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

ELECTRONIC SUPPLEMENTARY INFORMATION

Rapid analytical characterization of high-throughput chemistry screens utilizing desorption electrospray ionization mass spectrometry

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Reagents and Materials

All reagents were purchased from commercial sources and used directly without further purification. Catalysts, precatalysts, ligands, and bases were purchased from Sigma Aldrich.

Experimental Details

Instrumentation

A commercially available DESI 2D Ion Source (Prosolia, Inc., Indianapolis, IN) was fitted onto a Q Exactive^{TM} HF Hybrid Quadrupole-Orbitrap^{TM} mass spectrometer (Thermo Scientific^{TM}, San Jose, CA) and was used in high resolution full scan mode. The instruments were independently controlled by commercially available software (Omni Spray 2D, Prosolia and XCalibur 4.0.27, Thermo Scientific).

A commercially available Waters ACQUITY UPLC-MS system with a Waters SQD mass spectrometer was used for the LC/MS experiments (Waters Corporation, Milford, MA). The system was operated using MassLynx 4.1 software, and data was analysed with Openlynx 4.1 software.

DESI Source Properties

DESI Parameters: The DESI source exact distances were tuned specifically to the solvents used, but spray angles and gas pressure remained the same. The following parameters were used for all experiments: The incidence of spray angle (marked on the spray boom): 57.9 °; Nitrogen Pressure: 115 PSI.

DESI Solvent: The preferred solvent for the experiments was LC/MS grade 80/20/0.1 acetonitrile/water/formic acid. The use of LC/MS solvent kept the system clean which allowed for less maintenance needs and fine tuning of spray. A clean and optimized system allowed for solvent flowrates of 2-3 µL/min, but when the system was dirty (or even when the emitter tip had been damaged) a solvent flowrate of 5 µL/min was required to obtain adequate spray.

DESI 2D MS Experiments

Point-to-Point Oscillate Experiment (PTP-OSC): The PTP-OSC experiment has a motion template where a start point along the distance to oscillate and number of replicates are defined. The oscillation only occurs in the x-axis (actually along the column from the plate's reference), so any replicates will actually sample the same path. In this experiment only one well is sampled per data file acquired. The scan rate of the DESI 2D stage was set to 1950 µm/sec, the Oscillation distance was set to 3.000 mm, and the number of replicate was set to 2. These parameters resulted in a 0.10 min acquisition time, which is the shortest ms method time available commercially for a QExactive hf.

MS Parameters for the PTP-OSC DESI experiment: The following source parameters were used: Spray voltage: 4.00 kV; Capillary temperature: 300 °C; S-lens RF level: 50.0. The following ms scan parameters were used: Resolution: 60,000; Polarity: Positive; AGC: 5e6; Maximum injection time: 50 ms; Scan range: Variable, depending on starting material and product molecular weight

XCalibur Method for the PTP-OSC DESI experiment: The following method properties were used: Use lock masses: off; Chrom. Peak width: 1 sec; General Runtime: 0.10 min; In-source CID: 0.0 eV. The following FULL MS-SIM scan properties were used: Microscans: 1; Resolution: 60,000; Polarity: Positive; AGC: 5e6; Maximum injection time: 50 ms; Scan range: Variable, depending on starting material and product molecular weight; Spectrum data: Centroid

Start Point Constant Velocity Experiment (SP-CV): The SP-CV experiment has a motion template where a start point along the distance to travel defined. There is only one scan path that occurs in the x-axis (actually along the column from the plate's reference). In this experiment eight wells are sampled per data file acquired. The scan rate of the DESI 2D stage was set to 3333.3 µm/sec, the distance traveled was set to 73.000 mm (to acquire all eight wells), 12 rows were collected per full plate, and the step size was 9.00 mm between columns. These parameters resulted in a 0.37 min acquisition time per eight wells (one column).

MS Parameters for the SP-CV DESI experiment: The following source parameters were used: Spray voltage: 4.00 kV; Capillary temperature: 300 °C; S-lens RF level: 50.0. The following ms scan parameters were used: Resolution: 60,000; Polarity: Positive; AGC: 5e6; Maximum injection time: 50 ms; Scan range: Variable, depending on starting material and product molecular weight

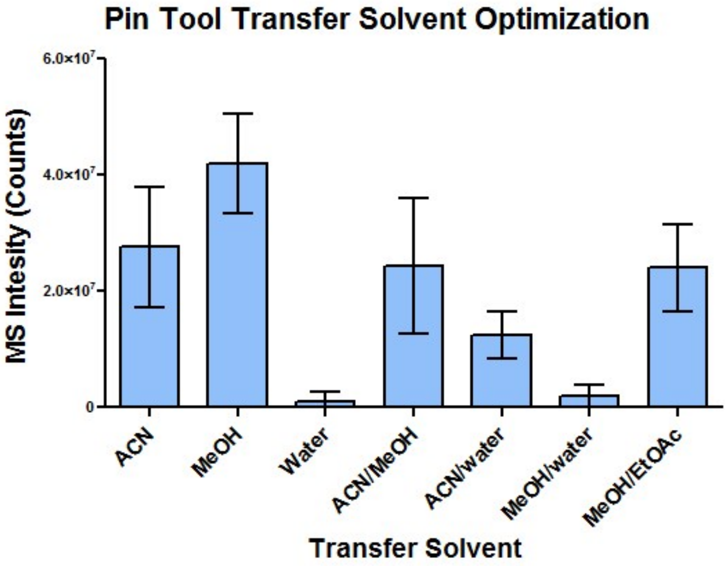
XCalibur Method for the SP-CV DESI experiment: The following method properties were used: Use lock masses: off; Chrom. Peak width: 1 sec; General Runtime: 0.37 min; In-source CID: 0.0 eV. The following FULL MS-SIM scan properties were used: Microscans: 1; Resolution: 60,000; Polarity: Positive; AGC: 5e6; Maximum injection time: 50 ms; Scan range: Variable, depending on starting material and product molecular weight; Spectrum data: Centroid

UPLC/MS Experiments

UPLC/MS Conditions: The Waters SQD ms was operated in ESI mode. The column used was a Waters BEH C8, 1.7 µm (2.1 mm × 30 mm). The UPLC conditions used were the following: Gradient: [0→0.1 min 1% A, 0.1→1.1 min 1%→100% A, 1.1→1.3 min 100% A, 1.3→1.4 min 100%→1% A] acetonitrile (A) and 10 mM ammonium acetate in water (B); Flow rate: 1.0 mL/min; Column temperature: 55 °C

Pin tool transfer solvent optimization

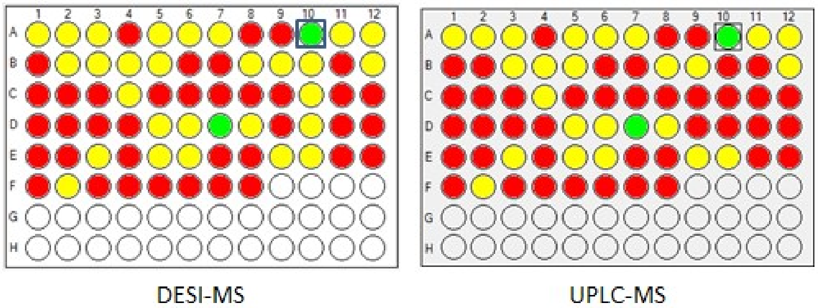
Verapamil was dissolved in solvents at the concentration of 0.1 mg/mL. The solvents evaluated in the experiment shown are: Acetonitrile (ACN); Methanol (MeOH); Water; (1:1) ACN/MeOH v/v; (1:1) ACN/water v/v; (1:1) MeOH/water v/v; (1:1) MeOH/EtOAc v/v. These stock solutions were spotted onto sample array slide with 500 nL pin tools (50 ng Verapamil/well) with 8 replicates. The wells were analysed under our optimal experiment conditions where the DESI stage moves at 3333.3 µm/sec. The maximum intensity of the verapamil protonated ion in each of the wells was used for the calculating the mean, standard deviation, and coefficient of variation (used in S.I. Figure 1). Methanol and (1:1) MeOH/EtOAc had the lowest CV's of 20.1% and 31.1%, respectively. Other organic solvent performed well, but polar solvents such as water or (1:1) MeOH/water performed poorly, and this lack of material transfer was evident during the spotting process. The CV's of the experiment could be decreased by increasing sample concentration and/or slowing the stage speed, but we found it pertinent to keep conditions similar to the all applications discussed in the manuscript.



S.I. Figure 1. Graphical comparison of the efficient transfer of Verapamil in various solvents via 500 µL pin tool

UPLC-MS MS peak areas vs. DESI-MS Intensities Data Comparison for Buchwald Project Example Screen

Visualized in the plots below are comparison of the UPLC-MS data and the DESI-MS data for the same reaction plate. S.I. Figure 2 contains the data browser processed heat maps that are typically used for interpretation of successful reactions. S.I. Figure 3 contains the same data (UPLC-MS peak area and DESI-MS Intensities) plotted against each other forming a correlation. The plot is not completely linear as there is variance from sample to sample for each of the systems (based both on sample composition and inherent variance of mass spectrometry methods. Also, when signal drops to the background the values become quite variable. Even with the variability, we consistently find this tool to be useful in identifying the most successful reactions.



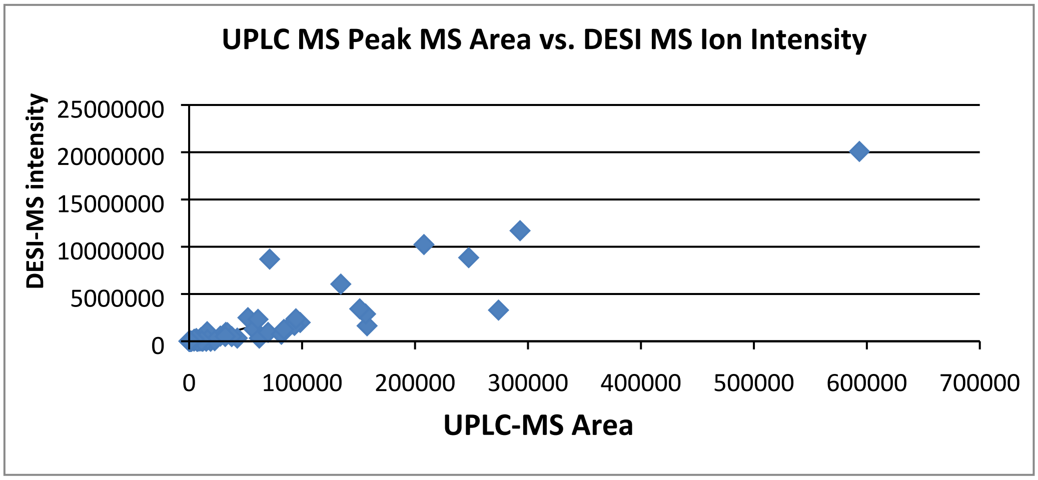
DESI-MS

	1	2	3	4	5	6	7	8	9	10	11	12
A	🟨	🟨	🟨	🟥	🟨	🟨	🟨	🟥	🟥	🟩	🟨	🟨
B	🟥	🟨	🟨	🟨	🟨	🟥	🟥	🟨	🟨	🟨	🟥	🟨
C	🟥	🟥	🟥	🟨	🟥	🟥	🟥	🟥	🟥	🟨	🟥	🟥
D	🟥	🟥	🟥	🟥	🟨	🟨	🟩	🟨	🟥	🟨	🟥	🟥
E	🟥	🟥	🟨	🟥	🟨	🟨	🟥	🟥	🟨	🟨	🟥	🟥
F	🟥	🟨	🟥	🟥	🟥	🟥	🟥	🟥	○	○	○	○
G	○	○	○	○	○	○	○	○	○	○	○	○
H	○	○	○	○	○	○	○	○	○	○	○	○

UPLC-MS

	1	2	3	4	5	6	7	8	9	10	11	12
A	🟨	🟨	🟨	🟥	🟨	🟨	🟨	🟥	🟥	🟩	🟨	🟨
B	🟥	🟥	🟨	🟨	🟨	🟥	🟥	🟨	🟨	🟥	🟥	🟨
C	🟥	🟥	🟥	🟨	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟥
D	🟥	🟥	🟥	🟥	🟨	🟨	🟩	🟨	🟥	🟥	🟥	🟥
E	🟥	🟥	🟨	🟥	🟨	🟨	🟥	🟥	🟨	🟨	🟥	🟥
F	🟥	🟨	🟥	🟥	🟥	🟥	🟥	🟥	○	○	○	○
G	○	○	○	○	○	○	○	○	○	○	○	○
H	○	○	○	○	○	○	○	○	○	○	○	○

S.I. Figure 2. Comparison between DESI-MS (left) and UPLC-MS (right) analytical data for Buchwald coupling.



S.I. Figure 3. Comparison between DESI-MS (left) and UPLC-MS (right) analytical data for Buchwald coupling.