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Microwave- and ultrasound-assisted Suzuki–Miyaura cross-coupling reactions catalyzed by Pd/PVP

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Abstract

Suzuki–Miyaura reactions using Pd/PVP as a catalyst source were carried out in water–ethanol solution. Under MW, sonication or thermal condition yields were very similar, from moderate to very good, in a variety of examples. However, TOFs were very different, 750/h under MW, 250/h under sonication, and 28/h under thermal conditions. Studies carried out under sonication showed that the whole system after product extraction can be re-used at least twice without any noticeable loss of yield.

Cross-coupling reactions represent an extremely versatile tool in organic synthesis.[1] The Suzuki cross-coupling reactions of arylboronic acids and aryl halides provide an effective synthetic route to biaryls.[2] The coupling reaction of arylboronic acid derivatives with arylhalides in the presence of $Pd(PPh_3)_4$ and base to afford biaryls was first reported in 1981.[3]

Catalysis with nanoparticles has undergone explosive growth during the past decade. Because nanoparticles are attractive catalysts compared to other bulk catalytic materials due to their high surface tension, nanoparticles in colloidal solution, as well as supported nanoparticles, have been used as catalysts.[4] El-Sayed's group[5] has deeply studied palladium nanoparticles stabilized in polyvinylpirrolidone (PVP) and verify that the amount of PVP can determine the particle size. So, they successfully tested the activity of Pd/PVP in Suzuki reactions and obtained good yields.[6] Sonogashira cross-coupling reaction was also investigated using Pd/PVP as a catalyst in a ligandless and copper free-system with high yields.[7] Finally, still with this system, Heck reactions showed to be conveniently carried out and furnished reaction products with high yields.[8]

Microwave (MW) as a non-conventional energy source has become a very popular and useful technology in organic chemistry.[9] The main attraction of using MW is to short reaction times in cleaner systems[10] even under solventless conditions.[11] In addition, presently, there is no doubt that there is no particular MW effect,[12] that is MW irradiation is just a simple, rapid, and effective way of energy transfer to a reaction medium provide if it is polar enough to suffer the absorption of MW energy.[13] Consequently, MW irradiation has been vastly applied in organic synthesis including C–C cross-coupling reactions.[14]

Other non-thermal way of energy transfer is ultrasound irradiation,[15] where cavitation plays the central role. Under sonication several examples indicated that high yields and short reaction times are attainable,[16a–d] and applications of this energy transfer process on cross-coupling reactions have been published in the literature.[16e–g]

Our group has been expanding the use of microwave[17a] and ultrasound[17b] technologies, as well as, other phosphine-free systems in cross-coupling reactions.[18] In the present work, we wish to present new protocols to obtain biaryls via Suzuki–Miyaura reaction conditions under microwave and ultrasound irradiation using Pd/PVP as a catalyst source.

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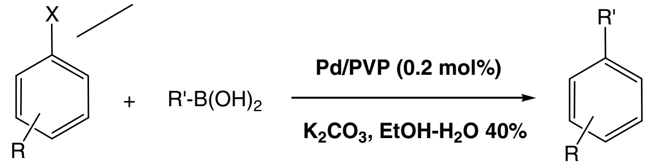
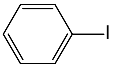
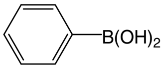
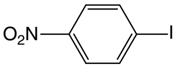
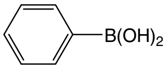
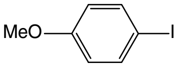
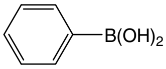
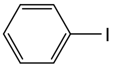
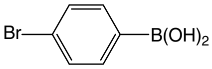
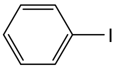
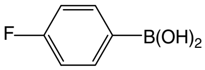
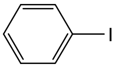
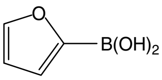
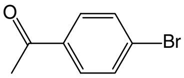
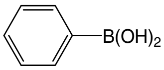


Scheme 1.

In our initial efforts towardthe use of MW irradiation in the Suzuki–Miyauracross-coupling reaction, using Pd/PVP as a catalyst (Scheme 1), we choose not to employ any ligand but PVP and use a very environmentally correct solvent mixture, 40% aqueous ethanol,which in previous examples[3,18b–e] was shown to be suitable to re-use.

We tested, as a model system, the reaction of iodobenzene with phenylboronic acid, using potassium carbonate as a base, 0.2 mol % Pd/PVP (previously prepared according to Narayanan and El-Sayed[6b]) in aqueous ethanolic solution under microwave irradiation. In parallel, to compare reaction times, thermal heating was also used. Both MW and thermal heating furnished the reaction product in quantitative yield, but in much shorter reaction time under MW (Table 1).[19] Other aryl halides and boronic acids were also tested under both conditions and the results are described in Table 1.

Table 1
Suzuki–Miyaura reaction between different aryl halides and boronic acids[a]

Entry	Aryl halide	Boronic acid	TC [b,c] (%)	MW [b,d] (%)
1			100	100
2			99	86
3			99	85
4			62	63
5			60	67
6			70	81
7			78	83

[a] Reaction condition: aryl halide (1 mmol), boronic acid (1 mmol), K_2CO_3 (2 mmol), Pd/PVP solution (0.2 mol %) in 15 mL of EtOH-H_2O 40% solution.

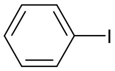
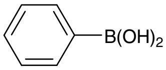
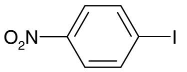
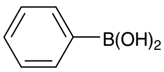
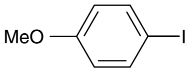
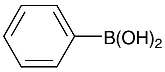
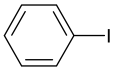
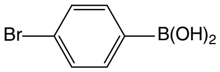
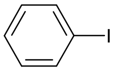
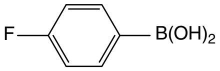
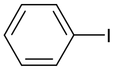
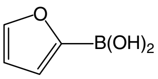
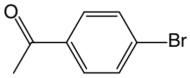
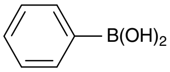
[b] Conversion determined by GC–MS.

[c] Thermal condition: 80 °C, 18 h.

[d] Microwave condition: 220 W, 40 min (Monomode Microwave CEM Discover).

The model reaction afforded 100% of conversion in biphenyl at 80° after 18 h, while under microwave irradiation the same result was obtained in 40 min using a potency of 220 W (entry 1).[20] Other aryl halides were tested in both the conditions. The reactions of 4-nitroiodobenzene and the 4-iodoanisole with phenylboronic acid, the furnished products with high yields (entries 2 and 3). When the boronic acids were changed to 4-bromophenylboronic acid and 4-fluorophenylboronic acid reaction with iodobenzene furnished reasonable yields (entries 4 and 5). In the first case (entry 4), no homosubstrate reaction was noticed showing much higher selectivity in the oxidative addition step to 4-nitroiodobenzene. Reaction between 2-furanboronic acid and iodobenzene gave Suzuki product with very good yield (entry 6). The less reactive 4-bromoacetophenone in coupling with phenylboronic acid afforded biaryl also in very good yield (entry 7). All the compounds were characterized and analyzed by GC–MS, ^{1}H NMR, and ^{13}C NMR.[21] In general, the microwave-assisted reactions furnished somewhat better yields than those under thermal conditions in much lower reaction times. In all the cases, considering the fact that 0.2% molar of the Pd(0) catalyst is used, turnovers between 300 (entry 5) and 500 (entry 1) were obtained in both the conditions, but TOFs (turnover frequency = number of mol of product·mol of catalyst^{-1}h^{-1}) were 27 times better under MW, that is, in entry 1 a TON of 500 was obtained in 40 min, TOF of 750/h, under MW and in 18 h, TOF of 28/h, under thermal conditions.

Table 2
Suzuki–Miyaura reaction under ultrasound using Pd/PVP[a]

Entry	Aryl halide	Boronic acid	Yield[b] (%)
1			83
2			100[c]
3			80
4			99
5			94
6			47
7			86

[a] Reaction condition: aryl halide (1 mmol), (hetero)arylboronic acid (1 mmol), Pd/PVP (0.2 mol %), K_2CO_3 (2 mmol), EtOH-H_2O 40% solution (15 mL) under ultrasound irradiation by 5 h.

[b] Determined by GC–MS.

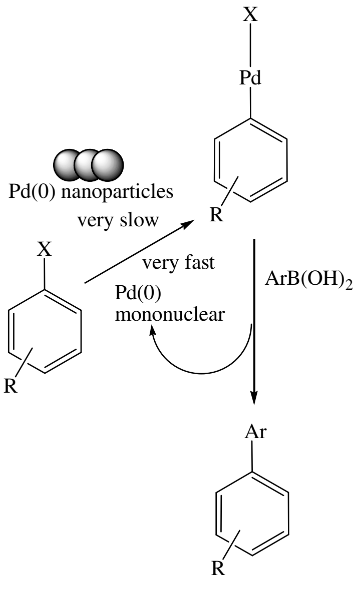
[c] 2 h reaction.

To go further, we start investigating the above reaction systems under ultrasound irradiation,[19,22] Table 2, and observed very good reaction yields after 5 h reaction. Interestingly, as expected, 4-nitroiodobenzene reacted faster than iodobenzene, that is, 100% conversion is achieved with the former in only 2 h (27% conversion after the first hour) while the latter needs 5 h to complete conversion. In addition, we did not observe formation of homocoupling products common in ultrasound-assisted coupling reaction.[23] Although better than under thermal condition, in reaction time terms, sonication was observed to be worse than MW irradiation, but was successful with all the substrates tested.

The reason to investigate sonication was based on the fact that we and other groups[24] have previously showed that normally Pd(0) stabilized nanoparticles are the sources of soluble Pd(0)/Pd(II) species that would be the actual catalysts in very low loadings[25] (Scheme 2). We, therefore, hypothesized that cavitation would play a role in disaggregating Pd(0) stabilized nanoparticles furnishing very reactive (solvated) Pd(0) mononuclear species which could improve turnover frequencies.

The fact that reaction under sonication was faster than thermal reaction but slower than MW assisted reaction indicated that cavitation only accelerated oxidative addition on the Pd(0) cluster surface (stabilized in PVP) and did not furnish free active solvated mononuclear Pd(0) species. So, turnover frequency under sonication was between 125 and 250/h keeping the same TONs observed above.

Recycling the whole reaction media showed no noticeable loss in reaction yields up to 2 cycles with high yields, that is, the extraction of products with hexane and the addition of 4-nitroiodobenzene, and phenylboronic acid under ultrasound furnished 98% and 97% yields, 1st and 2nd re-use, respectively.



Scheme 2.

In summary, the main advantage of microwave-assisted production of the biaryls is the shorter reaction times. All the reactions were successful and furnished good yields. We showed that very low loadings of Pd/PVP were sufficient to catalyze the reactions. The ultrasound-assisted Suzuki reaction furnished biaryls with high yields and shorter reaction time in comparison to thermal condition. Both MW and sonication can be useful to short reaction times in these reactions. Very high turnovers were observed in all the cases. Using MW turnover frequencies of up to 750/h was observed. No particular cavitation effect was observed in the sonicated systems.

Acknowledgment

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19. *General procedure for Suzuki reaction:* In a 25 mL reaction flask containing aryl halide (1 mmol), boronic acid (1 mmol), K_2CO_3 (2 mmol), Pd/PVP (0.2 mol %) in $EtOH/H_2O$ 40% solution (15 mL) were employing at 80 °C by 24 h, when in microwave heating for 40 min (potency of 220 W) or for 5 h under ultrasound irradiation. After the reaction was completed, the reaction mixture was extracted with hexane, dry under sodium sulfate, and the solvent was eliminated by vaccum. The crude product was analyzed by GC–MS, ^{1}H NMR, and ^{13}C NMR.
20. Monomode microwave CEM Discover. See more details in <www.cem.com>.
21. *Biphenyl*: Whitesolid. ^{1}H NMR(200 MHz, $CDCl_3$) δ 7.41–7.46 (2H, m), 7.50–7.55 (4H, m), 7.68–7.70 (4H, m); ^{13}C NMR(50 MHz, $CDCl_3$) δ 127.2, 127.3, 128.8, 141.3; GC–MS: $m/z = 76, 77, 153, 154$ (M^+). *4-Methoxybiphenyl*: Whitesolid. ^{1}H NMR(200 MHz, $CDCl_3$) δ 3.80 (3H, s), 6.95 (2H, d), 7.32 (1H, d), 7.38 (2H, t), 7.51–7.55 (4H, m); ^{13}C NMR(50 MHz, $CDCl_3$) δ 55.35, 114.27, 126.70,128.19, 128.77, 133.82, 140.88, 159.22; GC–MS: $m/z = 115, 141, 169, 184$ (M^+). *4-Nitrobiphenyl* – yellow solid. ^{1}H NMR($CDCl_3$, 200 MHz) δ 8.30 (d, 2H),7.74 (d, 2H),7.64 (d, 2H),7.52–7.44 (m, 3H). ^{13}C NMR($CDCl_3$, 50 MHz) δ 147.6, 147.1, 138.8, 129.2, 128.9, 127.8, 127.4, 124.1. GC–MS:$m/z = 77, 115, 154, 199$ (M^+). *4-Phenylacetophenone*: Paleyellow solid. ^{1}H NMR(200 MHz, $CDCl_3$) δ 2.65 (3H, s), 7.51–7.41 (3H, m), 7.71–7.62 (4H, m), 8.04 (2H, d); ^{13}C NMR(50 MHz, $CDCl_3$) δ 26.67, 127.23, 128.27, 28.94, 128.99, 135.87, 139.86, 145.77, 197.77; GC–MS: $m/z = 76, 152, 181, 196$ (M^+). *4-Fluorobiphenyl*:White solid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.56–7.53 (m, 4H), 7.40 (t, 2H), 7.33 (t, 1H), 7.15 (t, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 163.7, 161.3, 140.3, 137.4, 137.3, 128.8, 128.7, 128.6,127.3, 127.0, 115.7, 115.5. GC–MS: $m/z = 77, 95, 172$ (M^+). *2-Phenylfuran*:Colorless liquid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.68 (t, 2H), 7.44 (d, 1H), 7.39–7.24 (m, 3H), 6.64 (d, 1H), 6.45 (dd, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 154.2, 142.3, 131.1, 128.9, 127.5, 124.0, 111.8, 105.1. GC–MS: $m/z = 65, 77, 115, 144$ (M^+).
22. Sonication was performed in a thermostatic Branson 1210 ultrasonic cleaner with a frequency of 47 kHz and a power of 250 W.
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