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High-intensity ultrasound and microwave, alone or combined, promote Pd/C-catalyzed aryl–aryl couplings

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Abstract—Pd-catalyzed homo- and cross-couplings of boronic acids and aryl halides were successfully carried out both in aqueous media under high-intensity ultrasound (US) and in DME under microwave (MW). Heterogeneous catalysis with Pd/C was employed, avoiding phosphine ligands and phase-transfer catalysts. In a trial series involving 15 different iodo- and bromoaryls and 7 boronic acids, both energy sources drastically reduced reaction times affording biaryls in acceptable to good yields. With palladium(II) acetate as catalyst, electron-deficient aryl chlorides also reacted, affording a few biaryls in acceptable yields. Ullmann-type zinc-mediated homocoupling of iodo- and bromoaryls in the presence of Pd/C under CO_2 atmosphere was achieved in aqueous media under US, though not under MW. Suzuki homo- and cross-couplings were also carried out in a new reactor developed in our laboratory, featuring combined US and MW irradiation, further improving a green synthetic method.

Because the biaryl motif is present in a large variety of common organic compounds (natural products, pharmaceuticals, herbicides, conducting polymers and liquid crystalline materials), developing straightforward and environment-friendly reactions for aryl–aryl coupling is a matter of wide interest. Great progress in biaryl synthesis has been achieved by Pd-catalyzed couplings according to Stille,[1] Suzuki–Miyaura[2] and Kumada–Tamao–Hiyama.[3] As the Suzuki–Miyaura reaction (SMR) of arylboronic derivatives with aryl halides is more easily amenable to scale-up, it is currently used not only in the laboratory but industrially as well.[4] To make it more environment-friendly one important goal still lies ahead, that is, the employ of water as solvent and of easily removable palladium on charcoal (Pd/C) as catalyst,[5] avoiding the use of toxic phosphine ligands. The Ullmann reaction, first reported in 1901,[6] has long been employed to generate a C–C bond between two aromatic nuclei; recent improvements have broadened its range of application.[7]

Microwave (MW) heating has emerged as a powerful technique by which reactions can be brought to completion in minutes rather than hours or days. Its application to Suzuki reactions is well documented.[8] However, with regard to industrial applications MW heating[9] is probably not as promising as high-intensity ultrasound (US).[10,11] Although the latter has been widely exploited in organic synthesis, to the best of our knowledge only two recent applications to the SMR have been reported.[12,13] Pd/C can offer an alternative to conventional homogeneous catalysis for C–C bond formation,[14,15] particularly in SMR, either in organic[16] or aqueous media.[17] In fact it has been employed to catalyze fine chemical preparations, including Suzuki reactions.[18] Compared to other expensive and air-sensitive Pd catalysts, Pd/C can be more easily handled, recovered from the reaction mixture by simple filtration and reused. We recently showed that US strongly promotes Pd/C-catalyzed Suzuki homocouplings, cutting reaction times down to 90 min or less and increasing

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Keywords: Suzuki–Miyaura reaction; Ullmann reaction; Ultrasound; Microwave; Biaryls; Pd/C.

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isolated yields.[19] Bubbled molecular oxygen, or simply air, provided a very convenient way to oxidize Pd(0) to an intermediate Pd(II) species (Ar–[Pd]–Ar) in the catalytic cycle.

In the present work both Suzuki homo- and cross-couplings were carried out under US (20.5 kHz, 40 W/cm^2) and, by way of comparison, under MW (700 W, DME as solvent) in the presence of 50% water-wet 10% Pd/C (Degussa E 106 NE/W 10) (0.05 mmol) and K_2CO_3 in THF/water 1:1 or DME/water 1:1. Our reactors enabled us to work under argon atmosphere, as required in Suzuki cross-couplings. Figure 1 summarizes the three different types of Pd/C-catalyzed aryl–aryl couplings

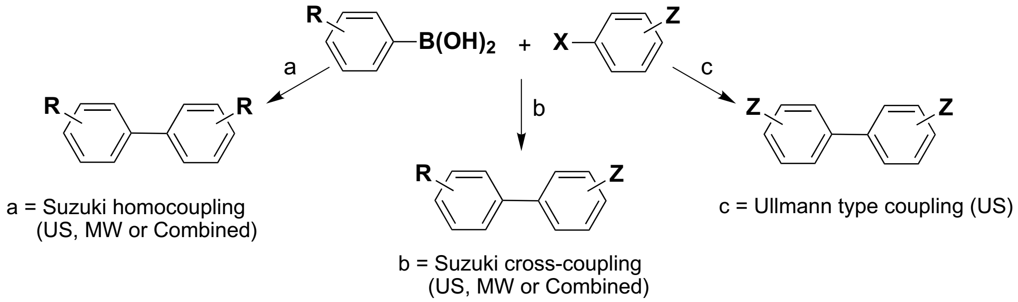
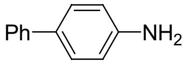
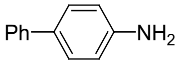
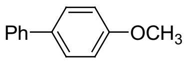
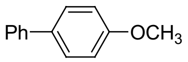
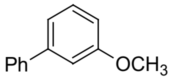
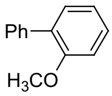
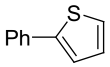
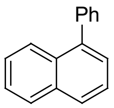
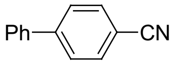
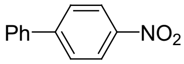
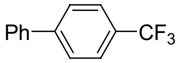


Figure 1. Pd/C-catalyzed aryl–aryl couplings under MW and US, alone or combined.

Table 1. Suzuki cross-couplings with phenylboronic acid[22]

Entry	Aryl halide	US yield, %	MW yield, %	Product
1	4-Iodoaniline	90	86	
2	4-Bromoaniline	97	90	
3	4-Iodoanisole	72	78	
4	4-Bromoanisole	61	74	
5	3-Bromoanisole	54	64	
6	2-Bromoanisole	79	70	
7	2-Iodothiophene	40	37	
8	1-Iodo-naphthalene	32	63	
9	4-Bromobenzonitrile	78	74	
10	4-Chloro-nitrobenzene	22[a]	30[b]	
11	4-Chloro-benzotrifluoride	19[a]	25[b]	

[a] $Pd(OAc)_2$, DME/H_2O 1:1, $Cs_2(CO_3)_2$.

[b] $Pd(OAc)_2$, DME, $Cs_2(CO_3)_2$.

that could take place. The Ullmann-type Zn-mediated homocoupling proceeded only under US (Table 4), while no reaction was observed under MW.

All relevant parameters were carefully monitored when working under US;[20] during MW runs the temperature was approximately monitored with an infrared thermometer (MX2 Raytek) and more accurately measured at the end of the reaction with a thermocouple thermometer. The MW oven (700 W) was alternatively turned on for 4 s and off for 6 s during the whole run (20 min).[21] GC–MS analysis of the reacted mixtures evidenced that couplings had taken place and starting materials had disappeared; in some instances (entries **4–6** and **10**) traces of homocoupling products were also detected.

When Pd/C was replaced with palladium(II) acetate, chloroaryls also underwent Suzuki cross-coupling with phenylboronic acid, both under US and MW, affording a few biaryls (**10**, **11**) in moderate yields.

Tables 1 and 2 report reaction yields under either energy source.

With the aim to evaluate the effect of combined US/MW irradiation on Suzuki couplings, we resorted to the prototype of a novel flow reactor (Figs. 2 and 3) to carry out some of the reactions listed in Tables 1 and 2, choosing those with the lowest yields (entries **5**, **7**, **10**, **12** and **14**). DME/water 2:1 was used as solvent and reacting mixtures were thermostatted at 45–48 °C. In all cases after 1 h irradiation (US 20.5 kHz, 40 W/cm^2; MW 700 W) GC–MS analysis found the expected products exclusively, in higher yields than were achieved using US or MW individually (Table 3).

Table 2. Suzuki homocouplings[23]

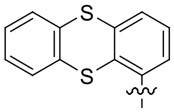
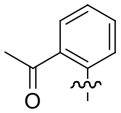
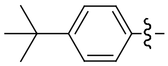
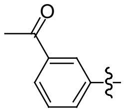
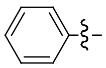
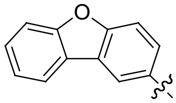
Entry	Ar–B(OH)$_2$/Ar–Ar	US yield, %	MW yield, %
12		48	55
13		80	88
14		68	74
15		71	70
16		86	90
17		72	66

Figure 2. Reactor prototype featuring combined US/MW irradiation.

Figure 3. Reactor prototype featuring combined US/MW irradiation.

Although geometric and operational differences did not permit reaction conditions to be rigorously equalized in our three reactors, we concluded however that our improved yields were significant on the basis of the

Table 3. Compared yields of Suzuki reactions under US or MW alone (from Tables 1 and 2) and under combined US/MW

Entry	Aryl halide	Boronic acid	US yield, %	MW yield, %	Comb.US/MW yield, %
5	3-Bromoanisole	Phenylboronic	54	64	88
7	2-Iodothiophene	Phenylboronic	40	37	59
10	4-Chloro-nitrobenzene	Phenylboronic	22	30	57
12	—	Thianthrene-1-boronic	48	55	69
14	—	4-*t*-Butylboronic	68	74	86

following experiments. When the reactions listed in Table 3 were carried out in the flow reactor with either the US or the MW power switched off, observed yields did not significantly differ from those reported in Tables 1 and 2.

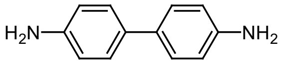
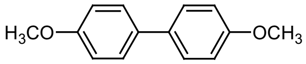
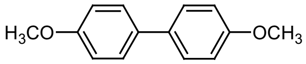
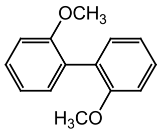
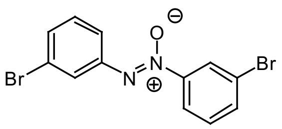
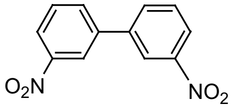
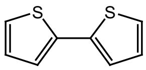
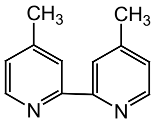
The novel prototype developed in our laboratory for combined US/MW irradiation is shown in Figures 2 and 3. It consists of:

An air-cooled probe equipped with a titanium horn, working at about 20.5 kHz.
An US-reaction vessel (made of titanium) in which the horn is inserted. It is cooled by a flow of either tap-water or refrigerated oil.
Two lengths of thermostatted coaxial tubing and a peristaltic pump by which the reacting mixture is circulated between the US-cell and another vessel (the MW-cell, made of Teflon®) placed inside a MW oven. With the small reaction volumes required for the present study (45–80 mL) the MW-cell could be replaced by a bend of the coaxial tubing itself (Fig. 3).
Another pump by which silicone oil, refrigerated by a chiller, is circulated in countercurrent through the outer compartment of the coaxial tubing.

Work is in progress to clarify the role of each energy source in promoting Pd-catalyzed C–C couplings. Pd/C-catalyzed aryl–aryl couplings by the Zn-mediated Ullmann reaction were not observed under MW, but proceeded well under US in DME/H_2O 1:1 under CO_2 bubbling. 3-Bromonitrobenzene afforded, beside the expected 3,3′-dinitrobiphenyl, the 3,3′-dibromo-azoxybenzene, arising from a reductive *N–N* coupling.

Table 4 shows the results of Ullmann-type Zn-mediated homocouplings carried out under US (90 min, 20.5 kHz, 45 °C).

Table 4. Ullmann-type Zn-mediated homocouplings under US in DME/H_2O 1:1

Entry	Aryl halide	US yield, %	Product
18	4-Iodoaniline	34	
19	4-Iodoanisole	58	
20	4-Bromoanisole	47	
21	2-Bromoanisole	24	
22	3-Bromonitrobenzene	21	
		10	
23	2-Bromo-thiophene	26	
22	2-Bromo-4-methylpyridine	19	

By way of comparison most of the reactions reported in Tables 1–4 were also carried out under conventional conditions (stirring at room temperature or heating under reflux). Low yields or even no reaction were observed after 4 h.

In summary, working under US we were able to carry out ligand-free Pd/C-catalyzed Suzuki cross- and homocouplings in aqueous media, affording the corresponding biaryls in acceptable to good yields. The same products were obtained in comparable yields under MW using DME as solvent. Further improvements in terms of yield and reaction time were achieved by means of a novel flow reactor developed in our laboratory, featuring combined US and MW irradiation. Sonochemical zinc-mediated Ullmann homocouplings were successfully carried out in aqueous media under CO_2 bubbling in the presence of Pd/C. These advances should make biaryl synthesis both more efficient and greener.

Acknowledgements

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20. Cravotto, G.; Omiccioli, G.; Stevanato, L. *Ultrason. Sonochem.* **2005**, *12*, 213–217.
21. For MW irradiation we used a modified domestic oven (Candy MSA 20M), a Carius-type Pyrex tube (ACE Glassware) (50 mL) sealed with a pressure-resistant screw cap serving as reaction vessel.
22. *General procedure for Suzuki cross-coupling*: under an argon atmosphere the phenylboronic acid (1 mmol) was reacted under US irradiation (20.5 kHz, 90 min) at 45 °C with the aryl halide (1 mmol) and K_2CO_3 (2 mmol) in THF/H_2O or DME/water 1:1 (25 mL), with Pd/C (0.05 mmol) as catalyst. When working under MW, DME was used as solvent and the oven was cycled as follows: on for 5 s, off for 4 s, power 700 W (20 min).
23. *General procedure for Suzuki homocoupling*: see Ref. 22 (Ar was replaced by O_2 atmosphere).