Suzuki-Miyaura coupling reactions in aqueous microdroplets with catalytically active fluorous interfaces

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Electronic Supplementary Information (ESI)

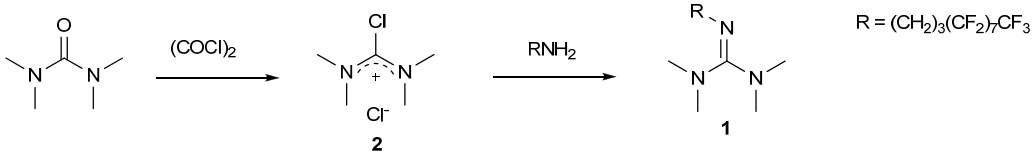
General preparative methods

Unless indicated otherwise, reagents and solvents were purchased and used without purification. Aqueous solutions were prepared using deionised (DI) water from a Milli-Q purifier or HPLC grade water.

For the synthesis of **1**, triethylamine (TEA) was dried over KOH and distilled before use. Dry solvents were obtained from stills or purchased anhydrous. Air- or moisture-sensitive reactions were conducted in oven-dried glassware under a positive pressure of nitrogen. Liquids and solutions for these reactions were transferred by gas-tight syringe.

^{1}H NMR spectra were recorded on a Brüker Avance 500 Cryo Ultrashield (500 MHz) spectrometer and are reported in ppm using the solvent residual peak as an internal standard ($CDCl_3$: 7.26 ppm). Data are reported as (integration, multiplicity, coupling constant in Hz). Proton-decoupled ^{13}C NMR spectra were recorded at 125 MHz and are reported in ppm using solvent as an internal standard ($CDCl_3$: 77.36 ppm).

Synthesis of 2-(1H,1H,2H,2H,3H,3H-perfluoroundecyl)-1,1,3,3-tetramethylguanidine (1):



This procedure was modified from Li *et al.*[1] and Fujisawa *et al.*[2] N,N,N',N'-tetramethylurea (TMU) (0.98 mL, 8.15 mmol) and oxalyl chloride (1.15 mL, 13.6 mmol) were added slowly at rt to 1,2-dichloroethane (11.7 mL). The reaction was then heated to 60 °C for 2 h, and allowed to cool to rt. The solvent and residual oxalyl chloride were removed *in vacuo* to give Vilsmeyer salt intermediate **2**, a pale yellow solid which was used in the subsequent step without further purification.

To acetonitrile (ACN) (13.2 mL) cooled in an ice bath were added 1H,1H,2H,2H,3H,3H-perfluoroundecylamine (2.12 mL, 6.90 mmol) and TEA (1.06 mL, 7.59 mmol). Vilsmeyer salt **2** (1.319 g) was dissolved in ACN (6.6 mL), and added slowly to the reaction solution. An additional portion of ACN (3.3 mL) was used to rinse the flask containing **2**, and this was transferred to the reaction mixture. After stirring on ice for 5 minutes, the ice bath was removed to verify that the exothermic reaction had subsided. The reaction mixture warmed to rt and was refluxed for 3 h. After cooling to rt, NaOH (0.55 g, 13.8 mmol) dissolved in a minimal amount of water was added dropwise with vigorous stirring. After stirring for 10 min, the mixture was extracted with DCM, concentrated *in vacuo*. A portion of residual organic layer was dissolved in DCM, washed with water, and concentrated *in vacuo*. The resulting material was purified by dissolution into FC-77 (fluorinated solvent) followed by filtration through a

syringe filter (0.45 μm PTFE). The fluorous phase was then concentrated *in vacuo* to give **1** as a light yellow viscous liquid.

δ_H (500 MHz; CDCl3) 3.20 (2H, t, 6.4), 2.76 (6H, s), 2.70 (6H, s), 2.21-2.13 (2H, m), 1.87-1.83 (2H, m); δ_C (125 MHz, CDCl3) δ 161.2, 121-109 (weak CF_2 and CF_3 signals), 48.2, 40.0, 39.2, 29.1, 23.4; HRMS calculated: 576.1302, found: 576.1293

Fluidic methods

The fluorous and aqueous phases were loaded into plastic syringes (BD) with 21G disposable needles attached. PTFE tubing (0.75 mm ID) was fitted over the needles and used to transport the liquid to the droplet formation tee. To form the droplets a 0.75mm bore CTFE tee (Thames Restek Ltd) was connected such that the fluorous and aqueous phases entered the tee at right angles to each other with the third exit connected to an additional length of PTFE tubing (0.75 mm ID) for the reaction tube. Flow rates were maintained using Harvard PHD 2000 infusion syringe pumps. For recyclability experiments, a peristaltic pump (Masterflex C/L, Cole Parmer) was used to recycle the fluorous phase. Channels were imaged in real time using an inverted Olympus IX71 microscope connected to a Phantom fast camera.

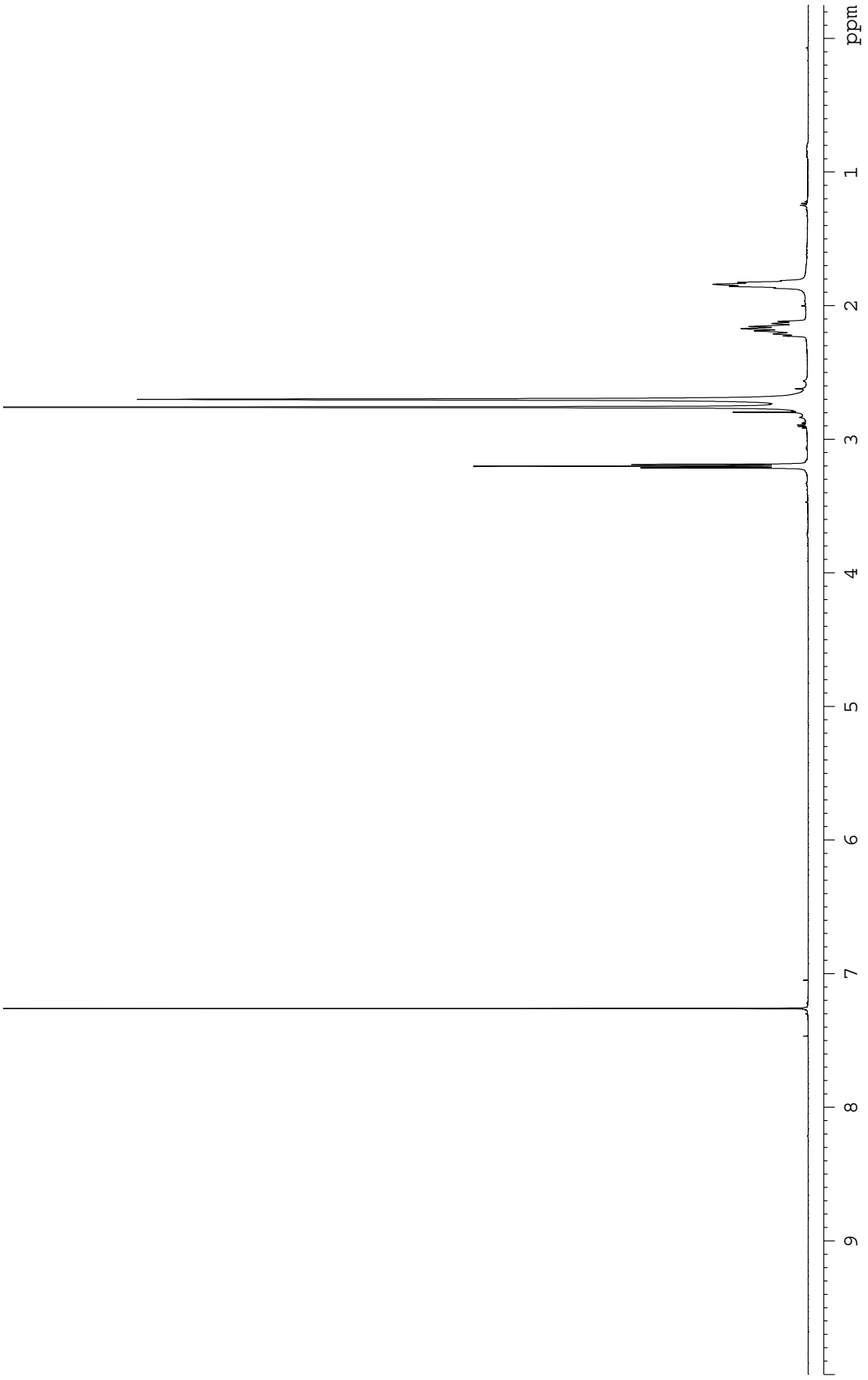
All Suzuki-Miyaura reactions were performed at room temperature under ambient atmosphere. Reactions were performed using an aqueous solution of K_2CO_3 (136 mM), arylboronic acid (55 mM), and aryl halide (45 mM). The fluorous catalyst solution was prepared by first dissolving ligand **1** and $Pd(OAc)_2$ (in a 2:1 molar ratio) in DCM, followed by subsequent concentration *in vacuo* after 3 h. The resulting residue was dissolved in FC-77 to produce the catalyst solution used in microfluidic experiments (0.136 mM $Pd(OAc)_2$, 0.272 mM **1**). Fluorous/aqueous flow rates of 690/414 μl/h were used except for the reaction shown in Table 1, Entry 5, which was conducted using fluorous/aqueous flow rates of 319/96 μl/h to facilitate an extended residence time and higher catalyst loading. Reactions were quenched by placing the end of the tube in a vial containing in 0.2 N HCl (with stirring). The quenched reaction mixture was dissolved in methanol, and yields were determined using HPLC-UV by comparing product peak integration to a calibration curve produced using commercially available products. The products were further characterized using LC-MS.

References:

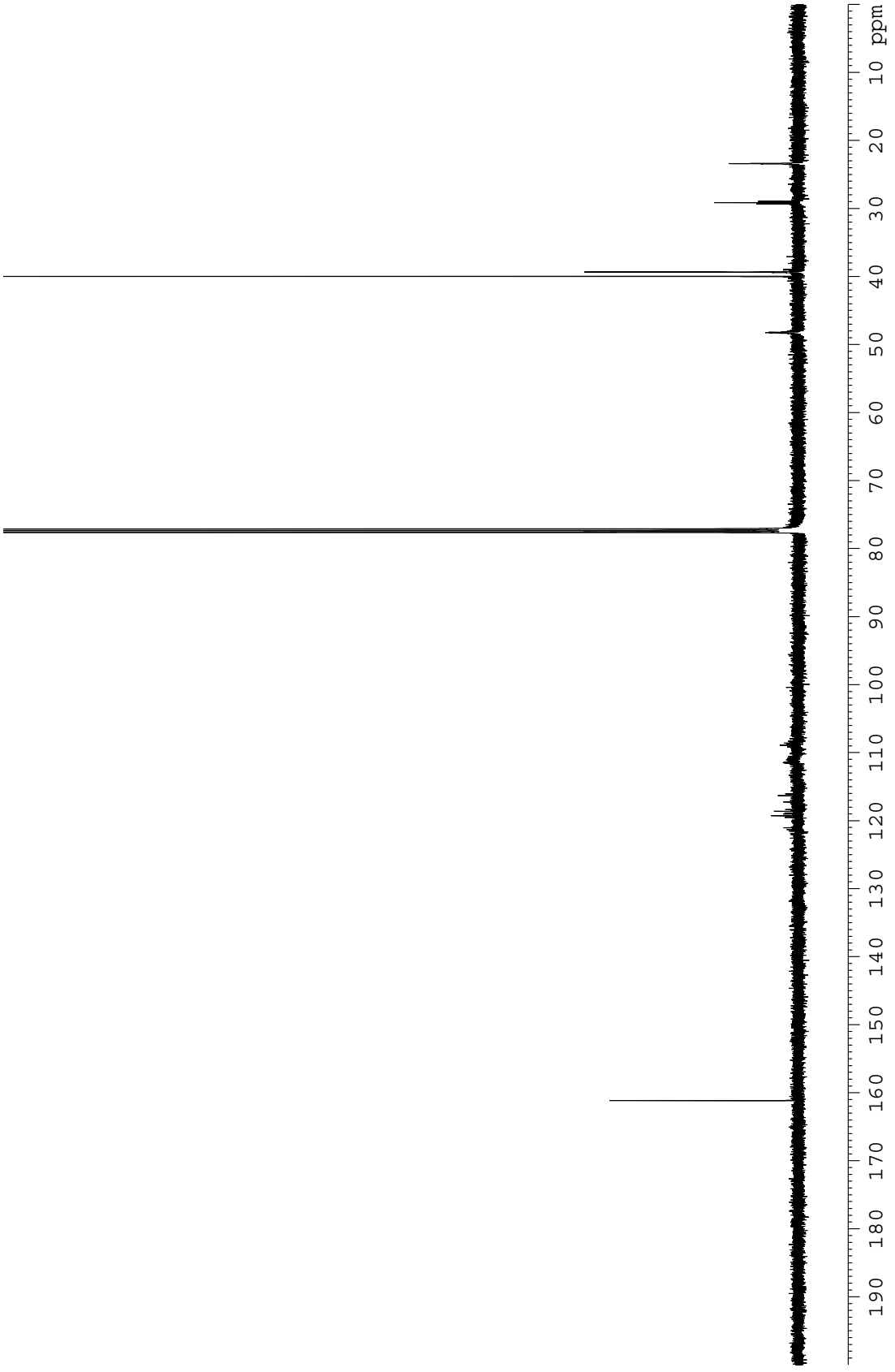
1 S. Li, Y. Lin, J. Cao and S. Zhang, *J. Org. Chem.*, 2007, **72**, 4067.

2 T. Fujisawa, K. Tajima, and T. Sato, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 3529.

^{1}H NMR of **1**



^{13}C NMR of **1**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