Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.

ELECTRONIC SUPPLEMENTARY INFORMATION

Accelerated multi-reagent copper catalyzed coupling reactions in micro droplets and thin films

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EXPERIMENTAL DETAILS

Reagents: Reagents were purchased from Sigma Aldrich (Milwaukee, WI) and used without any further purification.

ESI experiments: Configuration of the reaction apparatus is shown in Figure 1a. A small piece of KimWipe (1cm x 1cm) was rolled and plugged into one end of a borosilicate glass capillary (Sutter Instrument, Novato, CA, O.D.:1.5mm, I.D.:0.86mm). This was placed into a round bottom flask along with a magnetic stirrer with the KimWipe plug at the bottom of the flask. For the C-O coupling reaction, 1.5 mM of alcohol, 0.050 mM of copper(I) iodide, 0.10 mM of 3,4,7,8-tetramethyl-1,10-phenanthroline (Me_4Phen) and 1.5 mM of base was then placed in the round bottom flask. The solvent used was toluene. For the C-N coupling reaction, 1.5 mM of the sulfonamide, 2mM of the base and 0.020 mM of copper(I) oxide was placed in the flask. The solvent used was THF: Water (3:1). The flask was sealed with a rubber septum. A ~15 cm long fused silica capillary (Polymicro Technologies, Phoenix, AZ, O.D.: 360µm, I.D.: 100µm) was passed through the septum with the aid of a precision needle until it reached the borosilicate glass capillary. The other end of the fused silica was positioned in front of the MS inlet with the aid of a second precision needle. The flask was then connected to a nitrogen supply where the flow was set to 1L/min. The positive pressure of nitrogen helps the reaction mixture flow through the fused silica capillary. The first minute or so is used to make sure that we have a stable spray from the fused silica capillary. This can be done by observing spectra online or by illuminating the spray with the aid of a laser pointer. Both methods were employed to confirm the presence of a steady spray. Once the spray was found to be steady, 1.0 mM of 3-iodopyridine in 1.5 ml of toluene (for C-O coupling) and 3-iodopyridine in THF:water (3:1) (for C-N coupling) was added to the flask with the help of a syringe. A voltage of +3 kV was applied to the precision needle and spectra were recorded using an LTQ ion trap mass spectrometer (Thermo Fisher Scientific, San Jose, CA).

Paper spray experiments coupled with APCI: Configuration of this reaction setup is shown in Figure 1b. The reactants were mixed the same stoichiometric amounts as in the ES experiments. The resultant reaction mixture was filtered and loaded into a syringe that was used to spray the reaction mixture onto a small (about 1 cm on a side) equilateral triangle cut from Whatman Chromatography paper (Cat No. 3001-861, Buckinghamshire, UK). A voltage of +7kV was applied to the paper and a flow rate of 20µL/min was used. When paper spray was used in conjunction with APCI, the setup was just slightly modified to include a silver APCI needle right in front of the paper spray plume. The APCI needle was held at a voltage of +3kV for all experiments.

ESI experiments for offline collection (C-O coupling): Configuration of the ES apparatus is shown in Figure 1c. The reagents were mixed and loaded onto a Hamilton syringe and operated with the aid of a Hamilton syringe pump. The flow rate was kept constant at 30 µL/min. The collection surface was a grounded 20ml scintillation vial. The scintillation vial was cooled in a mixture of dry ice and acetone during collection to prevent evaporation of the collected product. An external power supply was used to apply voltage (+5 kV) to the needle.

ESI experiments for offline collection (C-N coupling): The ES setup used for offline collection of the C-N coupling product is very similar to what is shown in Figure 1a. the setup shown is slightly modified to include 2 additional fused silica lines and hence aid in multiplexing. The collection surface used was glass wool that was contained in a 20 ml Falcon tube (Fisher Scientific, New Hampshire, USA). An external power supply was used to apply voltage (+4 kV) to the fused silica lines. The total spray time was 40 min.

Bulk/batch experiments: Bulk experiments were performed by placing stoichiometric amounts of reagents in a closed round bottom flask. The C-O coupling reaction (using ethanol and 3-iodopyridine) was carried out at 90°C for 12 hours. The reaction mixture was diluted with ethyl acetate, washed with saturated brine and dried over sodium sulfate. Reduced pressure distillation was used for purifying the product. The C-N coupling reaction (using different sulfonamides and 3-iodopyridine) was carried out in a closed system at to 130°C for 30 hours. The reaction mixture was allowed to cool and diluted the methanol. The extract was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude product was then loaded onto a column and purified. All products were characterized using ^{1}H NMR spectroscopy.

EXPERIMENTAL RESULTS

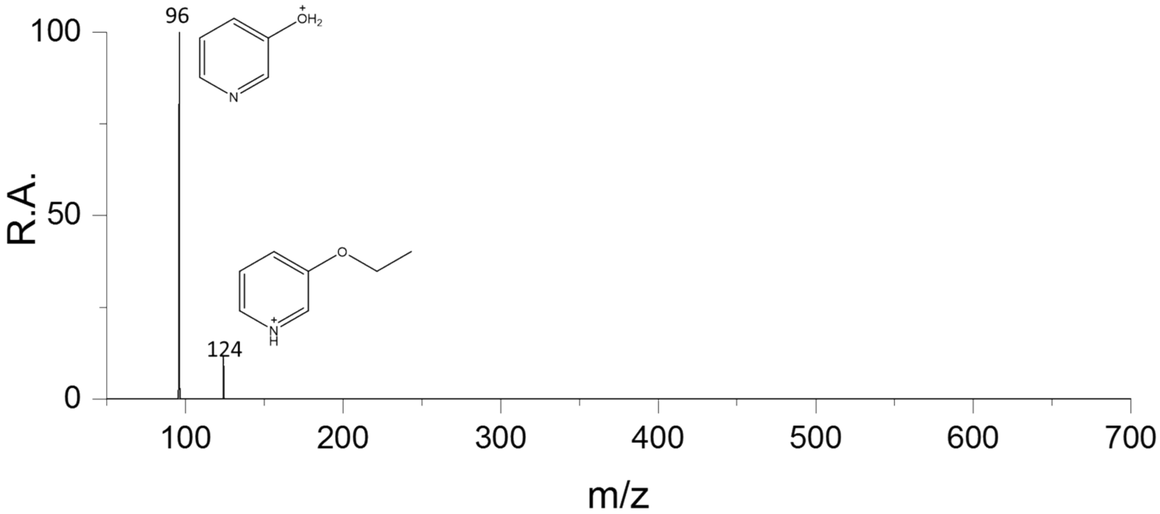

Fig. S1: MS/MS of ions with *m/z* 124

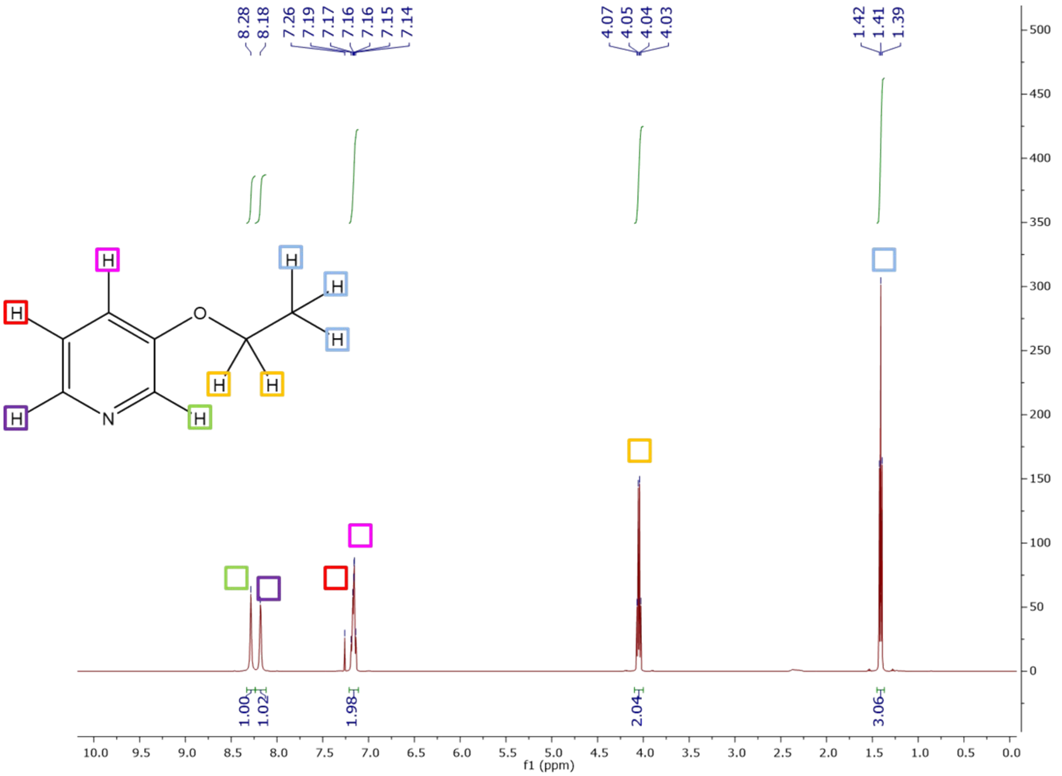

Fig. S2: ^{1}H NMR of C-O coupling product - offline collection using ES

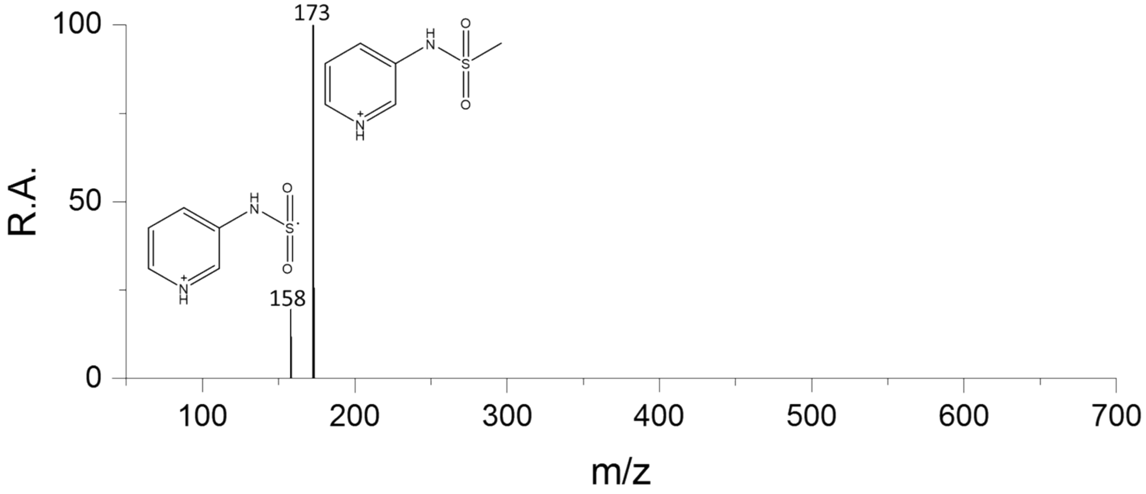

Fig. S3: MS/MS of ions with *m/z* 173

Table S1: Systems explored for the C-N coupling reaction between 3-iodopyridine and methanesulfonamide

BASE	SOLVENT	CATALYST	COMMENTS
CESIUM CARBONATE	Water	Cu_2O	Spectrum dominated by Cs peaks
	Methanol	Cu_2O	Spectrum dominated by Cs peaks
POTASSIUM CARBONATE	Methanol:Water (3:1)	Cu_2O	No product formation
SODIUM ETHOXIDE	Methanol	Cu_2O	No product formation
	Isobutyrylcyclohexanone	CuI	No product formation
SODIUM HYDROXIDE	Methanol	Cu_2O	No product formation
	Methanol:Water (1:1)	CuI	No product formation
POTASSIUM HYDROXIDE	Isobutyrylcyclohexanone + DMF	CuI	No product, only DMF peaks seen
	Isobutyrylcyclohexanone + THF:Water (1:1)	CuI	Product formed
	THF:Water (3:1)	Cu_2O	Product formed

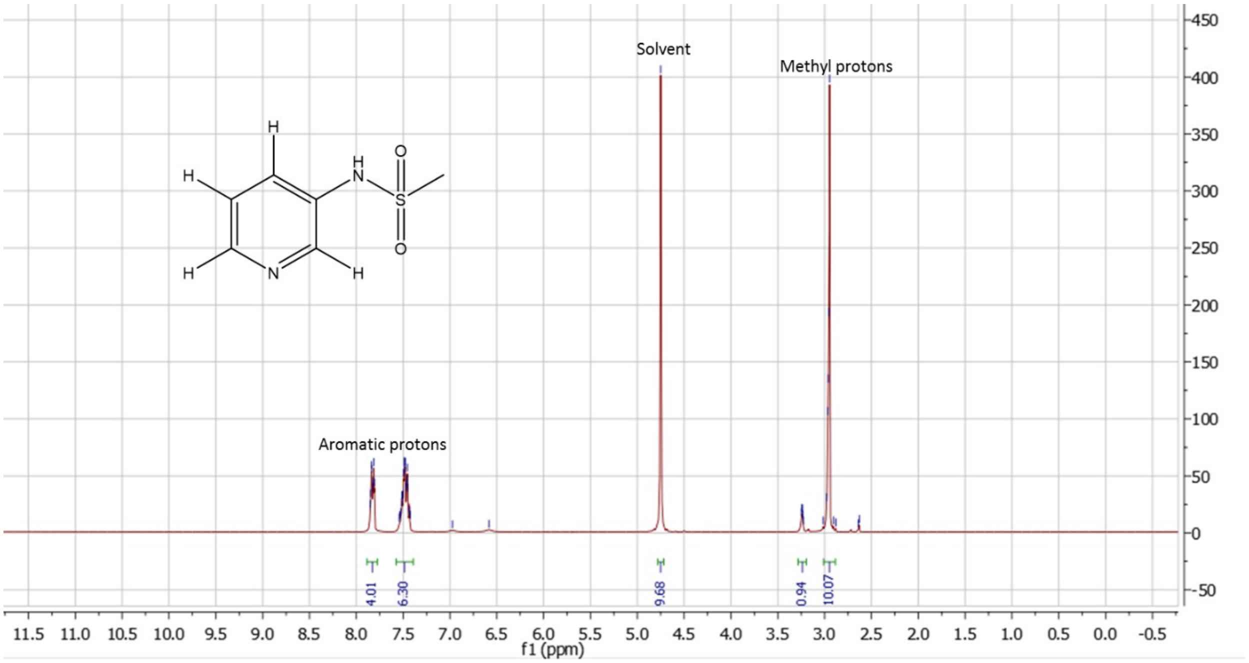

Fig. S4: ^{1}H NMR of C-N coupling product – offline collection using ES. Solvent: Methanol-d_4

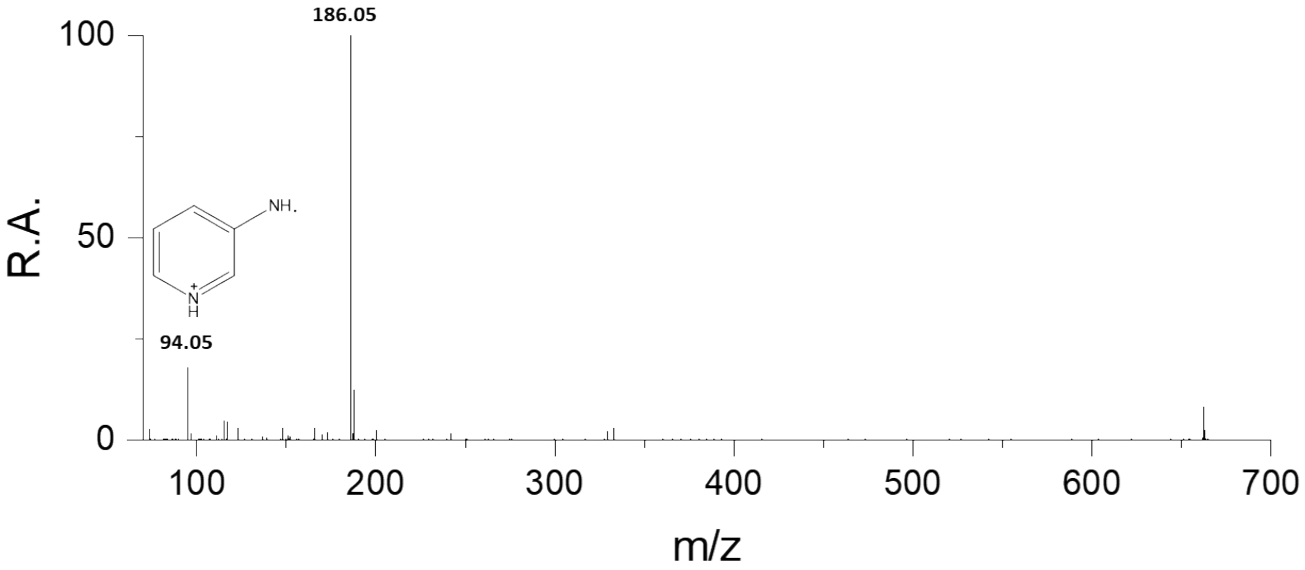

Fig. S5: High-resolution MS of the bulk reaction using ethanesulfonamide as the starting reagent showing the radical cation of the pyridylsulfonamide as the major reaction product

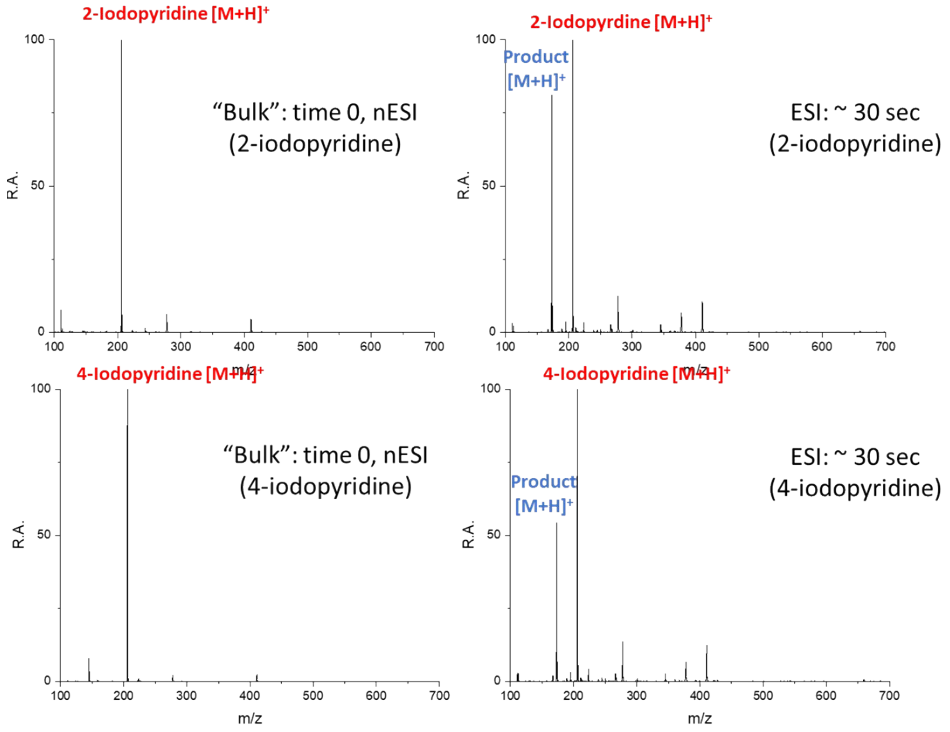

Fig. S6: MS for the C-N coupling reaction of methanesulfonamide with 2-iodopyridine (top row) and 4-iodopyridine (bottom row)

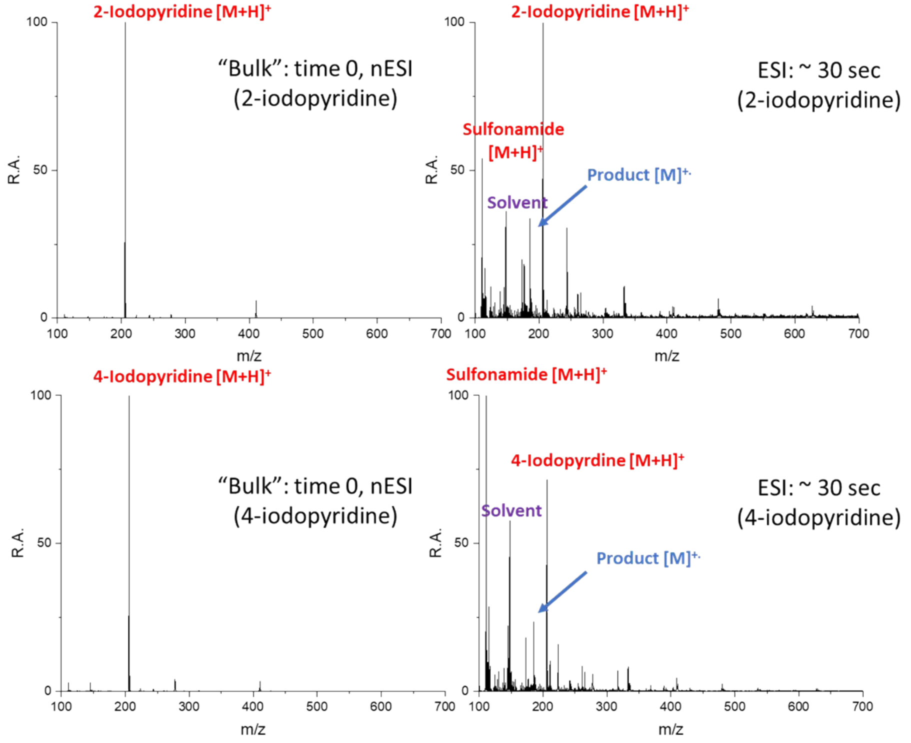

Fig. S7: MS for the C-N coupling reaction of ethanesulfonamide with 2-iodopyridine (top row) and 4-iodopyridine (bottom row)