

the runs was achieved. Evaluating GC-FID conversions at shorter time intervals (5 and 10 min) also did not provide any indication of significant differences in reaction rate or selectivities between the two heating modes.

Since the comparatively short reaction time of 15 min and the complex processing nature of the Negishi cross-coupling protocol-involving the initial independent preparation of organozinc species 2 and a preactivation of the Ni/C catalyst-was not ideal for a more detailed kinetic comparison study between microwave and conventional heating, we have selected the Ullmann-type diaryl ether formation shown in Scheme 1b as a second example.<sup>[15]</sup> Here, activation of the Cu/C catalyst is not required and the two coupling partners are commercially available. Again, the published protocol was followed as closely as possible, applying 3.8 mol% of the Cu/C catalyst, 0.5 equivalents of 1,10-phenanthroline ligand, 1.0 equivalent of phenol 5, and 1.5 equivalents of aryl bromide 4.<sup>[15]</sup> Preliminary optimization experiments indicated that high conversion levels to diaryl ether 6 could also be obtained at 150 °C (instead of 180 °C)<sup>[15]</sup> within 30 min, which made the transformation more practical for the planned comparison studies. Similar to the case with the Negishi cross-coupling discussed above, the heating profiles for microwave and oil-bath runs were matched by applying suitable microwave power levels and oil-bath temperatures, respectively (see Figure S2 in the Supporting Information). As shown in Table 1, the results obtained by microwave and oil-bath heating experiments were virtually identical, clearly indicating the absence of any "specific microwave effect" as a result of selective catalyst heating.

Despite the fact that both transformations were performed in a microwave transparent solvent and the data presented in Figure 1 provide clear evidence that at least one of the catalysts (Ni/C) is strongly microwave absorbing, we conclude that the rate enhancements seen in transforma-

Table 1. Comparison of microwave heating and conventional heating for the Ullmann-type diaryl ether formation of aryl bromide **4** with phenol **5** (Scheme 1b).<sup>[a]</sup>

<i>t</i> <sup>[b]</sup> [min]	Heating method <sup>[c]</sup> ((150±4) $^{\circ}$ C)	Conversion <sup>[d]</sup> [%]
5	MW	49/44/43
	conventional	50/46/47
10	MW	57/58/57
	conventional	59/58/59
20	MW	69/74/76
	conventional	72/74/72
30	MW	81/86/87 (81) <sup>[e]</sup>
	conventional	84/84/85 (76) <sup>[e]</sup>

[a] Phenol **5** (1.0 mmol), aryl bromide **4** (1.5 equiv), 1,10-phenanthroline (0.5 equiv), dioxane (2 mL), Cu/C (3.8 mol%). Microwave experiments were carried out by using a CEM Discover system with a 10 mL fiber-optic probe setup. Conventionally heated experiments were performed in a preheated oil bath by selecting an appropriate bath temperature (see Figure S2 in the Supporting Information). For further information see the Experimental Section. [b] Fixed hold time, the ramp times were similar (~6 min) for both heating modes (see Figure S2 in the Supporting Information). [c] Internal reaction temperature measured by fiber-optic sensor. [d] Determined by GC-MS analysis (peak area% of diaryl ether **6**). Entries reflect multiple experiments. For a graphical representation, see Figure S3 in the Supporting Information. [e] Isolated yields.

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tions of this type<sup>[13-15,21]</sup> are essentially the result of a standard thermal effect, switching from reflux conditions to a sealed-vessel microwave experiment at significantly higher temperatures. As with other related examples recently investigated in our laboratories,<sup>[25,31]</sup> we ascribe the absence of a "specific microwave effect" in these cases to the fact that although the heterogeneous metal catalyst itself can be a strongly microwave absorbing material when irradiated under suitable conditions (Figure 1),<sup>[25]</sup> for the actual reaction mixtures containing several other microwave-absorbing components (substrates, ligand, additives, bases) any effect derived from selective heating of the comparatively small quantities of heterogeneous metal catalyst will be masked. In addition, it should be emphasized that for both reactions discussed in Scheme 1, experimental evidence suggests that the actual catalytic process is of a homogeneous rather than heterogeneous nature, involving soluble catalytic species of Ni and Cu leaching from the charcoal support.<sup>[15,26]</sup>

Suzuki cross-couplings by using Pd/C and Pd/Al<sub>2</sub>O<sub>3</sub> catalysts: As an alternative example to the Ni and Cu-catalyzed carbon-carbon and carbon-heteroatom bond-formation reactions discussed above (Scheme 1) we next turned our attention to Pd-catalyzed Suzuki-Miyaura biaryl couplings<sup>[32]</sup> that involve heterogeneous Pd catalysts. A plethora of examples of Suzuki-Miyaura cross-couplings utilizing different forms of immobilized Pd catalysts have been reported,<sup>[33]</sup> and in many cases the benefits of performing these processes by utilizing microwave heating-typically reducing reaction times from hours to a few minutes-have been emphasized in the literature.<sup>[3,5-12]</sup> The specific example chosen for our investigations discussed herein involved the cross-coupling of aryl chloride 7 with phenylboronic acid (8) in the presence of Pd/C under aqueous conditions (Scheme 2). This Suzuki-Miyaura cross-coupling was chosen since work by Arvela and Leadbeater published in 2005 has shown that microwave irradiation in conjunction with simultaneous cooling of the reaction mixture by compressed air-under otherwise identical reaction conditions (120°C, 10 min)-led to a markedly improved product yield (91% versus 60%) relative to normal microwave heating.<sup>[6]</sup> Under "simultaneous cooling" conditions, the reaction vessel is cooled from the outside by compressed air while being irradiated by microwaves.<sup>[34]</sup> This generally allows a higher level of microwave power to be directly administered to the reaction mixture thereby potentially enhancing any specific microwave effects that are dependent on the electric field strength.<sup>[6,9a,17,28,34-36]</sup> By monitoring internal reaction temperatures with fiber-optic probes and carefully adjusting the temperature and/or flow of the external cooling gas, experiments can be performed in which at constant bulk reaction temperatures distinctly different microwave power levels can be applied. We speculated that the previously observed effects<sup>[6]</sup> could have been due to a "selective heating" of the Pd/C catalyst by utilizing the simultaneous cooling conditions.

Applying our reactor setup equipped with a fiber-optic internal temperature probe as described above and by following as closely as possible the conditions reported in the original reference<sup>[6]</sup> we have reproduced the Suzuki-Miyaura coupling shown in Scheme 2. A Pd/C catalyst specifically optimized for cross-coupling chemistry was employed (E 104 CA/W 5% Pd), which is characterized by a high Pd dispersion, a low reduction degree, and a high water content.<sup>[37]</sup> As described by Arvela and Leadbeater,<sup>[6]</sup> we found that applying 1 mol% of Pd/C catalyst, 1.3 equiv of boronic acid 8, 3.7 equiv of sodium carbonate base, and 1 equivalent of tetrabutylammonium bromide (TBAB) as additive provided optimum results leading to the highest conversions. By using a moderate 8 W of initial maximum magnetron output power to ramp the temperature to the desired 120°C within 3-4 min (see Figure S4 in the Supporting Information), followed by a 5 min hold time at 120°C consistently provided GC-FID conversions to biaryl 9 in the region of 80-90%, with only small amounts of starting material  $7 (\sim 10\%)$  and biphenvl homocoupling product (<3%) being observed (Table 2, entry 1). These results were comparable to the data published previously by Arvela and Leadbeater employing a slightly longer overall reaction time (10 min).<sup>[6]</sup> Increasing the initial maximum magnetron output power to 25 W shortened the ramp time to 1 min (overall irradiation time 6 min), but otherwise did not change the outcome of these coupling reactions (Table 2, entry 2). Although a considerably higher amount of microwave power was applied by using the simultaneous cooling method to reach and maintain the same bulk temperature of 120 °C (20 versus 7.6 W average power, see Figure S5 in the Supporting Information), the results in our hands both in terms of conversion and selectivity were more or less identical to the noncooled runs (Table 2, entry 3). In fact, this outcome is in line with more recent work published by the Leadbeater group, demonstrating that simultaneous cooling in this cross-coupling reaction is not required when working on a larger scale.<sup>[38]</sup> Ultimately, the Suzuki-Miyaura cross-coupling was also performed by using conventional heating, again matching heating profiles carefully by choosing an appropriate oil-bath temperature (see Figure S4 in the Supporting Information). As can be seen from the data presented in Table 2 (entry 4),





it appears that a "specific microwave effect" of any kind is not in operation here. By inspection of GC-FID traces that compare the crude reaction mixture composition, no significant differences in conversion or selectivities between runs

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Table 2. Comparison of microwave heating and conventional heating for the Suzuki–Miyaura cross-coupling of aryl chloride **7** with boronic acid **8** (Scheme 2).<sup>[a]</sup>

Entry	Catalyst	$T [^{\circ}C]/t [min]$	Heating method <sup>[b]</sup>	Conversion <sup>[c]</sup> [%]
1	Pd/C	120/5	MW (8 W)	87/87/85/84 (80) <sup>[d]</sup>
2	Pd/C	120/5	MW (25 W)	83
3	Pd/C	120/5	MW (sim. cooling)	86
4	Pd/C	120/5	conventional	87/90/83/81 (82) <sup>[d]</sup>
5	$Pd/Al_2O_3$	120/5	MW (8 W)	37/38/40
6	Pd/Al <sub>2</sub> O <sub>3</sub>	120/5	conventional	38/37/35
7	$Pd/Al_2O_3$	150/20	MW (12 W)	92
8	$Pd/Al_2O_3$	150/20	conventional	85

[a] Aryl chloride 7 (1.0 mmol), phenylboronic acid (8) (1.3 equiv),  $Na_2CO_3$  (3.7 equiv), TBAB (1.0 equiv), Pd/C (1 mol%, 5% w/w) or Pd/Al<sub>2</sub>O<sub>3</sub> (1 mol%, 10% w/w) catalyst, H<sub>2</sub>O (2 mL). Microwave experiments were carried out by using a CEM Discover system with a 10 mL fiber-optic probe setup. Conventionally heated experiments were performed in a preheated oil bath by selecting an appropriate bath temperature (see Figures S4, S5, and S7 in the Supporting Information). For further information see the Experimental Section. [b] The maximum nominal magnetron microwave power is given in parentheses. [c] Determined by GC-FID analysis (peak area% of biphenyl 9). Entries reflect multiple experiments (where appropriate). [d] Isolated yields.

performed in an oil bath or under microwave conditions (with or without simultaneous cooling) were seen (see Figure S6 in the Supporting Information). Isolated yields in the range of 80% were also comparable.

At this stage, we considered the use of a different support material for the Pd-metal catalyst. Since charcoal itself is a strongly microwave-absorbing material (Figure 1),<sup>[39]</sup> most of the microwave energy absorbed by the solid catalyst (Ni/C, Cu/C, Pd/C) may in fact be absorbed by the support and not by the metal impregnated on the support. Therefore, we repeated the Suzuki–Miyaura cross-coupling shown in Scheme 2 by utilizing Pd/Al<sub>2</sub>O<sub>3</sub> as a heterogeneous catalyst,<sup>[8b]</sup> with Al<sub>2</sub>O<sub>3</sub> being essentially microwave transparent (tan  $\delta = 0.006604$ ).<sup>[4b,18f]</sup> A comparison of heating profiles under microwave conditions for Pd/C and Pd/Al<sub>2</sub>O<sub>3</sub> confirmed that Pd/C is a far better microwave absorber than Pd/Al<sub>2</sub>O<sub>3</sub> (Figure 2). To achieve high conversions for the Suzuki–Miyaura cross-coupling with 1 mol % Pd/Al<sub>2</sub>O<sub>3</sub> cata-



Figure 2. Microwave heating profiles for 100 mg samples of Pd/C (10% w/w) and Pd/Al<sub>2</sub>O<sub>3</sub> (10% w/w) suspended in CCl<sub>4</sub> (2.0 mL) in a 10 mL quartz reaction vessel at constant 150 W magnetron output power (single-mode reactor, fiber-optic temperature measurement).

lyst, an increased reaction temperature of 140–150 °C and an extended reaction time of 20 min was required. Applying the originally optimized 120 °C/5 min conditions a moderate ~38 % conversion was obtained by using both microwave and oil-bath heating (Table 2, entries 5 and 6). Gratifyingly, at 150 °C, a 92 % conversion was achieved under microwave conditions (entry 7), closely matched by an 85 % conversion under oil-bath conditions when applying similar heating profiles (entry 8; see Figure S7 in the Supporting Information).

Therefore, it appears that for the Suzuki-Miyaura crosscoupling shown in Scheme 2, which utilizes a heterogeneous Pd catalyst with a microwave-transparent support, selective heating of the transition metal is either not observed or has no influence on reaction rate and selectivity. Given the fact that here the reaction medium (H<sub>2</sub>O, Na<sub>2</sub>CO<sub>3</sub>, TBAB) is strongly microwave absorbing-as evidenced by the comparatively low microwave power required for heating (Figure S5)-this is perhaps not surprising. In addition, it should be emphasized that as with the Ni/C and Cu/C chemistry described above (Scheme 1), there is substantial evidence in the literature that transition-metal-catalyzed cross-coupling reactions that utilize Pd/C as a catalyst do in fact involve homogeneous Pd species.<sup>[37,40,41]</sup> The insoluble Pd/C catalyst acts as a reservoir of soluble, active Pd species, generated under the reaction conditions by chemical interaction of the catalyst with one or more of the components of the liquid phase.<sup>[40,41]</sup> Thus, although the used metal catalyst is of a heterogeneous nature, it is not clear if selective heating of the catalyst by microwave irradiation can have an influence on a subsequent reaction step occurring in solution phase. The results obtained herein are in agreement with our recent work on Heck-Mizoroki couplings catalyzed by Pd/C.<sup>[31]</sup>

Hydrogenation reactions by using Pd/C and Pd/Al<sub>2</sub>O<sub>3</sub> catalysts: At this point, it became evident that in the cross-coupling chemistry examples described above in Schemes 1 and 2, specific microwave effects by selective heating of the heterogeneous catalysts do not play a role, because 1) there were generally too many other microwave absorbing species present in the reaction mixture masking any "superheating" of the catalyst and/or 2) since the mechanism of these crosscouplings is likely to be of a homogeneous nature; therefore, the rate-determining step may occur in solution phase and not on the surface of the microwave absorbing catalyst. Therefore, we considered hydrogenation reactions as almost ideal model transformations to study the role of specific microwave effects resulting from selective catalyst heating. Hydrogenations involving molecular hydrogen and a heterogeneous precious-metal catalysts are genuinely heterogeneous in nature, with the hydrogenation step occurring at the surface of the heterogeneous catalyst.[42] Since microwavetransparent hydrogen is the only required reagent and the solvent can often be of an unpolar-low microwave absorbing-nature, the hydrogenation of standard olefins appeared to be an ideal model reaction to evaluate the occurrence of specific microwave effects and the role of selective catalyst heating. In fact, recently published work by Vanier comparing conventional and microwave-heated hydrogenations catalyzed by Pd/C for a variety of substrates has indicated a special role that microwave irradiation plays in these processes (apart from heating).<sup>[17]</sup> Applying otherwise identical reaction conditions (solvent, time, temperature, hydrogen pressure), significant differences in conversions between conventionally heated and microwave-irradiated hydrogenations with Pd/C were reported.<sup>[17]</sup> To gain further insight into the potential involvement of selective heating effects in these heterogeneous hydrogenations, we have reinvestigated two of the examples described in the original reference.

Our first case study involved the hydrogenation of diene **10** to the saturated butane **11** employing low-absorbing ethyl acetate (tan  $\delta = 0.059$ )<sup>[24]</sup> as the solvent and a standard 10% Pd/C catalyst (Scheme 3). By using an 80°C reaction



Scheme 3. Hydrogenation of (E,E)-1,4-diphenyl-1,3-butadiene (10).<sup>[17]</sup>

temperature, 50 psi (3.5 bar) hydrogen pressure and a 1 mol% Pd catalyst loading, Vanier has reported full conversion to **11** in the microwave run, relative to only 55% by applying conventional heating in a preheated oil bath after a 5 min reaction time (hold time). The temperature profiles were carefully matched by using a fiber-optic probe setup to ensure the validity of the results.<sup>[17]</sup>

We have repeated the hydrogenation of diene 10 by following the conditions reported by Vanier as close a possible, by using the identical pre-pressurized single-mode microwave reactor setup fitted with an internal fiber-optic temperature probe.<sup>[17,18c]</sup> The progress of the hydrogenation could be nicely followed online by monitoring the hydrogen pressure decrease in the sealed-vessel experiments and offline by GC-FID monitoring. Indeed, in the first trials, we have observed that the microwave experiments at 80 °C provided complete conversion to butane 11 (97% isolated yield), whereas in the conventionally heated runs that utilize a preheated oil bath at the same internal temperature and apply a very similar temperature profile (see Figure S8 in the Supporting Information) the conversions were significantly lower (70-80%). In addition, the formation of a partially hydrogenated product 12,<sup>[43]</sup> not mentioned in the original study,<sup>[17]</sup> was also observed. These experiments were repeated numerous times but the results essentially remained unchanged.

After considerable experimentation and variations of conditions we realized that the stirring speed applied in both types of heating experiments plays a critical role on the outcome of the hydrogenation processes. A systematic analysis of the stirring speed on the hydrogenation of diene **10** under both microwave and oil-bath conditions is presented in Table 3, with each experiment being repeated three times to

Table 3. Comparison of microwave heating and conventional heating in dependence on the stirring speed for the hydrogenation of (E,E)-1,4-diphenyl-1,3,-butadiene (Scheme 3).<sup>[a]</sup>

Entry	Heating method <sup>[b]</sup>	Stirring rate	Conversion/selectivity <sup>[c]</sup> [%] 10/11/12
1	MW	_	26/51/23
2	MW	low	1/80/19
3	MW	medium	0/>99/0
4	MW	high	0/>99/0
5	conventional	_	36/43/21
6	conventional	100	22/57/21
7	conventional	200	17/60/23
8	conventional	400	11/66/23
9	conventional	800	1/84/15
10	conventional	1200	0/>99/0

[a] Diene **10** (0.5 mmol), Pd (1 mol%, 10% Pd/C), H<sub>2</sub> (4 bar), 80°C, EtOAc (2 mL), 20 W maximum magnetron output power. [b] Microwave experiments were carried out by using a CEM Discover system with a 10 mL fiber-optic probe setup in conjunction with a gas-loading system. Conventionally heated experiments were performed by using the same setup in a preheated oil bath by selecting an appropriate bath temperature (see Figure S8 in the Supporting Information). For further information see the Experimental Section. [c] Product composition analyzed by GC-FID (peak area%). Entries reflect the median values of three experiments (s.d.  $\pm 5$ %).

ensure statistical relevance. For the microwave experiments, the four available stirring levels on the single-mode reactor (off, low, medium, high)<sup>[44]</sup> were compared to a range of stirring speeds (0-1200 rpm) available on the magnetic stirrer/ hotplate used to heat the oil bath for the conventionally heated runs. As can be clearly seen, stirring plays a dominant role on these hydrogenations. Without stirring, comparatively moderate conversions were experienced for both the microwave (74%, entry 1) and the oil-bath runs (64%, entry 5). Going to higher stirring speeds consistently improved conversions in both heating modes. It should be particularly emphasized that full conversion to the desired butane 11 was also obtained in a conventionally heated experiment (Table 3, entry 10). The perhaps surprisingly large influence that the stirring speed exerts on the outcome of these hydrogenations<sup>[45]</sup> can be interpreted as a classic example of mass-transfer limitation, as hydrogen contained in the top part of the reaction vial (headspace) needs to diffuse to the liquid phase in the bottom part in which the catalytic process occurs and hydrogen is consumed.<sup>[46]</sup> Increased stirring influences the gas-liquid interfacial area and thus effects the hydrogenation rate, which is a known phenomenon in hydrogenation chemistry.<sup>[46]</sup> From a chemical engineering standpoint it is apparent, that the 10 mL cylindrical tube used for most microwave experiments in single-mode reactors today, in particular, in combination with a comparatively ineffective magnetic stirring system, is not an ideal reactor for gaseous transformations of this type.

Following the arguments made above for the Suzuki– Miyaura cross-coupling we have additionally evaluated the use of a  $Pd/Al_2O_3$  catalyst for the hydrogenation of diene **10**. The results were almost identical to those observed for Pd/C, with no indication of any selective heating effects on CHEMISTRY

the Pd-metal catalyst (see Table S1 in the Supporting Information).

As a final example in this investigation we have looked at the more challenging hydrogenation of cholesterol (13) to cholestanol (14) (Scheme 4),<sup>[47]</sup> since in this case a dramatic difference between the microwave hydrogenation compared to the oil-bath run was reported by Vanier.<sup>[17]</sup> While under



Scheme 4. Hydrogenation of cholesterol (13).<sup>[17]</sup>

microwave conditions with simultaneous cooling full conversion was obtained, the conventional hydrogenation employing otherwise identical reaction conditions produced only 3% product.<sup>[17]</sup> In our hands, the major effect that magnetic stirring plays in these transformations again became immediately evident (Table 4). As in the case of diene 10, we found that full conversion to the reduced product 14 at 80°C and 4 bar H<sub>2</sub> pressure could also be achieved by employing conventional heating with an appropriate stirring speed that ensures adequate mass transfer of H<sub>2</sub> from the gas to the liquid phase. Interestingly, in this case, in which only one equivalent of H<sub>2</sub> is required, the conversions after 5 min without stirring were very low (<10%) for both heating modes (Table 4, entries 1 and 5). Note that in our hands microwave experiments with a high stirring rate led to full conversion without the necessity to utilize the simultaneous cooling option (Table 4, entry 4).

Table 4. Comparison of microwave heating and conventional heating in dependence on the stirring speed for the hydrogenation of cholesterol (13) (Scheme 4).<sup>[a]</sup>

Entry	Heating method <sup>[b]</sup>	Stirring rate	Conversion <sup>[c]</sup> [%]
1	MW	_	9
2	MW	low	95
3	MW	medium	94
4	MW	high	>99
5	conventional	0	5
6	conventional	100	49
7	conventional	200	89
8	conventional	400	93
9	conventional	800	97
10	conventional	1200	>99

[a] Cholesterol (13) (0.5 mmol), Pd (1 mol%, 10% Pd/C), H<sub>2</sub> (4 bar), 80 °C, EtOAc (2 mL), 20 W maximum magnetron output power. [b] Microwave experiments were carried out by using a CEM Discover system with a 10 mL fiber-optic probe setup in conjunction with a gas-loading system. Conventionally heated experiments were performed by using the same setup in a preheated oil bath by selecting an appropriate bath temperature (see Figure S9 in the Supporting Information). For further information see the Experimental Section. [c] Conversion analyzed by GC-FID (peak area%). Entries reflect the median values of three experiments (s.d.  $\pm 4$ %).

As the stirring speeds in the microwave reactor are unknown,<sup>[44]</sup> it is not possible to directly correlate the results obtained under microwave conditions with the conversions seen in the oil-bath experiments. In our opinion, however, it is evident that stirring plays a dominant role in these hydrogenations and it, therefore, appears likely that the previously observed differences between conventionally and micro-

wave heated hydrogenations of diene **10** and cholesterol  $(13)^{[17]}$  were in fact due to different stirring speeds in the two sets of heating experiments, rather than to a selective heating effect of the catalyst.

To confirm if—in addition to the effect of stirring—selective heating of the Pd/C catalyst by

microwave irradiation plays any role in this transformation, an experiment that utilizes simultaneous cooling (see above)<sup>[34-36]</sup> of the reaction mixture was performed. By using the microwave-assisted hydrogenation of diene 10 under "low" stirring conditions leading to an incomplete conversion as a reference (Table 3, entry 2), the same experiment was repeated with simultaneous cooling at the same 80°C internal reaction temperature by using compressed air. In contrast to the standard microwave experiment, this allowed a considerably higher amount of microwave power to be delivered to the reaction mixture and the Pd/C catalyst (55 versus 20 W, see Figure S10). However, the outcome of the hydrogenation was more or less identical with only minor changes (<5%) in conversion/selectivity being observed. The involvement of any significant contribution of selective heating of the Pd/C catalyst in these hydrogenation reactions therefore seems unlikely.

In a final set of experiments both olefinic substrates **10** and **13** were also hydrogenated over a Pd/C catalyst in a continuous flow high pressure/high temperature hydrogenation device (H-Cube).<sup>[48]</sup> Employing 80 °C and a substrate concentration of 0.1 M in ethyl acetate full conversions were achieved up to a flow rate of  $0.5 \text{ mLmin}^{-1}$ , which resulted in near quantitative isolated product yields (see Experimental Section for details).

To support the hypothesis that selective heating of the generally strongly microwave-absorbing Pd catalysts does not play a major role in the kinetics of the hydrogenations shown in Schemes 3 and 4 we have additionally studied the morphology of the catalysts exposed to microwave irradiation and conventional heating by SEM. Strong superheating of the conducting Pd particles on the catalyst surface by interaction with a microwave field to temperatures above the measured bulk temperatures of 80 °C may be evidenced by modifications of either the Pd species present on the support and/or a catalyst surface restructuring of the heterogeneous catalyst particles (sintering).<sup>[8b,12b,18c,49]</sup> In the case of the hydrogenation reactions of diene **10** at 80 °C bulk temperature no detectable changes in the morphology of the used cat-

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alyst particles were seen for both Pd/C and Pd/Al<sub>2</sub>O<sub>3</sub> when comparing microwave and oil-bath conditions. Even for catalyst samples exposed to high levels of microwave power in a microwave transparent medium (as in Figure 2) no differences in particle morphology to catalysts exposed to conventional heating were seen (see Figures S11 and S12 in the Supporting Information).

#### Conclusion

In summary, we have performed a critical investigation of several transition-metal-catalyzed carbon-carbon/carbonheteroatom cross-coupling protocols and hydrogenation reactions carried out by microwave heating employing strongly microwave-absorbing heterogeneous catalysts. Employing a suitable reactor equipped with internal fiber-optic temperature probes, comparison studies between microwave and conventional heating at the same reaction temperature were performed, which demonstrated that essentially no differences between the two heating modes existed. Anticipated changes in reactivity and/or selectivity resulting from selective heating of the generally strongly microwave absorbing catalysts ("specific microwave effects") were not seen. We ascribe this to the fact that although the heterogeneous metal catalyst itself can be a strongly microwave absorbing material when irradiated under suitable conditions, for the actual reaction mixtures typically containing several other microwave-absorbing components (solvent, substrates, ligand, additives, bases) any effect derived from selective heating of the comparatively small quantities of heterogeneous metal catalyst will be masked, even when using a lowabsorbing solvent, such as ethyl acetate. In general, the selective heating of solid-metal catalysts under microwave conditions is a rather complex phenomenon depending strongly on the type of support, particle size (surface-tovolume ratio), electromagnetic field strength (power density), and a variety of other factors. More research is therefore required to ascertain under what conditions microwaveinduced selective heating effects in metal-catalyzed solidliquid reactions can be exploited for organic synthesis.

Additionally, we have observed that for hydrogenation reactions agitation plays a major role in controlling mass transfer from the gas to the liquid phase, and therefore significantly influences the rate of hydrogenation. Careful attention must thus be given to the stirring rate in microwaveassisted hydrogenations, in particular when comparisons with conventionally heated experiments are performed.

### **Experimental Section**

**General remarks**: <sup>1</sup>H NMR spectra were recorded on a Bruker 300 MHz instrument. <sup>13</sup>C NMR spectra were recorded on the same instrument at 75 MHz. Chemical shifts ( $\delta$ ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, t, q, and m are used to indicate singlet, doublet, triplet, quadruplet, and multiplet. Low-resolution mass spectra were obtained on an Agilent 1100 LC/MS instrument by using at-

mospheric pressure chemical ionization (APCI) in positive or negative mode. GC-FID analysis was performed on a Trace-GC (ThermoFisher) with a flame ionization detector by using a HP5 column ( $30 \text{ m} \times 0.250 \text{ mm} \times 0.025 \text{ µm}$ ). After 1 min at 50 °C, the temperature was increased in 25 °Cmin<sup>-1</sup> steps up to 300 °C and kept at 300 °C for 4 min. The detector gas for the flame ionization is H<sub>2</sub> and compressed air (5.0 quality). GC-MS spectra were recorded by using a Thermo Focus GC coupled with a Thermo DSQ II (EI, 70 eV). A HP5-MS column ( $30 \text{ m} \times 0.250 \text{ mm} \times 0.025 \text{ µm}$ ) was used with helium as the carrier gas (1 mLmin<sup>-1</sup> constant flow). The injector temperature was set to 280 °C. After 1 min at 50 °C, the temperature was increased in 25 °Cmin<sup>-1</sup> steps up to 300 °C and kept at 300 °C for 4 min.

Microwave irradiation experiments were generally carried out in a CEM Discover instrument with appropriate internal fiber-optic temperature control by using 10 mL Pyrex vials.<sup>[28]</sup> Zinc insertion reactions were carried out in a Emrys Optimizer EXP (Biotage AB, Uppsala, Sweden). Flow hydrogenations were performed in an H-Cube from Thales Nanotechnology (Budapest, Hungary).<sup>[48]</sup> Flash chromatography separations were performed on a Biotage SP1 instrument by using petroleum ether/ ethyl acetate mixtures as the eluent. All products synthesized in this study are known in the literature and have been identified and characterized by <sup>1</sup>H NMR spectroscopy and MS analysis. Ni/C<sup>[13]</sup> and Cu/C<sup>[15]</sup> were prepared according to literature protocols from activated charcoal Darco KB-G (Aldrich, catalog no. 675326). 5% Pd/C (E 104 CA/W 5% Pd, catalog no. 643181-10G), 10 % Pd/C (catalog no. 205699-10G) and 10 % Pd/  $Al_2O_3$  (catalog no. 76000–10G) were also obtained from Aldrich. For the insertion reaction zinc dust from Strem (catalog no. 93-3060, 325 mesh) was used. All other chemicals were obtained from Aldrich, Acros Organics, or Alfa Aesar and used as received.

Preparation of 4-tolyl-zinc iodide: Zinc dust (817 mg, 12.5 mmol) and anhydrous LiCl (211 mg, 5 mmol) were placed into a flame-dried, argonpurged 10 mL Biotage microwave process vial. The vial was capped and dry THF (1.5 mL) was added. The slurry was stirred and 1,2-dibromoethane (0.03 mL, 2.18 mg, 0.35 mmol) was added through the septum. The reaction mixture was heated until ebullition. Subsequently, trimethylchlorosilane (0.01 mL, 8.58 mg, 0.08 mmol) was added and the mixture was again heated until ebullition (in some cases heating was not necessary because ebullition started spontaneously). In the next step, 4-iodotoluene (545 mg, 2.5 mmol) was dissolved in dry THF (1.0 mL) and added to the reaction mixture. The sealed microwave vial was placed into an Emrys Optimizer EXP microwave reactor and subjected to microwave irradiation at 150°C for 30 min (pre-stirring 30 s, sample absorption: normal). After the microwave irradiation was completed, the remaining zinc dust was allowed to sediment and a sample was taken, hydrolyzed, and subjected to GC-FID analysis (in every case the conversion was >97%). The remaining solution was taken up into a syringe and used for the subsequent Negishi reaction.

Negishi coupling of aryl chloride 1 with 4-tolyl-zinc iodide (Scheme 1a): Under a positive argonflow, Ni/C (135 mg, 8.2 mol %, 3.6 % Ni/C loading (w/w), 0.082 mmol Ni) and triphenylphosphine (70 mg, 0.27 mmol) were put into a flame-dried, argon-purged 10 mL CEM microwave process vial. The vial was capped with a Teflon-coated septum and an alumina crimp, dry 1,4-dioxane (1.0 mL) was added by a cannula and syringe and the reaction mixture was stirred for 20 min. n-Butyllithium (0.06 mL, 2.5 M in hexane, 0.15 mmol) was added dropwise and the reaction mixture was stirred for another 5 min. The vial was opened and under a positive argon flow 4-chlorobenzonitrile (1) (137 mg, 1.0 mmol) and 4-tolyl-zinc chloride (2) (1.0 M in dry THF, 1.5 mL, 1.5 mmol, see above) were added and the vial sealed tight by using the CEM Discover pressure/fiber-optic attenuator<sup>[28]</sup> and placed into the CEM discover microwave unit or a preheated oil bath to be heated under the following conditions (see Figure S1 in the Supporting Information): 1) Microwave: 1 min 27 W maximum microwave power, 4 min 10 W maximum microwave power, and 15 min 17 W of maximum microwave power with a set temperature of 150°C. Stirring was set at high. 2) Oil bath: The oil-bath temperature was set to 190°C and stirring was set to 400 rpm. The vial assembly was put into the oil bath for 20 min, which included 5 min for an inner temperature of 150°C to be reached. This temperature remained constant

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 $(\pm 2^{\circ}C)$  for the following 15 min (hold time). After the reaction mixture was cooled down to ambient temperature, a 100 µL sample was transferred into a syringe, filtered by using a syringe filter, diluted with EtOAc (1 mL) and subjected to GC-MS analysis. For the purpose of isolation, the reaction mixture was filtered through a pad of Celite that was then washed with EtOAc (50 mL). The organic phase was washed with an aqueous H2O2 solution (10 wt %, 50 mL). The phases were separated, the aqueous phase was re-extracted with EtOAc (20 mL), and the combined organic phases were dried over Mg<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated and the obtained residue was taken up in a small amount of EtOAc and transferred to a silica-samplet, which was then dried for 2 h at 70 °C. Subsequent automated silica-gel flash chromatography with petroleum ether/EtOAc (0 to 40% gradient) as the eluent gives diaryl 3 as a paleyellow solid with the following physical properties: M.p. 101 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta = 2.45$  (s, 3H; CH<sub>3</sub>), 7.32 (d, J = 8.0 Hz, 2H; aromatic), 7.52 (d, J=8.0 Hz, 2H; aromatic), 7.68 (d, J=8.6 Hz, 2H; aromatic), 7.72 ppm (d, J = 8.6 Hz, 2H; aromatic); <sup>13</sup>C NMR (75 MHz,  $\mathsf{CDCl}_3)\!\!:\; \delta\!=\!145.6,\; 138.8,\; 136.3,\; 132.6,\; 129.9,\; 127.5,\; 127.1,\; 119.1,\; 110.6,\;$ 21.2 ppm; GC-EIMS: *m*/*z* (%): 193 (100), 178 (11), 91 ppm (9).

Ullmann-type diaryl ether formation of aryl bromide 4 and phenol 5 (Scheme 1b, Table 1): Cu/C (30.0 mg, 3.8 mol %, 8.1 % Cu/C (w/w), 0.038 mmol Cu), 4-hydroxyanisole (5) (124.0 mg, 1.0 mmol), Cs<sub>2</sub>CO<sub>3</sub> (390.0 mg, 1.2 mmol), and 1,10-phenanthroline (90.0 mg, 0.5 mmol) were placed into a flame-dried, argon-purged 10 mL CEM microwave process vial equipped with a magnetic stir bar. The vial was capped with a Teflon-coated septum and an alumina crimp, purged with argon and dry 1,4-dioxane (2 mL) was added. The reaction mixture was stirred for 30 min at 250 rpm. The vial was opened and under a positive argon flow 4-bromoacetophenone (4) (298.6 mg, 1.5 equiv) was added and the vial was sealed tight by using the CEM Discover pressure/fiber-optic attenuator<sup>[28]</sup> and placed into the CEM Discover microwave unit or a preheated oil bath to be heated under the following conditions (see Figure S2 in the Supporting Information): 1) Microwave: 3 min ramp time at 32 W maximum microwave power, 3 min ramp time at 25 W maximum microwave power, and 25 W maximum microwave power for the indicated hold times (Table 1). Stirring was set at high. The maximum temperature was set to 150 °C. 2) Oil bath: The oil-bath temperature was set to 170 °C and stirring was set to 400 rpm. The vial was put into the oil bath for the indicated hold time plus 6 min ramp time, which was needed to reach an inner temperature of 150 °C. This temperature remained constant ( $\pm$ 4°C) for the following hold time. After the reaction was stopped and cooled down to ambient temperature, a 100 µL sample of the reaction mixture was transferred into a syringe, filtered by using a syringe filter, diluted with EtOAc (1 mL), and subjected to GC-MS analysis. For the purpose of isolation, the reaction mixture was filtered through a pad of Celite, which was washed with EtOAc (50 mL). The filtrate was concentrated under reduced pressure, the residue was taken up in a small amount of EtOAc and transferred to a silica-samplet, which was dried for 2 h at 70°C. Subsequent automated silica-gel flash chromatography with petroleum ether/EtOAc (0-20%) gave diarylether 6 as white solid. M.p. 49°C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta = 2.57$  (s, 3H; C(O)CH<sub>3</sub>), 3.84 (s, 3H; OCH<sub>3</sub>), 6.99 (m, 6H; aromatic), 7.93 ppm (d, 2H; aromatic); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta = 196.7$ , 162.9, 156.7, 148.5, 131.4, 130.6, 121.7, 116.4, 115.1, 55.7, 26.4 ppm. GC-EIMS: m/z (%): 242 (67), 227 (100).

Suzuki–Miyaura coupling of aryl chloride 7 with phenylboronic acid (8) (Scheme 2, Table 2): Aryl chloride 7 (142.5 mg, 1.0 mmol), phenylboronic acid (8) (158.5 mg, 1.3 mmol), Na<sub>2</sub>CO<sub>3</sub> (392 mg, 3.7 mmol), TBAB (322 mg, 1.0 mmol), 5% Pd/C (48 mg, 0.01 mmol Pd, 56% water) or 10% Pd/Al<sub>2</sub>O<sub>3</sub> catalyst (10.6 mg, 0.01 mmol Pd), water (2 mL), and a magnetic stir bar were placed in a 10 mL CEM microwave process vial. The vial was sealed tight by using the CEM Discover pressure/fiber-optic attenuator<sup>[28]</sup> and placed into the CEM Discover microwave unit or a preheated oil bath to be heated under the conditions given in Table 2. Before the reaction was run, the mixture was stirred for 20 s to ensure sufficient mixing of the reagents. After allowing the reaction mixture to cool down to RT, a 50 µL sample was transferred into a syringe, filtered by using a syringe filter, diluted with EtOAc (1 mL) and subjected to GC-MS analysis. For the purpose of isolation, the reaction vessel was

opened and the contents poured into a separation funnel. Water (30 mL) and ethyl acetate (30 mL) were added and the organic material extracted and removed. After further extraction of the aqueous layer with ethyl acetate, combining the organic washings and drying them over MgSO<sub>4</sub>, the solvent was removed under reduced pressure, leaving the crude biaryl product **9**. The product was purified and isolated by chromatography with hexane/ethyl acetate as eluent to provide the pure substance. M.p. 87 °C (lit.<sup>[50]</sup> 87–88 °C); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  =3.87 (s, 3 H; OCH<sub>3</sub>), 6.99 (d, *J*=8.8 Hz, 2H; aromatic), 7.34 (t, *J*=7.4 Hz, 1H; aromatic), 7.43 (t, *J*=7.7 Hz, 2H; aromatic), 7.54–7.59 ppm (m, 4H; aromatic); MS (pos. APCI): *m/z* (%): 184 (100) [*M*+1]<sup>+</sup>.

Hydrogenation of diene 10 and cholesterol (13) (Schemes 3 and 4, Tables 3 and 4): General procedure for batch experiments: 10% Pd/C (5.3 mg, 0.005 mmol) in a 10 mL CEM microwave process vial was added to a solution of 1,4-diphenyl-1,3-butadiene (10, 103 mg, 0.500 mmol) or cholesterol (13, 193 mg, 0.500 mmol) in EtOAc (2.0 mL). The vessel was flushed with argon for 2 min before being sealed tight by using the CEM Discover pressure/fiber-optic attenuator<sup>[28]</sup> and placed into the CEM Discover microwave unit or a preheated oil bath to be heated under the conditions given in Tables 3 and 4. A gas addition accessory for the microwave unit was used for H2 loading.[18c] The reaction vial was connected to a H<sub>2</sub> cylinder and to an external pressure controlling system equipped with a valve and an exit tube for venting the vial at the end of the reaction. The reaction mixture was purged two times with hydrogen, charged to 4 bar, and then closed off to the source of hydrogen. The reaction was heated in a preheated oil bath or by microwave irradiation to 80°C and held for 5 min (see Figures S8 and S9 in the Supporting Information). Upon cooling to ambient temperature, internal gas was released and the reaction mixture was filtered through Celite and evaporated to give the desired products 11/12 and 14. For the GC-MS analysis of cholesterol, a microwave-assisted derivatization protocol was carried out by employing acetic anhydride and pyridine (3:2 v/v) at 100 °C for 25 min.[51]

*1,4-Diphenylbutane* (11): White solid; m.p. 53 °C (lit.<sup>[17,52]</sup> 52–53 °C); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta = 1.72$  (dt, J = 7.0, 3.2 Hz, 4H; 2CH<sub>2</sub>), 2.62 (t, J = 6.7 Hz, 4H; 2CH<sub>2</sub>), 7.20–7.24 (m, 6H; aromatic), 7.28–7.34 ppm (m, 4H; aromatic). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta = 142.6$ , 128.4, 128.2, 125.6, 35.8, 31.1 ppm; MS (pos. APCI): m/z (%): 210 (100) [M+1]<sup>+</sup>.

*1,4-Diphenyl-1-butene* (**12**): Comparison of the <sup>1</sup>H NMR spectrum with literature data<sup>[53]</sup> confirmed the identity of this compound. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$ =2.74–2.82 (m, 2H; CH<sub>2</sub>); 3.02 (t, *J*=8.2 Hz, 2H; CH<sub>2</sub>), 6.40 (dt, *J*=15.8, 6.6 Hz, 1H; CH), 6.67 (d, *J*=15.8 Hz, 1H; CH), 7.51–7.27 ppm (m, 10H; aromatic).

Cholestanol (14): White crystals; m.p. 141 °C (lit.<sup>[54]</sup> 142 °C); the <sup>1</sup>H NMR spectrum of this sample was in full agreement with the spectrum obtained from a commercial sample of 14; MS (pos. APCI): m/z (%): 388 (100)  $[M+1]^+$ .

Flow hydrogenations of diene 10 and cholesterol (13): General procedure:<sup>[48]</sup> A 25 mL stock solution of diene 10 (0.1 M) and cholesterol (13) (0.1 M) in EtOAc was prepared in a glass vial. The reaction parameters (0.5 mL min<sup>-1</sup> flow rate, full H<sub>2</sub>) were selected on the H-Cube fitted with a 10% Pd/C CatCart and the processing was started, whereby initially only pure solvent was pumped through the system until the instrument had achieved the desired reaction parameters and stable processing is assured. At that point, the sample inlet line was switched to the vial containing the substrate. For preparative experiments, the total reaction mixture (5 mL, 0.5 mmol) is collected and the cartridge subsequently washed with pure solvent for 5 min to remove any substrate/product still adsorbed on the catalyst. Evaporation of the solvent provides the desired products 12 (97% yield) and 14 (95% yield), respectively, which were isolated and characterized as described above.

**Determination of metal loading in Ni/C and Cu/C catalysts by ICP-MS**: Ni/C and Cu/C samples from the freshly prepared catalysts (dried at 120°C) were analyzed in the following way: Aliquots (~50 mg, weighed to 0.1 mg) of the samples were mixed with HNO<sub>3</sub> conc. (5 mL) and digested in an MLS Ultraclave III microwave reactor (EMLS/Milestone) at 250°C for 30 min. The digested samples were further diluted and Ni and Cu determined with ICP-MS.

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**SEM of Pd/C and Pd/Al<sub>2</sub>O<sub>3</sub> catalysts**: Microscopy was performed on a SEM ZEISS Ultra55 high-resolution scanning microscope equipped with an in lens SE (secondary electron) detector for high contrast topography imaging and an in-column ESB (electron-selective backscattered electron) detector for low kV high resolution imaging. The microscope is equipped with an energy-dispersive X-ray spectrometer (EDAX Genesis) for elemental analysis.

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- M. Hajek in *Microwaves in Organic Synthesis*, 2nd ed. (Ed.: A. Loupy), Wiley-VCH, Weinheim, 2006, pp. 615–652.
- [2] a) B. Desai, C. O. Kappe, *Top. Curr. Chem.* 2004, 242, 177; b) B. Toukoniitty, J.-P. Mikkola, D. Y. Murzin, T. Salmi, *Appl. Catal. A* 2005, 279, 1.
- [3] For general reviews on microwave-assisted transition-metal catalysis, see: a) P. Appukkuttan, E. Van der Eycken, *Eur. J. Org. Chem.* 2008, 1133; b) P. Nilsson, K. Olofsson, M. Larhed, *Top. Curr. Chem.* 2006, 266, 103; c) N. E. Leadbeater, *Chem. Commun.* 2005, 2881; d) C. O. Kappe, D. Dallinger, *Mol. Diversity* 2009, *13*, 71; e) M. Larhed, C. Moberg, A. Hallberg, *Acc. Chem. Res.* 2002, *35*, 717.
- [4] a) M. Gupta, E. Wong Wei Leong, *Microwaves and Metals*, Wiley, New York, **2007**; b) D. R. Baghurst, D. M. P. Mingos, *Chem. Soc. Rev.* **1991**, *20*, 1; c) C. Gabriel, S. Gabriel, E. H. Grant, B. S. Halstead, D. M. P. Mingos, *Chem. Soc. Rev.* **1998**, *27*, 213.
- [5] a) M. G. Organ, S. Mayer, F. Lepifre, B. N'Zemba, *Mol. Diversity* 2003, 7, 211; b) G. Palmisano, W. Bonrath, L. Boffa, D. Garella, A. Barge, G. Cravotto, *Adv. Synth. Catal.* 2007, *349*, 2338; c) X. Xie, J. Lu, B. Chen, J. Han, X. She, X. Pan, *Tetrahedron Lett.* 2004, *45*, 809.
- [6] R. K. Arvela, N. E. Leadbeater, Org. Lett. 2005, 7, 2101.
  [7] A. Stadler, B. H. Yousefi, D. Dallinger, P. Walla, E. Van der Eycken, N. Kaval, C. O. Kappe, Org. Process Res. Dev. 2003, 7, 707.
- [8] a) M. S. Pillai, A. Wali, S. Satish, US Patent 200300625, 2003; b) P.
   He, S. J. Haswell, P. D. I. Fletcher, *Appl. Catal. A* 2004, 274, 111.
- [9] a) I. R. Baxendale, C. M. Griffith-Jones, S. V. Ley, G. K. Tranmer, *Chem. Eur. J.* **2006**, *12*, 4407; b) A. K. Sharma, J. K. Gowdahalli, S. Amin, *J. Org. Chem.* **2007**, *72*, 8987; c) J. Gil-Moltó, S. Karlström, C. Najera, *Tetrahedron* **2005**, *61*, 12168; d) M. R. Pitts, *Platinum Met. Rev.* **2008**, *52*, 64.
- [10] C. Schmöger, T. Szuppa, A. Tied, F. Schneider, A. Stolle, B. Ondruschka, *ChemSusChem* 2008, 1, 339.
- [11] a) G. Shore, S. Morin, M. G. Organ, Angew. Chem. 2006, 118, 2827; Angew. Chem. Int. Ed. 2006, 45, 2761; b) E. Comer, M. G. Organ, J. Am. Chem. Soc. 2005, 127, 8160; c) G. Shore, M. G. Organ, Chem. Commun. 2008, 735; d) G. Shore, S. Morin, D. Mallik, M. G. Organ, Chem. Eur. J. 2008, 14, 1351.
- [12] a) B. M. Choudary, S. Madhi, N. S. Chowdari, M. L. Kantam, B. Sreedhar, J. Am. Chem. Soc. 2002, 124, 14127; b) K. Mennecke, R. Cecilia, T. N. Glasnov, S. Gruhl, C. Vogt, A. Feldhoff, M. A. L. Vargas, C. O. Kappe, U. Kunz, A. Kirschning, Adv. Synth. Catal. 2008, 350, 717; c) A. Barau, V. Budarin, A. Caragheorgheopol, R. Luque, D. J. Macquarrie, A. Prelle, V. S. Teodorescu, M. Zaharescu, Catal. Lett. 2008, 124, 204; d) J. Demel, S.-E. Park, J. Čejka, P. Štěpnička, Catal. Today 2008, 132, 63.
- [13] B. H. Lipshutz, B. A. Frieman, C.-T. Lee, A. Lower, D. M. Nihan, B. R. Taft, *Chem. Asian J.* **2006**, *1*, 417.
- [14] a) T. A. Butler, E. C. Swift, B. H. Lipshutz, Org. Biomol. Chem. 2008, 6, 19; b) B. H. Lipshutz, T. Butler, E. Swift, Org. Lett. 2008, 10, 697.

- [15] B. H. Lipshutz, J. B. Unger, B. R. Taft, Org. Lett. 2007, 9, 1089.
- [16] a) U. Kazmaier, S. Hähn, T. D. Weiss, R. Kautenburger, W. F. Maier, *Synlett* **2007**, 2579; b) S. P. Andrews, A. F. Stepan, H. Tanaka, S. V. Ley, M. D. Smith, *Adv. Synth. Catal.* **2005**, *347*, 647.

FULL PAPER

- [17] G. S. Vanier, Synlett 2007, 0131.
- [18] a) E. Heller, W. Lautenschläger, U. Holzgrabe, *Tetrahedron Lett.* 2005, 46, 1247; b) A. N. Parvulescu, E. Van der Eycken, P. A. Jacobs, D. E. De Vos, J. Catal. 2008, 255, 206; c) L. Piras, E. Genesio, C. Ghiron, M. Taddei, *Synlett* 2008, 1125; d) U. R. Pillai, E. Sahle-Demessie, R. S. Varma, *Green Chem.* 2004, 6, 295; e) B. Toukoniitty, O. Roche, J.-P. Mikkola, E. Toukoniitty, F. Klingstedt, K. Eränen, T. Salmi, D. Y. Murzin, *Chem. Eng. J.* 2007, *126*, 103; f) B. Toukoniitty, J. Wärnå, J.-P- Mikkola, M. Helle, H. Saxén, D. Y. Murzin, T. Salmi, *Chem. Eng. Process.* 2009, 48, 837; g) Y.-M. Ma, X.-Y. Wei, X. Zho, K.-Y. Cai, Y.-L. Peng, R.-L. Xie, Y. Zong, Y.-B. Wei, Z.-M. Zong, *Energy Fuels* 2009, 23, 638.
- [19] a) R. Cecilia, U. Kunz, T. Turek, *Chem. Eng. Process.* 2007, *46*, 870;
  b) M. H. C. L. Dressen, B. H. P. van de Kruijs, J. Meuldijk, J. A. J. M. Vekemans, L. A. Hulshof, *Org. Process Res. Dev.* 2007, *11*, 865;
  c) A. H. Whittaker, D. M. P. Mingos, *J. Chem. Soc. Dalton Trans.* 2000, 1521;
  d) W. L. Perry, D. W. Cooke, J. D. Katz, A. K. Datye, *Catal. Lett.* 1997, *47*, 1.
- [20] a) H. Will, P. Scholz, B. Ondruschka, *Chem. Ing. Tech.* 2002, 74, 1057 and references therein; b) T. Durka, T. Van Gerven, A. Stan-kiewicz, *Chem. Eng. Technol.* 2009, 32, 1.
- [21] B. H. Lipshutz, B. R. Taft, Angew. Chem. 2006, 118, 8415; Angew. Chem. Int. Ed. 2006, 45, 8235.
- [22] B.H. Lipshutz, Adv. Synth. Catal. 2001, 343, 313, and references therein.
- [23] B. H. Lipshutz, P. A. Blomgren, J. Am. Chem. Soc. 1999, 121, 5819.
- [24] C. O. Kappe, Angew. Chem. 2004, 116, 6408; Angew. Chem. Int. Ed. 2004, 43, 6250.
- [25] T. Razzaq, J. M. Kremsner, C. O. Kappe, J. Org. Chem. 2008, 73, 6321. See in particular the Supporting Information, Figure S14 and S15.
- [26] a) S. Tasler, B. H. Lipshutz, J. Org. Chem. 2003, 68, 1190; b) B. H. Lipshutz, S. Tasler, W. Chrisman, B. Spliethoff, B. Tesche, J. Org. Chem. 2003, 68, 1177.
- [27] The differences in microwave absorption of the two unactivated catalysts shown in Figure 1 are therefore likely due to the different heating behavior of NiO and CuO at 2.45 GHz microwave irradiation (ref. [4b]), and may not necessarily reflect the heating characteristics of the activated zero-valent supported metal catalysts.
- [28] M. Hosseini, N. Stiasni, V. Barbieri, C. O. Kappe, J. Org. Chem. 2007, 72, 1417.
- [29] A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, Angew. Chem. 2006, 118, 6186; Angew. Chem. Int. Ed. 2006, 45, 6040.
- [30] P. Walla, C. O. Kappe, Chem. Commun. 2004, 564.
- [31] T. N. Glasnov, S. Findenig, C. O. Kappe, Chem. Eur. J. 2009, 15, 1001.
- [32] N. Miyaura, A. Suzuki, Chem. Rev. 1995, 95, 2457.
- [33] a) L. Yin, J. Liebscher, Chem. Rev. 2007, 107, 133; b) F.-X. Felpin, T. Ayad, S. Mitra, Eur. J. Org. Chem. 2006, 2679; c) M. Seki, Synthesis 2006, 2975.
- [34] a) B. L. Hayes, M. J. Collins, Jr., World Patent, WO 04002617, 2004;
  b) B. L. Hayes, *Aldrichimica Acta* 2004, *37*, 66.
- [35] a) B. K. Singh, P. Appukkuttan, S. Claerhout, V. S. Parmar, E. Van der Eycken, Org. Lett. 2006, 8, 1863; b) P. Appukkuttan, M. Husain, R. K. Gupta, V. S. Parmar, E. Van der Eycken, Synlett 2006, 1491;
  c) B. Singh, V. P. Mehta, V. S. Parmar, E. Van der Eycken, Org. Biomol. Chem. 2007, 5, 2962.
- [36] M. A. Herrero, J. M. Kremsner, C. O. Kappe, J. Org. Chem. 2008, 73, 36.
- [37] a) R. G. Heidenreich, K. Köhler, J. G. E. Krauter, J. Pietsch, Synlett 2002, 1118; b) K. Köhler, R. G. Heidereich, J. G. E. Krauter, J. Pietsch, Chem. Eur. J. 2002, 8, 622; c) R. G. Heidereich, J. G. E. Krauter, J. Pietsch K. Köhler, J. Mol. Catal. A 2002, 182–183, 499; K. Köhler, R. G. Heidenreich, S. S. Soomro, S. S. Pröckl, Adv. Synth. Catal. 2008, 350, 2930.

### CHEMISTRY

A EUROPEAN JOURNAL

- [38] M. D. Bowman, J. R. Schmink, C. M. McGowan, C. M. Kormos, N. E. Leadbeater, Org. Process Res. Dev. 2008, 12, 7078.
- [39] T. Besson, V. Thiery, J. Dubac in *Microwaves in Organic Synthesis*, 2nd ed. (Ed.: A. Loupy), Wiley-VCH, Weinheim, **2006**, pp. 416–455.
- [40] For a critical review, see: N. T. S. Phan, M. Van der Sluys, C. W. Jones, Adv. Synth. Catal. 2006, 348, 609.
- [41] For other key references, see: a) A. Biffis, M. Zecca, M. Basato, J. Mol. Catal. A 2001, 173, 249; b) D. Astruc, F. Lu, J. R. Aranzaes, Angew. Chem. 2005, 117, 8062; Angew. Chem. Int. Ed. 2005, 44, 7852; c) J. G. de Vries, Dalton Trans. 2006, 421; d) D. Astruc, Inorg. Chem. 2007, 46, 1884; e) A. M. Trzeciak, J. J. Ziółkowski, Coord. Chem. Rev. 2007, 251, 1281; f) A. Svennebring, P. J. R. Sjoeberg, M. Larhed, P. Nilsson, Tetrahedron 2008, 64, 1808.
- [42] a) S. Nishimura, Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis, Wiley-Interscience, New York, 2001;
  b) P. N. Rylander, Hydrogenation Methods, Academic Press, New York, 1990; c) P. N. Rylander, Catalytic Hydrogenation in Organic Synthesis, Academic Press, New York, 1979.
- [43] a) I. S. Cho, H. Alper, *Tetrahedron Lett.* **1995**, *36*, 5673; b) R. O. Hutchins, Suchismita, *Tetrahedron Lett.* **1989**, *30*, 55; c) B. M. Choudary, G. V. M. Sharma, P. Bharathi, *Angew. Chem.* **1989**, *101*, 506; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 465.
- [44] The correlation with actual stirring speeds in rpm are not disclosed by the instrument vendor.
- [45] An analysis of the effect of stirring on the Suzuki-Miyaura reaction (Scheme 2) demonstrated only minor variations in the product distribution as a result of choosing different stirring speeds on the microwave reactor.
- [46] a) J. Wang, Y. Wang, S. Xie, M. Qiao, H. Li, K. Fan, *Appl. Catal. A* 2004, 272, 29; b) B. W. Hoffer, P. H. J. Schoenmakers, P. R. M. Mooijman, G. M. Hamminga, R. J. Berger, A. D. van Langeveld,

J. A. Moulijn, *Chem. Eng. Sci.* 2004, 59, 259; c) N. Pestre, V. Meille, C. de Bellefon, *J. Mol. Catal. A* 2006, 252, 85; d) Y. Sun, R. N. Landau, J. Wang, C. LeBlond, D. G. Blackmond, *J. Am. Chem. Soc.* 1996, 118, 1348.

- [47] a) S. Nishimura, M. Murai, M. Shiota, *Chem. Lett.* **1980**, 1239;
  b) E. B. Hershberg, E. Oliveto, M. Rubin, H. Staeudle, L. Kuhlen, *J. Am. Chem. Soc.* **1951**, 73, 1144;
  c) H. R. Nace, *J. Am. Chem. Soc.* **1951**, 73, 2379;
  d) S. Nishimura, I. Takahashi, M. Shiota, M. Ishige, *Chem. Lett.* **1981**, 877;
  e) R. P. A. Sneeden, R. B. Turner, *J. Am. Chem. Soc.* **1955**, 77, 190;
  f) N. Ravasio, *J. Org. Chem.* **1991**, 56, 4329;
  g) N. Ravasio, M. Gargano, *J. Org. Chem.* **1993**, 58, 1259;
  h) M. S. Kwon, N. Kim, C. M. Park, J. S. Lee, K. Y. Kang, J. Park, *Org. Lett.* **2005**, 7, 1077.
- [48] M. Irfan, E. Petricci, T. N. Glasnov, M. Taddei, C. O. Kappe, *Eur. J. Org. Chem.* 2009, 1327, and references therein.
- [49] a) S. Horikoshi, J. Tsuzuki, F. Sakai, M. Kajitani, N. Serpone, *Chem. Commun.* 2008, 4501; b) B. Nigrovski, P. Scholz, T. Krech, N. V. Qui, K. Pollok, T. Keller, B. Ondruschka, *Catal. Commun.* 2009, *10*, 1473.
- [50] L. Bai, Y. M. Zhang, J.-X. Wang, Adv. Synth. Catal. 2008, 350, 315.
- [51] M. Damm, G. Rechberger, M. Kollroser, C. O. Kappe, J. Chromatogr. A 2009, 1216, 5875.
- [52] a) J. K. Kochi, J. Org. Chem. 1963, 28, 1960; b) R. Akiyama, S. Kobayashi, J. Am. Chem. Soc. 2003, 125, 3412; S, Kobayashi, J. Am. Chem. Soc. 2003, 125, 3412.
- [53] D. Habrant, B. Stengel, St. Meunier, C. Mioskowski, *Chem. Eur. J.* 2007, 13, 5433.
- [54] Y. M. Sheikh, M. Kaisin, C. Djerassi, Steroids 1973, 22, 835.

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