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Heck Reactions with Very Low Ligandless Catalyst Loads Accelerated by Microwaves or Simultaneous Microwaves/Ultrasound Irradiation

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Abstract: Heck couplings were carried out ligandless in air with very low catalyst loads under microwave or simultaneous microwave/ultrasound irradiation. Using ligand-free palladium(II) acetate [$Pd(OAc)_2$] in the range of 0.01–0.1 mol% or palladium-on-carbon (Pd/C) 10% in the range of 1.0–2.0 mol%, most aryl iodides and bromides gave high yields under conventional heating (120 °C) in 18 h. Microwave irradiation alone or, better still, combined with high-intensity ultrasound, strongly promotes the reaction, generally decreasing reaction times to 1 h. Electron-poor aryl chlorides such as 4-chloroacetophenone and 1-chloro-4-nitrobenzene reacted with styrene to afford high product yields in the presence of 0.25 mol% $Pd(OAc)_2$ or 2.0–3.0 mol% Pd/C. In several cases the addition of a co-catalyst, either rhodium tris(triphenylphosphine) chloride, 0.005 mol%, or a copper(I) salt (iodide or bromide), 2.0–4.0 mol%, proved very advantageous. 4-Bromo- and 4-chloroacetophenone afforded up to 15% of oxidation products, namely the corresponding 4-halobenzoic acid and 4-styrylbenzoic acid, a drawback that was avoided by working under a nitrogen atmosphere.

Keywords: Heck reaction; ligand-free; microwaves; palladium; ultrasound

Introduction

In the last years the Heck (or Mizoroki–Heck) reaction,[1–3] one of the most useful syntheses in organic chemistry, has become a veritable classic. Not only has it been thoroughly studied in the laboratory;[4] a myriad of important applications and related patents testify to its fundamental role in the preparation of a wide range of products.[5–7] Its scope has been further widened by the introduction of new generations of catalysts, comprising palladacycles, pincers and bulky electron-rich ligands for coupling reactions on aryl chlorides. As phosphine ligands are often difficult to separate from products, greener procedures now resort to "ligand-free" palladium catalysis, using either simple palladium salts, metallic palladium, or palladium nanoclusters immobilized on inorganic supports. Some recent reports even describe Heck reactions catalyzed by ligand-free palladium in trace amounts, an improvement to which such eminent authors as Beletskaya,[4] Reetz and de Vries[8,9] refer by the term "homeopathic catalyst quantities" to cover concentrations ranging from a few ppm to a few ppb. Using ligand-free $Pd(OAc)_2$ in the range between 0.01 and 0.10 mol% De Vries and co-workers observed very acceptable rates in the Heck reaction of bromobenzene with butyl acrylate. Under their conditions the addition of ligands or preformed palladacycles often had a retarding effect. When the catalyst-to-substrate ratio was further lowered to 0.00125 mol%, catalysis still occurred, but conversion was too slow to be practical.

If a soluble, ligand-free Pd catalyst could be induced to work effectively at a significantly lower level, its marginal cost and simplified work-up procedures would make its industrial use more advantageous than heterogeneous catalysis. Several reports describe Heck reactions carried out in the presence of Pd/C or a palladium catalyst dispersed on other supporting materials; their major drawbacks are the need for a high temperature and a longer reaction time.[11,12] Although high turnover numbers (TONs) have been attained using heterogeneous catalysts coupled with elaborate recycling strategies, a great simplification would result from the use of catalysts that are effective at such low levels that, in principle, they may not have to be recovered and recycled at all. As highlighted by Farina,[5] besides considerations of cost, an important concern is product contamination by the metallic catalyst, which in the case of pharmaceuticals must to be strictly controlled, usually not to exceed 10 ppm. It is easy to see that both the problems of cost and contamination will be automatically eliminated with catalysts that display TONs of 10^5 or higher. Thus any Pd-based technique with TONs of 10^5–10^6 and adequate turnover frequency (TOF) will be of great practical interest for pharmaceutical and fine chemical production.[10] A recent review by Jones and co-workers summarized the present knowledge on a much debated issue that is actually the main crux in this field of research: the true nature of catalytic species generated from different types of precatalysts and reaction conditions.[13]

The Heck reaction has been carried out in all possible reaction media (organic solvents, water, supercritical CO_2, ionic liquids) and under such unconventional conditions as ultrasound (US) and microwave (MW) irradiation. For example, Srinivasan employed $Pd(OAc)_2$ in an ionic liquid under US;[14] in other studies the sonochemical approach was used with Pd/C in NMP[15] or to form palladium nanoparticles at room temperature in an aqueous reaction medium.[16] Gedanken exploited power US to generate *in situ* amorphous carbon-activated palladium metallic clusters that proved an efficient catalyst for the Heck reaction.[17] In the last ten years more than 50 papers have appeared describing the advantages of MW heating when applied to the Heck reaction;[18,19] particular attention was paid to the vinylation of both electron-poor and electron-rich aryl chlorides. Reaction times were generally reduced from many days or hours down to few minutes.[20] MW heating[21,22] and US waves[23,24] are among the most simple, inexpensive and valuable tools in applied chemistry. Beside saving energy, these green techniques promote faster and more selective transformations. Recent developments[25–27] evidence that their combination (simultaneous or sequential) is possible, safe and well suited for automation and scaling-up.[28]

Ligand-free Pd-catalyzed homo- and cross-couplings of boronic acids with aryl halides have been successfully performed by our group in aqueous media under high-intensity US and MW, either alone or in a combined fashion.[29,30] We carried out combined irradiation in a flow reactor, obtaining the expected biaryls in higher yields and shorter time than using sonication or microwaves separately.[30] Proceeding from our previous experience on the catalysis of Suzuki[29,30] and Heck reactions[31] we present here our recent results on reactions carried out with a very low ligandless catalyst load under MW or simultaneous US/MW irradiation.

Results and Discussion

The present study was prompted by the excellent results we had achieved with the Suzuki reaction, that was greatly accelerated by combined MW/US irradiation as compared to either treatment used by itself or to conventional heating.[30] We developed two types of combined MW/US reactors.[32] The first uses two reaction cells (one for each kind of irradiation) joined by short lengths of tubing to allow the reacting liquid to circulate between them, while the second uses a single reaction cell for simultaneous irradiation with both energy sources. For the present work we employed the latter reactor, featuring a Pyrex® US horn inserted in a professional multimode MW oven (Figure 1).[33]

To begin with, couplings of styrene with 4-iodoanisole (Table 1, entries 1–8), 4-bromoanisole (entries 9–16) and 4-bromoacetophenone (entries 17–28) were carried out in the presence of $Pd(OAc)_2$ or 10% Pd/C; the amounts of catalyst were in the ranges of 0.01–0.1 mol% for $Pd(OAc)_2$ and 1.0–2.0 mol% for Pd/C (Scheme 1). All reactions were carried out in parallel under the following conditions: 1) under stirring and conventional heating in an oil bath; 2) under MW alone; 3) under combined MW/US irradiation. In order to improve yields, in certain cases we also stud-

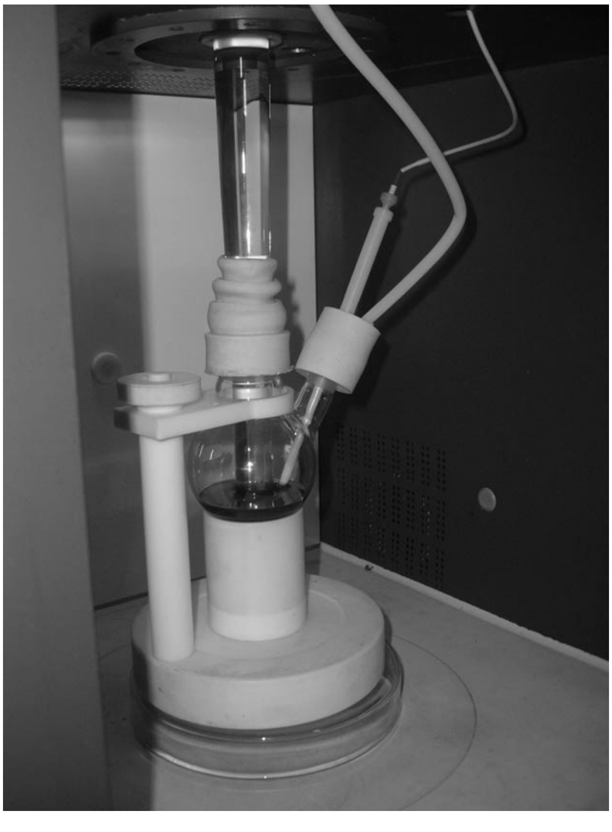


Figure 1. Standard set-up for simultaneous MW/US irradiation.

Table 1.

Entry[a]	Aryl halide	Catalyst (mol %)	Method	Time[b] [h]	Yield[c] [%]	Product[d] *E/Z ratio*	Conversion [%]
1	4-iodoanisole	Pd(OAc)$_2$ 0.1	Oil bath	18	94	**1a**/**1b**, 1:6	96
2	4-iodoanisole	Pd(OAc)$_2$ 0.01	Oil bath	18	88	**1a**/**1b**, 2:13	89
3	4-iodoanisole	Pd(OAc)$_2$ 0.01, CuI 2.0	Oil bath	18	91	**1a**/**1b**, 1:7	100
4	4-iodoanisole	Pd(OAc)$_2$ 0.05	MW	1.5	97	**1a**/**1b**, 2:9	100
5	4-iodoanisole	Pd(OAc)$_2$ 0.05	MW/US	0.5	99	**1a**/**1b**, 1:9	100
6	4-iodoanisole	Pd/C 1.0	Oil bath	18	97	**1a**/**1b**, 1:7	100
7	4-iodoanisole	Pd/C 1.0	MW	3	98	**1a**/**1b**, 1:5	100
8	4-iodoanisole	Pd/C 1.0	MW/US	1.5	99	**1a**/**1b**, 1:5	100
9	4-bromoanisole	Pd(OAc)$_2$ 0.05	Oil bath	18	95	**1a**/**1b**, 1:12	100
10	4-bromoanisole	Pd(OAc)$_2$ 0.01	Oil bath	18	32	**1a**/**1b**, 1:13	40
11	4-bromoanisole	Pd(OAc)$_2$ 0.01, Wilkinson 0.005	Oil bath	18	66	**1a**/**1b**, 1:16	86
12	4-bromoanisole	Pd(OAc)$_2$ 0.01	MW	3	29	**1a**/**1b**, 1:13	35
13	4-bromoanisole	Pd(OAc)$_2$ 0.01	MW/US	1.5	39	**1a**/**1b**, 1:14	43
14	4-bromoanisole	Pd/C 2.0	Oil bath	18	92	**1a**/**1b**, 1:16	94
15	4-bromoanisole	Pd/C 1.5	MW	3	89	**1a**/**1b**, 1:12	96
16	4-bromoanisole	Pd/C 1.5	MW/US	1.5	96	**1a**/**1b**, 1:13	98
17	4-bromoacetophenone	Pd(OAc)$_2$ 0.05	Oil bath	18	95	**2b**	100
18	4-bromoacetophenone	Pd(OAc)$_2$ 0.01	Oil bath	18	31	**2b**	40
19	4-bromoacetophenone	Pd(OAc)$_2$ 0.01, CuBr 3.0	Oil bath	18	39	**2b**	56
20	4-bromoacetophenone	Pd(OAc)$_2$ 0.01, Wilkinson 0.005	Oil bath	18	76	**2b**	95
20	4-bromoacetophenone	Pd(OAc)$_2$ 0.01, CuBr 3.0	Oil bath	18	39	**2b**	56
21	4-bromoacetophenone	Pd(OAc)$_2$ 0.01	MW	3	29	**2b**	35
22	4-bromoacetophenone	Pd(OAc)$_2$ 0.01	MW/US	1.5	41	**2b**	55
23	4-bromoacetophenone	Pd(OAc)$_2$ 0.01, CuBr 3.0	MW/US	1.5	51	**2b**	64
24	4-bromoacetophenone	Pd(OAc)$_2$ 0.01, CuBr 3.0	MW/US (N_2)	1.5	59	**2b**	67
25	4-bromoacetophenone	Pd/C 2.0	Oil bath	18	90	**1a**/**1b**, 1:68	97
26	4-bromoacetophenone	Pd/C 1.5	MW	3	93	**2b**	99
27	4-bromoacetophenone	Pd/C 1.5	MW/US	1.5	81	**2b**	100
28	4-bromoacetophenone	Pd/C 1.5	MW/US (N_2)	1.5	96	**2b**	100

[a] All reactions were carried out at 120 °C in DMA in the presence of TBAB (1 equiv.); TEA (1.5 equivs.) was used for entries 1–8, K_2CO_3 (1.5 equivs.) for entries 9–28.

[b] This does not include the ramp time (5 min) required to reach the temperature of 120 °C.

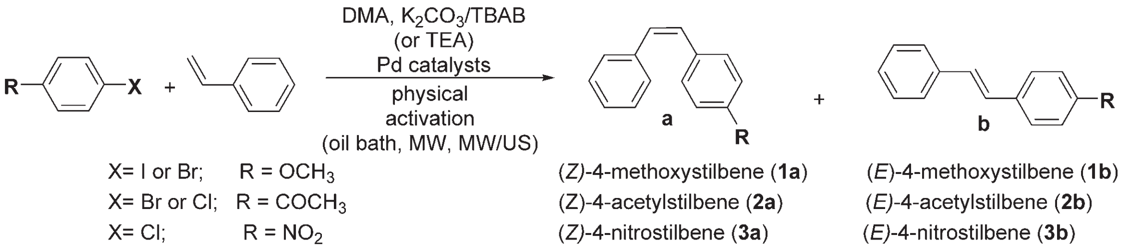
[c] These yields were calculated from calibration curves obtained with pure products; they include both stereoisomers *E/Z*.

[d] Product numbers refer to Scheme 1.

ied the effect of adding a co-catalyst such as CuI or CuBr (2–4 mol %) or rhodium tris(triphenylphosphine) chloride (Wilkinson's catalyst, 0.005 mol %).

The beneficial effect of copper(I) on cross-couplings (e.g., the Stille, Sonogashira, Glaser and Suzuki reactions) is well known.[34] Its catalytic effect was also exploited in the Heck reaction[35] and a possible mechanism for it was recently proposed by Li et al.[36] The role of CuI as cocatalyst is still unclear. After oxidation to Cu(II) it probably favours the oxidative addition of Pd(0) to the alkene; this could explain why we observed a co-catalytic effect only with Pd(II). The co-catalyst combination Pd(II)-Rh(I) it is not unprecedented;[37] Bankston et al. first described the use of Pd(II) acetate in association with Wilkinson's catalyst.[38]

Except for entries 1–8 where the base was TEA, for all the other reactions we used K_2CO_3 in the presence of TBAB. Results are summarized in Table 1. With 0.01–0.05 mol % Pd(OAc)$_2$ and 1–2 mol % Pd/C respectively, reactions with 4-iodoanisole and 4-bromoanisole gave very good results even under conventional heating (120 °C), although the starting material had not reacted completely after 10 h. MW and com-



Scheme 1.

bined MW/US strongly accelerated the reaction; the effect was more striking with 0.1–0.05 mol% Pd-$(OAc)_2$ than at lower catalyst loadings. With 0.05 mol% $Pd(OAc)_2$ under simultaneous MW/US irradiation 4-iodoanisole gave a 99% yield in 30 min (entry 5). Combined irradiation was extremely effective in the case of heterogeneous catalysis with 1–1.5 mol% Pd/C, giving quantitative yields after 1.5 h irradiation (entries 8, 16). In the coupling of 4-bromoacetophenone a catalyst load reduction from 0.05 to 0.01 mol% $Pd(OAc)_2$ was critical: under conventional heating (oil bath 120 °C, 18 h) the yield fell from 95% (entry 17) to 31% with only 40% conversion (entry 18). The addition of a co-catalyst was surprisingly effective: CuBr 3.0 mol% (entry 19) raised the yield to 39%; better still, a very small amount of rhodium tris(triphenylphosphine) chloride (0.005 mol%) sufficed to bring the reaction close to completion (entry 20). As shown in the tables, the favorable effects of the co-catalyst and MW or MW/US irradiation were additive. With 1.5 mol% Pd/C under combined MW/US irradiation, 4-bromoacetophenone also gave a good yield (81%) after only 1.5 h (entry 27). GC-MS analyses of the reacted mixtures showed in all cases the presence of two side products: 4-bromobenzoic acid (1–9%) and 4-styrylbenzoic acid (1–4%), respectively arising from the oxidation of the starting material and of the Heck coupling product. The same by-processes were observed with 4-chloroacetophenone, yielding 4-chlorobenzoic acid (1–10%) and 4-styrylbenzoic acid (1–5%). The highest percentages of these undesired products resulted from combined MW/US irradiation; however their formation could easily be avoided by working under nitrogen atmosphere (entries 24, 28 and 38).

In general under conventional heating 4-chloroacetophenone and 4-chloronitrobenzene reacted with styrene (18 h) in the presence of catalyst loads exceeding 0.25 mol% for $Pd(OAc)_2$ (entries 29 and 39) or 3 mol% for Pd/C. In these cases also, adding 0.005 mol% of Wilkinson's catalyst (entries 32, 42 and 45) or 4 mol% CuBr (entries 31, 34 and 41) considerably increased yields; moreover MW or combined MW/US irradiation strongly accelerated the reaction in all cases (see Table 2). Lowering the catalyst load from 0.5 to 0.25 mol% $Pd(OAc)_2$ (entries 39 and 40, respectively) critically affected the reaction of 4-chloronitrobenzene (98 *vs.* 12% yield). This precipitous fall could however be partly offset by adding 0.005 mol% of Wilkinson catalyst and proceeding with combined MW/US irradiation as before; the resulting yield was 58% after 1.5 h (entry 45).

In order to strictly compare performances under the three energy sources (oil bath, MW and MW/US) we carried out additional experiments with 4-bromoacetophenone and styrene using the same volumes of reacting mixture and the same reaction times. The catalyst load was uniformly $Pd(OAc)_2$ 0.5 mol% plus CuBr 3 mol%. Table 3 shows the dramatic increase of reaction rates caused by MW and MW/US irradiation.

Conclusions

In summary, we showed that Heck reactions can conveniently be carried out under simultaneous MW/US irradiation to afford high product yields while using very low ligandless catalyst loads. With styrene, electron-poor aryl chlorides, such as 4-chloroacetophenone and 4-chloronitrobenzene, gave good yields in 1 h in the presence of 0.25 mol% $Pd(OAc)_2$ and a co-catalyst (Wilkinson's 0.005 mol% or CuBr 4.0 mol%) or 2.0–3.0 mol% Pd/C. In most cases MW heating gave comparable results (although yields were 5-20% lower) in somewhat longer times, whereas under conventional heating acceptable yields were achieved only after 18 h. A possible scale-up of this protocol will require a careful analysis of costs, including energy consumption besides the cost of reactors.

Experimental Section

General Remarks

Commercially available reagents and solvents were used without further purification unless otherwise noted. Stock solutions in DMA of $Pd(OAc)_2$ (1 mg/mL) and Wilkinson's catalyst (1 mg/10 mL) were prepared just before use. Reactions were monitored by TLC on Merck 60 F_{254} (0.25 mm) plates, which were visualized by UV inspection and/or by heating after a spray with phosphomolybdic acid. Merck silica gel was used for column chromatography (CC). IR

Table 2.

Entry[a]	Aryl halide	Catalyst (mol %)	Method	Time[b] [h]	Yield[c] [%]	Product[d]	Conversion [%]
29	4-chloroacetophenone	$Pd(OAc)_2$ 0.5	Oil bath	18	95	**2b**	100
30	4-chloroacetophenone	$Pd(OAc)_2$ 0.25	Oil bath	18	51	**2b**	71
31	4-chloroacetophenone	$Pd(OAc)_2$ 0.25, CuBr 4.0	Oil bath	18	92	**2b**	95
32	4-chloroacetophenone	$Pd(OAc)_2$ 0.25, Wilkinson 0.005	Oil bath	18	75	**2b**	94
33	4-chloroacetophenone	$Pd(OAc)_2$ 0.25	MW	3	47	**2b**	65
34	4-chloroacetophenone	$Pd(OAc)_2$ 0.25, CuBr 4.0	MW/US	1.5	90	**2b**	100
35	4-chloroacetophenone	Pd/C 2.0	Oil bath	18	75	**2b**	100
36	4-chloroacetophenone	Pd/C 2.0	MW	3	61	**2b**	72
37	4-chloroacetophenone	Pd/C 2.0	MW/US	1.5	87	**2b**	100
38	4-chloroacetophenone	Pd/C 2.0	MW/US (N_2)	1.5	94	**2b**	100
39	4-chloronitrobenzene	$Pd(OAc)_2$ 0.5	Oil bath	18	98	**3b**	100
40	4-chloronitrobenzene	$Pd(OAc)_2$ 0.25	Oil bath	18	12	**3b**	25
41	4-chloronitrobenzene	$Pd(OAc)_2$ 0.25, CuBr 4.0	Oil bath	18	20	**3b**	37
42	4-chloronitrobenzene	$Pd(OAc)_2$ 0.25, Wilkinson 0.005	Oil bath	18	25	**3b**	45
43	4-chloronitrobenzene	$Pd(OAc)_2$ 0.25	MW	3	29	**3b**	38
44	4-chloronitrobenzene	$Pd(OAc)_2$ 0.25	MW/US	1.5	35	**3b**	45
45	4-chloronitrobenzene	$Pd(OAc)_2$ 0.25, Wilkinson 0.005	MW/US	1.5	58	**3b**	69
46	4-chloronitrobenzene	Pd/C 3.0	Oil bath	18	66	**3b**	73
47	4-chloronitrobenzene	Pd/C 3.0	MW	3	85	**3b**	95
48	4-chloronitrobenzene	Pd/C 3.0	MW/US	1.5	84	**3b**	96

[a] All reactions were carried out in DMA at 120 °C in the presence of K_2CO_3 (1.5 equivs.) and TBAB (1 equiv.).

[b] This does not include the ramp time (5 min) required to reach 120 °C.

[c] These yields were calculated from calibration curves obtained with pure products.

[d] Product numbers refer to Scheme 1.

Table 3.

Method[a]	Time [min]	Yield[%]	Products[b]	Conversion [%]
Oil bath	15	2	**2b**	4
Oil bath	30	44	**2b** (**2a** traces)	45
MW	15	68	**2b** (**2a** traces)	69
MW	30	87	**2b** (**2a** 3 %)	92
MW/US	15	88	**2b** (**2a** traces)	90
MW/US	30	99	**2b** (**2a** 3 %)	100

[a] Reacting mixture: 4-bromoacetophenone (1 mmol), styrene (1.5 mmol), $Pd(OAc)_2$ 0.5 mol %, CuBr 3 mol %, K_2CO_3 (1.5 mmol), TBAB (1 mmol), DMA (10 mL). The temperature was, for all entries, 120 °C.

[b] Product numbers that refer to Scheme 1.

spectra were recorded with a Shimadzu FT-IR 8001 spectrophotometer, NMR spectra with a Bruker 300 Avance at 25 °C. MW-promoted reactions were carried out in a professional oven, Microsynth-Milestone (Italy); this was also used for combined MW/US irradiation after a probe equipped with a Pyrex® horn was inserted in it (Figure 1).

General Procedure

The aryl halide (1 mmol), styrene (1.5 mmol) and the base (1.5 mmol) were dissolved in DMA (1 mL) in a Pyrex® pressure-resistant tube (for reactions under conventional heating); in DMA (10 mL) in a two-necked round-bottomed flask equipped either with a condensing tube for reactions under MW or with a elastomeric sleeve (Figure 1) to seal the system for reactions under combined MW/US. The base was TEA in the case of 4-iodoanisole, K_2CO_3 in the presence of TBAB (1 mmol) with all other substrates. Pd/C 10% or $Pd(OAc)_2$ and, in some cases, a co-catalyst were added to the mixture in the molar ratios indicated in Table 1 and Table 2. The mixtures were heated in an oil bath or in the MW oven under magnetic stirring or by simultaneous MW/US irradiation. The temperature, measured with an optical-fibre thermometer, was always kept constant at 120 °C; the reaction outcome was monitored by TLC (hexane/EtOAc, 9:1, as eluent) and GC.[39] Finally the reacted mixture was poured into 2 N H_2SO_4 (50 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4 and concentrated under vacuum.

The better to compare results obtained under MW alone and combined MW/US irradiation, we used the same oven in combination with a Pyrex® horn (20.3 kHz, 35 W). MW maximum power was in all cases 200 W for the temperature ramp up to 120 °C, while MW average power during the reaction time was 70 W when applied alone and 50 W when used in combination with US. After evaporation of the solvent from the reacted mixture, products were easily isolated by silica-gel column chromatography, using hexane/EtOAc mixtures in different ratios. Yields and conversion percents determined by GC analyses[40] were comparable to the isolated yields.

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References

[1] R. F. Heck, J. P. Nolley, *J. Org. Chem.* **1972**, *37*, 2320–2322.

[2] T. Mizoroki, K. Mori, A. Ozaki, *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581.

[3] R. F. Heck, in: *Comprehensive Organic Synthesis*, (Eds.: B. M. Trost, I. Fleming), Pergamon Press: Oxford, UK, **1991**, Vol 4, Chapter 4.3, p 833.

[4] I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009–3066.

[5] V. Farina, *Adv. Synth. Catal.* **2004**, *346*, 1553–1582.

[6] J. G. de Vries, *Can. J. Chem.* **2001**, *79*, 1086–1092.

[7] D. H. B. Ripin, D. E. Bourassa, T. Brandt, M. J. Castaldi, H. N. Frost, J. Hawkins, P. J. Johnson, S. S. Massett, K. Neumann, J. Phillips, J. W. Raggon, P. R. Rose, J. L. Rutherford, B. Sitter, A. M. Stewart, M. G. Vetelino, L. L. Wei, *Org. Process Res. Dev.* **2005**, *9*, 440–450.

[8] M. T. Reetz, E. Westermann, R. Lohmer, G. Lohmer, *Tetrahedron Lett.* **1998**, 39, 8449–8452.

[9] A. H. M. de Vries, J. M. C. A. Mulders, J. H. M. Mommers, H. J. W. Henderickx, J. G. de Vries, *Org. Lett.* **2003**, *5*, 3285–3288.

[10] W. A. Herrmann, C. Brossmer, K. Oefele, C.-P. Reisinger, T. Priermeier, M. Beller, H. Fischer, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1844–1848.

[11] R. G. Heidenreich, J. G. E. Krauter, J. Pietsch, K. Koehler, *J. Mol. Catal. A: Chem.* **2002**, 182–183 and 499–505.

[12] S. Mukhopadhyay, G. Rothenberg, A. Joshi, M. Baidossi, Sasson, Y. *Adv. Synth. Catal.* **2002**, *344*, 348–354.

[13] N. T. S. Phan, M. Van Der Sluys, C. W. Jones, *Adv. Synth. Catal.* **2006**, *348*, 609–679.

[14] R. R. Deshmukh, R. Rajagopal, K. V. Srinivasan, *Chem. Commun.* **2001**, 1544–1545.

[15] G. V. Ambulgekar, B. M. Bhanage, S. D. Samant, *Tetrahedron Lett.* **2005**, *46*, 2483–2485.

[16] Z. Zhang, Z. Zha, C. Gan, C. Pan, Y. Zhou, Z. Wang, M.-M. Zhou, *J. Org. Chem.* **2006**, *71*, 4339–4342.

[17] N. A. Dhas, H. Cohen, A. Gedanken, *J. Phys. Chem. B* **1997**, *101*, 6834–6838.

[18] M. Larhed, A. Hallberg, *J. Org. Chem.* **1996**, *61*, 9582–9584.

[19] R. K. Arvela, N. E. Leadbeater, *J. Org. Chem.* **2005**, *70*, 1786–1790.

[20] G. K. Datta, K. S. A. Vallin, M. Larhed, *Molecular Diversity* **2003**, *7*, 107–114.

[21] *Microwaves in Organic Synthesis*, (Ed.: A. Loupy), Wiley-VCH, Weinheim, **2006**.

[22] *Microwaves in Organic and Medicinal Chemistry*, (Eds.: C. O. Kappe, A. Stadler), Wiley-VCH, Weinheim, **2005**.

[23] T. J. Mason, J. Lorimer, *Applied Sonochemistry: Uses of Power Ultrasound in Chemistry and Processing*, Wiley-VCH, Weinheim, **2002**.

[24] G. Cravotto, P. Cintas, *Chem. Soc., Rev.* **2006**, *35*, 180–196.

[25] J.-M. Levêque, G. Cravotto, *Chimia* **2006**, *60*, 313–320.

[26] G. Cravotto, L. Boffa, M.; Bia, W. Bonrath, M. Curini, G. A. Heropoulos, *Synlett* **2006**, 2605–2608.

[27] G. Cravotto, P. Cintas, *Chem. Eur. J.* **2007**, *13*, 1902–1909.

[28] G. Cravotto, S. Di Carlo, M. Curini, V. Tumiatti, C. Roggero, *J. Chem. Tech. Biotech.* **2007** *82*, 205–208.

[29] G. Cravotto, G. Palmisano, S. Tollari, G. M. Nano, A. Penoni, *Ultrason. Sonochem.* **2005**, *12*, 91–94.

[30] G. Cravotto, M. Beggiato, A. Penoni, G. Palmisano, S. Tollari, J.-M. Levêque, W. Bonrath, *Tetrahedron Lett.* **2005**, *46*, 2267–2271.

[31] G. Cravotto, F. Demartin, G. Palmisano, A. Penoni, T. Radice, S. Tollari, *J. Organomet. Chem.* **2005**, *690*, 2017–2026.

[32] G. Cravotto, G. Omiccioli, C. Buffa, G. Dal Lago, *Italian Patent* VR 2004 A000167 IT, **2004**; C. Buffa, G. Cravotto, G. Omiccioli, *Italian Patent* TO 2006 A000766 IT, **2006**.

[33] Our patented probes feature non-metallic horns made of Pyrex®, fused quartz or polymers such as PEEK or PTFE; all these material are inert to MW irradiation. A commercial version of the whole MW/US reactor is now available from Danacamerini (TO, Italy) and Milestone (BG, Italy).

[34] a) V. Farina, S. Kapadia, B. Krishnan, C. Wang, L. S. Liebeskind, *J. Org. Chem.* **1994**, *59*, 5905–5911; b) S. P. H. Mee, V. Lee, J. E. Baldwin, *Angew. Chem. Int. Ed.* **2004**, *43*, 1132–1136; c) S. E. Denmark, T. Kobayashi, *J. Org. Chem.* **2003**, *68*, 5153–5159.

[35] a) S. Iyer, C. Ramesh, A. Sarkar, P. P. Wadgaonkar, *Tetrahedron Lett.* **1997**, *38*, 8113–8116; b) S. Iyer, V. V. Thakur, *J. Molecular Catal. A: Chem.* **2000**, *157*, 275–278; c) V. Declerck, J. Martinez, F. Lamaty, *Synlett* **2006**, 3029–3032.

[36] J.-H. Li, D.-P Wang, Y.-X. Xie, *Tetrahedron Lett.* **2005**, *46*, 4941–4944.

[37] a) T. Doi, N. Fujimoto, J. Watanabe, T. Takahashi, *Tetrahedron Lett.* **2003**, *44*, 2161–2165; b) R. Broussier, E. Bentabet, M. Laly, P. Richard, L. G. Kuzmina, P. Serp, N. Wheatley, P. Kalck, B. Gautheron, *J. Organomet. Chem.* **2000**, *613*, 77–85.

[38] D. Bankston, F. Fang, E. Huie, S. Xie, *J. Org. Chem.* **1999**, *64*, 3461–3466.

[39] GC-MS analyses were carried out on an Agilent Technologies 6850 Network GC System with 5973 Network Mass Selective Detector, using capillary column (length 30 m.; i. d. 0.25 mm; film thickness 0.25 μm). GC conditions were: injection split 1:20, injector temperature 250 °C, detector temperature 280 °C; temperature program: from 50 °C (3 min) to 80 °C at 3 °C/min, 80 °C to 300 °C at 10 °C/min (30 min); H_2 as carrier gas at 25 kPa.

[40] Retention times of starting materials and products were: 4-iodoanisole, 19.28 min; 4-bromoanisole, 17.22 min; 4-bromoacetophenone, 19.67 min; 4-chloroacetophenone, 18.06 min; 4-nitrochlorobenzene, 18.14 min; **1a**, 25.55 min; **1b**, 27.74 min; **2a**, 27.26 min, **2b**, 29.40 min; **3a**, 27.70 min; **3b**, 29.76 min.