An emerging reactor technology for chemical synthesis: Surface acoustic wave-assisted closed-vessel Suzuki coupling reactions

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\textbf{A B S T R A C T}

In this paper we demonstrate the use of an energy-efficient surface acoustic wave (SAW) device for driving closed-vessel SAW-assisted (CVSAW), ligand-free Suzuki couplings in aqueous media. The reactions were carried out on a mmolar scale with low to ultra-low catalyst loadings. The reactions were driven by heating resulting from the penetration of acoustic energy derived from RF Raleigh waves generated by a piezoelectric chip via a renewable fluid coupling layer. The yields were uniformly high and the reactions could be executed without added ligand and in water. In terms of energy density this new technology was determined to be roughly as efficient as microwaves and superior to ultrasound.

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\textbf{1. Introduction}

Very recently the first applications of surface acoustic waves (SAWs) in a lab on a chip device for use in organic chemical transformations on a drop scale have been described\cite{1–3}. In this paper we demonstrate the use of such a device for driving closed-vessel SAW-assisted (CVSAW), ligand-free Suzuki couplings in aqueous media. Operationally, this new technology obviates the need for oil baths, heating mantles, hot plates, ultrasonic baths and microwave cavities. Indeed it simply requires placing of a capped glass vial onto the surface of the chip.

Typically, Suzuki reactions involve palladium catalysed cross coupling between organoboronic acids and arylhalides \cite{4}. Recently, variants, including the use of trifluoroborates \cite{5}, organoboranes \cite{6} or boronic esters \cite{7} in place of boronic acids, triflates \cite{8} as pseudohalide coupling reagents and ionic liquids \cite{9–11} as the reaction medium have been reported. However, the availability of a wide range of functionalized, stable and less toxic boronic acids and halides still make them attractive partners for Suzuki coupling.

Reactions generally require heating and many reports have appeared on the use of microwave radiation as an excellent source of such heating \cite{12–15}. For the studies disclosed here we required the reactions to be carried out in a closed vessel. In order to exploit the energy contained in SAWs we employed paraffin oil, a high boiling low viscosity fluid, as a liquid couplant \cite{16}, as shown in Fig. 1.

Under these conditions the SAWs are transmitted into the paraffin oil as a bulk sound wave at a Rayleigh angle of 22.2 degrees (Fig. 1). As the bulk wave approaches the glass vessel, a Lamb wave is formed in the base of the vessel which acts to transmit the acoustic energy into the reaction solution within \cite{16}.

\textbf{2. Materials and methods}

\textbf{2.1. SAW apparatus}

All reactions were either performed on a 9.7 MHz, or a 19.5 MHz LiNbO\textsubscript{3} device. The SAWs were generated by applying a sinusoidal oscillating electrical signal output from an Agilent 33220A 20 MHz Function/Arbitrary waveform generator (Agilent Technologies, Santa Clara, California, USA), amplified by a 10 W RF amplifier (Amplifier Research, Souderton, Pennsylvania, USA), which was connected to a pair of IDTs (Al with 1 % Cu alloy). All four electrodes (two electrodes on each of the IDTs) were connected to the RF output of the amplifier to generate a standing wave. The signal generator was set to output a sine wave with the appropriate frequency for the device in use, and an amplitude of 230 mV\textsubscript{rms} when operating the 19.5 MHz SAW device or 450 mV\textsubscript{rms} when operating the 9.7 MHz device. The gain on the amplifier was adjusted to provide the required power to the SAW
device. Output power to the SAW device at the amplifier was measured using an Agilent U2004A 9 kHz to 6 GHz USB Power Sensor (with a range of –60 to +20 dBm or 1 nW to 100 mW) and displayed real-time on a computer screen using Power Panel (N1918A) software. To be within the measurable range of the power sensor, high power radio frequency attenuation was required and achieved by B498A High Power Attenuator, DC to 18 GHz, with 25 W average and 30 dBm fixed attenuation. The measured power was corrected for the applied attenuation in dBm and converted to watts. Reaction temperature was monitored using an analog probe with an insulated K-type thermocouple (HH501BJK, Omega, Stamford, Connecticut, USA).

The closed-vessel reactions were performed in glass vials (1.5 mL or 4.0 mL, flat-bottomed and screw capped), placed on the SAW device, using paraffin oil as a couplant between the LiNbO3 substrate and the glass vial.

2.2. Analytical equipment

Melting points were determined using Reichert hot stage melting point apparatus (Reichert, Austria) or a Stuart Scientific SMP3 melting point apparatus (Stuart Scientific, Stone, Staffordshire, UK).

Optical rotations were obtained using a PolAAR 2001 automatic polarimeter (Optical Activity Ltd., Huntingdon, Cambridgeshire, UK) using a 1 dm cell in CHCl3, at a wavelength of 589 nm (sodium D line), and are quoted as [α]D, concentration c/g (100 mL), solvent and recorded at rt.

Chiral HPLC was performed on an Agilent 1200 series HPLC system (Agilent Technologies, Santa Clara, California, USA), using a Chiracel OD-H (Daicel Chemical Industries Ltd., Kita-ku, Osaka, Japan) chiral analytical column (0.46×25 cm with particle size of 5 μm), with hexanes and/or PrOH as eluents.

1H NMR spectra were recorded at 300 MHz with a Bruker Avance DPX300 spectrometer and at 400 MHz with a Bruker Avance DRX400 spectrometer (Bruker BioSpin Corp., Billerica, Massachusetts, USA). The 1H spectra were obtained in CDCl3 stock solution (5.0 mL). The organic (0.001 g) and NaOAc (275 mg, 2.0 mmol), 3, 4-methoxybiphenyl (1.5 mL or 4.0 mL, flat-bottomed and screw capped), placed on the drop. The reaction mixture was heated using SAW irradiation (5–6 W) to maintain reflux throughout the reaction. The aqueous layer was extracted with CH2Cl2 (1.0 mL). The organic phase was dried over MgSO4, concentrated under vacuum, and purified by flash chromatography (EtOAc/hexanes 1:4) to afford the required biaryl product. Analytical data in agreement with the literature [17–22].

2.4. Method for Heck reaction using SAWs

A 4.0 mL glass vial, flushed with N2, was charged with Pd[dba]2 (16.4 mg, 18 μmol), and (S)-4-tert-butyl-2-f[2-(diphenylphosphino)phenyl]dihydrofuran (14 mg, 36 μmol), toluene (1.0 mL) was added to the vial and the suspension was shaken intermittently at rt. over a period of 10 min. To the resulting solution was added a solution of phenyl triflate (97.2 μL, 0.6 mmol), 2,3-dihydrofuran (227 μL, 3.3 mmol), and 1,8-bis-(dimethylamino) naphthalene (386 mg, 1.8 mmol) in toluene (1.0 mL). A 20 μL drop of paraffin oil was pipetted onto the LiNbO3 substrate and the glass vial was placed on the drop. The reaction was heated at reflux using SAW irradiation (8–9 W) for 25 min. The aqueous layer was extracted with CH2Cl2 (5.0 mL). The organic phase was dried over MgSO4, concentrated under vacuum, and purified by flash chromatography (EtOAc/hexanes 1:4) to afford 4-methoxybiphenyl 3 (164 mg, 89%) as a white solid. Analytical data were in agreement with the literature [19,20].

2.4.4. Method for Suzuki coupling reaction using conventional ultrasound [32]

Sonochemical reactions were carried out in a thermostated ultrasonic cleaning bath (Bronson S200; 120 W output power; 47 kHz). A direct comparison was made between the published sonochemical [32] and our SAW reactions with 4-methoxybromobenzene and phenylboronic acid used as substrates for the Suzuki cross couplings. The sonochemical reaction procedure was as follows: a mixture of aryl halide (0.5 mmol), phenylboronic acid (0.5 mmol), [bpin]2 [BF4] (0.5 g), Pd(OAc)2 (0.001 g) and NaOAc
the reaction setup was quite simple. An ethanol/water mixture containing Suzuki coupling partners was first added to the glass containing Pd(OAc)2 \( (400 \text{ MHz, CDCl}_3) \) as a white crystalline solid, m.p. 88–88 °C (lit. mp 89–89 °C) [19].

### 2.5.3. 4-Methoxybiphenyl (Table 1, entry 3)

Following the general procedure 2.4.1, using 3 μL of 5.35 \( \times 10^{-2} \) M Pd(OAc)2 stock solution and irradiating with SAWs for 8 min, afford, after purification, 4-methoxybiphenyl 3 (33 mg, 90%) as a white brown crystalline solid, m.p. 50–51 °C (lit. mp 51 °C) [18].

1H NMR (400 MHz, CDCl3) δ 7.54, (m, 2H); 7.45–7.37, (m, 4H); 7.30–7.25, (m, 1H); 6.76, (m, 2H); 3.71, (s, 3H).

13C NMR (100 MHz, CDCl3) δ 146.0, 141.3, 131.8, 128.8, 128.2, 126.5, 126.4, 115.5.

### 2.5.4. 4-Methylbiphenyl (Table 1, entry 4)

Following the general procedure 2.4.1, using 3 μL of 5.35 \( \times 10^{-2} \) M Pd(OAc)2 stock solution and irradiating with SAWs for 8 min, afford, after purification, 4-methylbiphenyl 2 (31 mg, 92%) as a brown crystalline solid, m.p. 44–45 °C (lit. mp 46–47 °C) [21].

1H NMR (400 MHz, CDCl3) δ 7.62–7.58, (m, 2H); 7.51, (m, 2H); 7.47–7.41, (m, 2H); 7.37–7.31, (m, 1H); 7.29–7.25, (m, 2H); 2.42, (s, 3H).

13C NMR (100 MHz, CDCl3) δ 141.3, 138.5, 137.2, 129.6, 128.9, 128.3, 126.9, 126.8, 114.4, 55.5.

### 2.5.5. 4-Methyl-4'-methoxybiphenyl (Table 1, entry 5)

Following the general procedure 2.4.1, using 3 μL of 5.35 \( \times 10^{-2} \) M Pd(OAc)2 stock solution and irradiating with SAWs for 30 min, afford, after purification, 4-methyl-4'-methoxybiphenyl 5 (33 mg, 83%) as a white crystalline solid, m.p. 105–108 °C (lit. mp 109–110 °C) [20].

1H NMR (400 MHz, CDCl3) δ 7.53, (m, 2H); 7.47, (m, 2H); 7.26–7.22, (m, 2H); 6.98, (m, 2H); 3.86, (s, 3H); 2.40, (s, 3H).

13C NMR (100 MHz, CDCl3) δ 159.1, 138.1, 138.5, 133.9, 129.6, 128.1, 126.7, 114.3, 55.5, 21.2.

### 2.5.6. 4-Acetyl-4'-methoxy-1,1'-biphenyl (Table 1, entry 6)

Following the general procedure 2.4.1, using 3 μL of 5.35 \( \times 10^{-2} \) M Pd(OAc)2 stock solution and irradiating with SAWs for 15 min, afford, after purification, 4-acetyl-4'-methoxy-1,1'-biphenyl 6 (44 mg, 97%) as a white crystalline solid, m.p. 154–155 °C (lit. mp 154–155 °C) [18].

1H NMR (400 MHz, CDCl3) δ 8.01, (m, 2H); 7.64, (m, 2H); 7.58, (m, 2H); 7.00, (m, 2H); 3.86, (s, 3H); 2.62, (s, 3H).

13C NMR (100 MHz, CDCl3) δ 197.8, 160.1, 145.5, 135.5, 132.4, 129.1, 128.5, 126.8, 114.6, 55.5, 26.7.

### 2.5.7. 4-Methyl-4-biphenylamine (Table 1, entry 7)

Following the general procedure 2.4.1, using 3 μL of 5.35 \( \times 10^{-2} \) M Pd(OAc)2 stock solution and irradiating with SAWs for 15 min, afford, after purification, 4-methyl-4-biphenylamine 7 (36 mg, 98%) as a white crystalline solid, m.p. 98–100 °C (lit. mp 98–100 °C).

1H NMR (400 MHz, CDCl3) δ 7.47–7.39, (m, 4H); 7.22, (d, J 7.9 Hz, 2H); 6.76, (m, 2H); 3.64, (s, 2H); 2.39, (s, 3H).

13C NMR (100 MHz, CDCl3) δ 145.7, 138.5, 136.0, 131.8, 129.5, 127.9, 126.4, 115.5, 21.2.

### 2.5.8. 4-Acetyl-3'-nitrobiphenyl (Table 1, entry 8)

Following the general procedure 2.4.1, using 3 μL of 5.35 \( \times 10^{-2} \) M Pd(OAc)2 stock solution and irradiating with SAWs for 12 min, afford, after purification, 4-acetyl-3'-nitrobiphenyl 8 (48 mg, 99%), as a white crystalline solid, m.p. 108–110 °C (lit. mp 110–111 °C) [17].

1H NMR (400 MHz, CDCl3) δ 8.47, (t, J 2.0 Hz, 1H); 8.25, (d, d, J 1.0 Hz, 2.0 Hz, 8.0 Hz, 1H); 8.08, (m, 2H); 7.95, (d, J 1.0 Hz, 2.0 Hz, 8.0 Hz, 1H); 7.72, (m, 2H); 7.65, (t, J 8.0 Hz, 1H); 2.66, (s, 3H).

13C NMR (75 MHz, CDCl3) δ 197.6, 149.0, 143.2, 141.7, 137.1, 133.3, 130.1, 129.3, 127.5, 123.0, 122.3, 26.8.

### 2.5.9. (R)-2-Phenyl-2,5-dihydrofuran (9)

(R)-2-Phenyl-2,5-dihydrofuran 9 was synthesised following the method for Heck reaction using SAWs 2.4.3. The product was determined to have an enantiomeric ratio of 94.5:5.5 by chiral HPLC (100% hexanes at 1.0 mL/min, detection at 197 nm, \( t_{R} \) = 27 min for the major isomer and 36 min for the minor isomer) [23].

### 2.5.10. Specific rotation \( \left[ \alpha \right]_{D}^{25} = +275 \, \text{c} \) (0.59, CHCl3)

1H NMR (400 MHz, CDCl3) δ 7.38–7.25, (m, 5H); 6.04, (d, d, J 1.6 Hz, 2.3 Hz, 6.1 Hz, 1H); 5.90, (d, d, J 1.6 Hz, 2.5 Hz, 6.3 Hz, 1H); 5.80, (d, d, J 2.0 Hz, 4.0 Hz, 7.9 Hz, 1H); 4.88, (d, d, J 1.7 Hz, 2.4 Hz, 6.0 Hz, 12.8 Hz, 1H); 4.78, (d, d, J 1.6 Hz, 2.5 Hz, 4.1 Hz, 12.8 Hz, 1H).

13C NMR (100 MHz, CDCl3) δ 142.2, 130.1, 128.6, 127.9, 126.8, 126.5, 88.1, 76.0.

### 3. Results and discussion

The reaction setup was quite simple. An ethanol/water mixture containing Suzuki coupling partners was first added to the glass reactor (typically a flat-bottomed, screw-capped 1.5 mL vial) and
then an ethanolic suspension of the catalyst was added. The total reaction volume was 600 mL. After the vial was closed and placed on the chip the device was switched on. The reaction mixture immediately began to heat up and in all cases reflux became evident within two minutes. A range of electronically diverse arylboronic acids and halides (Scheme 1) was employed in this study. Reaction times were typically 8–15 min. The only exception was a case where both aromatic partners bore an electron-donating substituent (Table 1—entry 5) which resulted in the reaction taking 30 min to complete. In most cases the product precipitated as a white crystalline solid once the reaction was allowed to cool to room temperature.

At the scale employed in this paper (0.2 mmol substrate) only about 6 W of power is consumed with reaction times comparable to other methods. This compares very favorably with other sources of energy, including microwaves [24–27], low and high power ultrasound [28–30] as well as conventional heating. Also, as SAWs are intrinsically safe no shielding was required during active experiments.

Scaled up, closed-vessel SAW reactions are also possible. For example, entry 3 in Table 1 was scaled up to 1 mmol in a 4 mL glass vial. The reaction required a longer reaction time of 25 min (as opposed to 10 min), providing the biaryl product in excellent yield (85–90%).

In order to provide some comparison with other heating methods we calculated the energy density\(^1\) required for the scaled up, closed-vessel, SAW-assisted Suzuki reaction. This was compared with the energy densities for the same coupling reaction, on a similar scale, using microwaves or ultrasound and was calculated by using the values of power consumed and reaction times mentioned in the literature (Table 2) [31,32]. The energy density for the SAW-assisted reaction was slightly larger than that required for the microwave-based process, but significantly less than that consumed by ultrasound. It also needs to be noted that the SAW devices employed in this study are very much at the prototype stage and have not yet had the benefit of design engineering and optimization.

An asymmetric Heck (Scheme 2) was carried out on a 0.6 mmol scale using a similar reaction setup to the Suzuki reactions, heated using SAWs for 3 h at 110 °C, which resulted in 71% yield with 90% ee (as measured by chiral HPLC of the major isomer on Daicel Chiracel OD-H), both comparable to the literature [33–35].

Somewhat parenthetically, we also found that these ligand-free Suzuki coupling reactions using traditional boronic acids proceed with high efficiency with low to ultra-low catalyst loadings. Running each reaction on a 0.2 mmol scale, with 0.0008–0.08 mol% catalyst loading, afforded the desired biaryl products in good to excellent yields. Ultra-low catalyst loading has previously been achieved by employing either (i) ligands with the palladium acetate catalyst and conventional boronic acids [36] or (ii)

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\(^1\) Energy density (kJ/mmol) = [Power (W) × Reaction time (sec)]/Moles of limiting reagent (mmol).
organotrifluoroborates [5] in combination with ligand-free palladium catalysis. Reusable solid supported palladium catalysts have also been reported for Suzuki couplings due to their ease and sustainable use. However, higher loadings were required and solvent-free reactions required much higher microwave power [37]. In examples where lower loading of reusable supported Pd catalysts (0.4 mol%) were used, longer reaction times (typically 20 h reflux) have been reported [17]. Even with the lower loading of the solid supported catalyst it has been reported that micro-equivalents of Pd are lost due to leaching of the catalyst during the reaction [17]. These roughly equate to the 0.0008 mol% catalyst used in entries 1, 6 and 8 (Table 1).

4. Conclusion

In conclusion, SAWs provide an operationally simple, excellent energy source for thermally-driven homogeneous, transition-metal catalyzed processes such as the Suzuki and Heck coupling reactions described here. As evidenced by our calculations the energy density for the SAW-assisted reaction was slightly larger than that consumed by ultrasound. These results indicate that this new, simple technology shows great potential for delivering energy to chemical reactions in a safe and efficient manner.

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