

Supplementary Information

The Energy Efficiency of Microwave and Conventionally-Heated Reactors Compared at *Meso*-Scale for Organic Reactions

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Explanatory Notes

Representative examples of the chemistry only are given here for all four reactions in one or more reactors, and at one or two scales and microwave power settings. See the Experimental Section in the main text for full discussion of how the energy usage data was collected and processed, and further notes on the individual microwave reactors used.

General Procedures. Reaction mixtures and products were analysed by reverse phase HPLC on an Agilent 1100 series instrument as follows. **Method 1:-** column, Waters Symmetry C18 3.5 μm , 50 mm x 3.0 mm i.d.; eluent A, 100% purified water with 0.03% v/v TFA; eluent B, 100% acetonitrile with 0.03% v/v TFA; flow rate 1.25 mL/min.; wavelength 230 nm; temperature 45 °C; injection volume 2 μL ; at t = 0 mins, 5% eluent B; at t = 6 mins, 95% eluent B; at t = 7.5 mins, 95% eluent B; post time 1.5 mins. **Method 3:-** column, Varian Polaris Amide C18 3.0 μm , 50 mm x 3.0 mm i.d.; eluent A, 100% purified water with 0.03% v/v TFA; eluent B, 100% acetonitrile with 0.03% v/v TFA; flow rate 1.25 mL/min.; wavelength 230 nm; temperature 45 °C; injection volume 2 μL ; at t = 0 mins, 5% eluent B; at t = 6 mins, 95% eluent B; at t = 7.5 mins, 95% eluent B; post time 1.5 mins. ^1H and ^{13}C NMR spectra were recorded on a Varian Inova 400 spectrometer at 400 and 100.6 MHz respectively with chemical shifts given in ppm relative to TMS at $\delta=0$.

$\text{S}_{\text{N}}\text{Ar}$ Reaction on 1 L scale in CEM MARS (800 W) (Scheme 1). 1,2-Dichloro-4-nitrobenzene (**1**) (98 g, 500 mmol) and 4-cyanophenol (**2a**) (66.5 g, 550 mmol) were charged to a 3 L three-neck flask and dissolved in DMA (980 mL) to give a yellow solution. Potassium carbonate (105 g, 750 mmol) was added to give a slurry. The flask was transferred to the cavity of a CEM MARS microwave and fitted with a mechanical stirrer driving a PTFE paddle, an external water condenser on the side arm of the stirrer adaptor, and a fibre optic probe in a thermowell in one of the 3 L flask side adaptors. Stirring was set to 200 rpm and the reaction mixture heated to 140 °C over 8 minutes on the 800 W setting (100% power available), then held at 140 °C for 10 minutes. The reaction mixture was cooled to ~70 °C by fan air over 30 minutes, then transferred to a large conical flask (including the insoluble potassium salts). Water (800 mL) was added dropwise over ~30 minutes with good mechanical stirring. Considerable heat of mixing was generated and an off-white solid was precipitated. The reaction mixture was cooled

further in an ice-water bath and the precipitate isolated by filtration. The product was washed by displacement three times with water (300 mL each) and dried in a vacuum oven at 40 °C with an air bleed to yield the substituted diphenyl ether (**3a**) as a pale cream solid (138 g, 100%). HPLC (method 3, RT 4.50 mins, 99%); ¹H NMR (400 MHz, CDCl₃) δ 8.42 (1H, d, J = 2.4 Hz), 8.17 (1H, dd, J = 9.0, 2.6 Hz), 7.70-7.74 (2H, m), 7.09-7.15 (3H, m); ¹³C NMR (100.6 MHz, CDCl₃) δ 158.79, 156.31, 144.39, 134.56, 126.85, 123.81, 120.26, 118.95, 118.06, 108.42.

S_NAr Reaction on 2 L scale in the Jacketed Reactor Vessel. 1,2-Dichloro-4-nitrobenzene (**1**) (196 g, 1.0 mol) and 4-cyanophenol (**2a**) (133 g, 1.1 mol) were charged to a jacketed 3 L reactor vessel and dissolved in DMA (1960 mL) to give a yellow solution. Potassium carbonate (210 g, 1.5 mol) was added to give a slurry. The flask was fitted with a mechanical stirrer driving a PTFE paddle, a water condenser PTFE-protected thermocouple. Stirring was set to 200 rpm and the reaction mixture heated through the jacket by a Julabo FP 50 heater-chiller unit (8 L heating fluid capacity) to between 130 and 135 °C over 38 minutes and held in this temperature range for ~15 minutes to achieve >99% conversion (by HPLC). The reaction mixture was cooled to 55 °C (without active chilling) over 31 minutes and worked up as noted above.

Alkylation Reaction on 2 L scale in CEM MARS (1600 W) (Scheme 2). 4-Methoxyphenol (mequinol, **2b**) (251 g, 2.0 mol), iso-butenylchloride (**4**) (222 g, 241 mL, 2.4 mol) and NMP (2.0 L) were charged to a 3 L three-neck flask to give a pale yellow solution. Potassium carbonate (423 g, 3.0 mol) was added to give a slurry. The flask was transferred to the cavity of a CEM MARS microwave and fitted with a mechanical stirrer driving a PTFE paddle, an external water condenser on the side arm of the stirrer adaptor, and a fibre optic probe in a thermowell in one of the 3 L flask side adaptors. Stirring was set to 200 rpm and the reaction mixture heated to 150 °C over 9.6 minutes on the 1600 W setting (100% power available), then

held at 150 °C for 10 minutes. The reaction mixture was cooled to ~80 °C by fan air over 28 minutes, then free cooled to RT. The potassium salts were removed by filtration and the reaction mixture diluted with water (1500 mL) added dropwise. **Care:** Considerable heat of mixing was generated; the following extraction should not be carried out until the mixture has been re-cooled to RT. The cool reaction mixture was extracted sequentially with three portions of MTBE (500 mL, 400 mL and 300 mL). The combined MTBE extracts were washed sequentially with dilute aqueous NaOH solution (200 mL, 0.25 M), water (200 mL) and dilute brine (200 mL). The MTBE extracts were then dried over MgSO₄ and concentrated to dryness to yield the allyl ether product (**5**) as a pale orange oil which crystallised on standing (315 g, 88%). HPLC (method 1, RT 4.70 mins, 100%); ¹H NMR (400 MHz, CDCl₃) δ 6.80-6.89 (4H, m), 5.08 (1H, d, J = 0.8 Hz), 4.97 (1H, d, J = 1.2 Hz), 4.38 (2Hs), 3.76 (3H, s), 1.82 (3H, d, J = 0.8 Hz).

Diels-Alder Reaction on 2 L scale in CEM MARS (1600 W) (Scheme 3). Anthracene (**6**) (428 g, 2.4 mol) and maleic anhydride (**7**) (235 g, 2.4 mol) in DCB (1883 mL) were charged to a 3 L three-neck flask to give a yellow slurry. The flask was transferred to the cavity of a CEM MARS microwave and fitted with a mechanical stirrer driving a PTFE paddle, an external water condenser on the side arm of the stirrer adaptor, and a fibre optic probe in a thermowell in one of the 3 L flask side adaptors. Stirring was set to 200 rpm and the reaction mixture heated to 180 °C over 10.5 minutes on the 1600 W setting (100% power available), then held at 180 °C for 8 minutes. Both solids had dissolved by ~100 °C to give a dark orange solution. Vigorous boiling in the flask was seen at 180 °C but not in the condenser external to the flask. (Alternatively the reaction mixture was heated on the same scale in the MARS or in the 3 L jacketed reaction vessel to 140 °C for 120 minutes). The reaction mixture was cooled to 64 °C by fan air over 60 minutes, during which time a dense white solid formed (from 145 °C). The reaction mixture was cooled further in an ice-water bath and the precipitate isolated by filtration. The product was washed by

displacement twice with toluene (400 mL each) and dried in a vacuum oven at 60 °C with an air bleed to yield the Diels-Alder adduct (**8**) as a white granular solid (647 g, 98%). HPLC (method 3, RT 4.14 mins, 97%); ¹H NMR (400 MHz, d₆-DMSO) δ 7.44-7.48 (2H, m), 7.30-7.34 (2H, m), 7.14-7.20 (4H, m), 4.87 (2H, m), 3.65 (2H, m); ¹³C NMR (100.6 MHz, d₆-DMSO) δ 171.50, 141.07, 139.05, 127.03, 126.50, 124.82, 124.43, 47.89, 44.30.

Diels-Alder Reaction on 1 L scale in Anton Paar Synthos 3000 (1400 W). Anthracene (**6**) (11.1 g, 2.4 mol) was added to maleic anhydride (**7**) (6.1 g, 2.4 mol) in DCB (49 mL) in each of 16 Synthos PTFE reaction tubes. **Note:** anthracene must be added to the pre-dispensed DCB solvent to stop anthracene settling around the magnetic stirring bar, and to allow the air trapped in the granular anthracene to escape more readily. Total anthracene was 178 g (1.0 mol), total maleic anhydride 98 g (1.0 mol), total DCB 784 mL and the total combined volume 1040 mL. A magnetic stirring bar was added to each tube which was capped and sealed in its ceramic case and placed in the 16-position rotor. One tube was fitted with a gas-bulb thermometer; the temperature in the others was monitored by IR-pyrometer. The rotor was placed in the cavity of an Anton Paar Synthos 3000 microwave reactor. The reaction mixtures were heated with magnetic stirring to 180 °C over ~10 minutes with 1400 W available power, held at 180 °C for ~8 minutes, then cooled by fan air to 49 °C over 30 minutes. The combined reaction mixtures were cooled further in an ice-water bath and the combined precipitate isolated by filtration. The product was washed by displacement twice with toluene (200 mL each) and dried in a vacuum oven at 60 °C with an air bleed to yield the Diels-Alder adduct (**8**) as a white granular solid (264 g, 96%). HPLC (method 3, RT 4.14 mins, 99%). Other data as above.

Preparation of Reaction Mixture for the Heck Reaction (Scheme 4). Methyl acrylate (**10**) (95 mL, 1050 mmol, 1.05 eqs) and di-*iso*-propylethylamine (262 mL, 1500 mmol, 1.50 eqs)

were added to a solution of 4-bromoacetophenone (**9**) (199 g, 1000 mmol) dissolved in DMA (1700 mL) and thoroughly mixed. In a separate flask, tetrabutylammonium bromide (1.11 g, 4.0 mmol, 0.4 mol%) was added to a solution of Pd(OAc)₂ (225 mg, 1.0 mmol, 0.1 mol%) dissolved in DMA (290 mL) to give a dark orange solution. This solution was added to the first solution to give the reaction mixture as a light orange solution. The reaction mixture could be used immediately, or stored in a sealed vessel for some time if required (at least one week if volatile components could not evaporate). Reactions were performed in the jacketed reaction vessel, the MARS and the Synthos as noted above. Reactions in the CEM Voyager and Milestone FlowSYNTH were performed as noted in the text, after pre-filtration of the reaction mixture through a grade 3 sinter to ensure no particulates were present. A typical work-up procedure follows.

Typical Work-Up Procedure for the Heck Reaction. Any solid HBr salts of Hunig's base were decanted beforehand. Warm water (950 mL) was added to the well-stirred dark-brown reaction mixture (950 mL, 373 mmol) over 15-20 minutes. Considerable heat of mixing was generated and a orange/pink slurry produced. Once the mixture had cooled back to RT (with cooling water if required), the precipitate was isolated by filtration and the product cake slurry washed twice with water and once by displacement (each wash 250 mL). The product was dried in a vacuum oven at 50 °C with an air bleed to yield methyl 3-(4-acetylphenyl)acrylate (**11**) as an off-white or cream solid (72 g, 95%). HPLC (method 1, RT 3.63 mins, 97%); mp 98-99 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.97 (2H, dt, J = 8.8, 1.8 Hz), 7.71 (1H, d, J = 16.0 Hz), 7.61 (2H, dd, 6.8, 1.6 Hz), 6.53 (1H, d, J = 16.0 Hz), 3.83 (3H, s), 2.62 (3H, s); ¹³C NMR (100.6 MHz, CDCl₃) δ 197.2, 166.9, 143.2, 138.66, 138.0, 128.8, 128.1, 120.3, 51.8, 26.6.