

SUPPORTING INFORMATION

High Throughput Experimentation and Continuous Flow Evaluation of Nucleophilic Aromatic Substitution Reactions

Zinia Jaman¹, David L Logsdon¹, Botond Szilágyi², Tiago J. P. Sobreira¹, Deborah Aremu¹, Larisa Avramova¹, R. Graham Cooks^{*1}, and David H. Thompson^{*1}

¹Department of Chemistry, Purdue University, Bindley Bioscience Center, 1203 W State St, West Lafayette, IN 47906, USA

²Davidson School of Chemical Engineering, Purdue University, West Lafayette, IN 47907-2100, USA

Corresponding Authors

davethom@purdue.edu; cooks@purdue.edu

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High throughput bulk experimentation

Experimentation:

High throughput S_NAr experimentation in bulk was performed in 96-well metal block assemblies (Analytical Sales and Services, Inc., NJ, USA). The reaction mixtures were prepared in 1 mL glass inserts of the 96-well metal block. All the reagent transfers and mixing were performed using a Beckman Coulter i7 liquid handling robot. The stock solutions were 111 mM for amines and aryl halides, and the base stock solution concentration was 1.25 M in NMP or 1,4-dioxane. The final reaction concentrations were 50 mM (1 equiv.) both for the amines and aryl halides, and 125 mM (2.5 equiv.) for the bases. All solutions were prepared in appropriate solvent, and they were added to the 96-well plate in a ratio of 9:9:2 (amine:aryl halide:base). Additional solvent was used instead of base for the ‘no base’ condition. For DESI-MS HTE, 384 well plates were prepared from the 96 well plates using the robot; a 384 pintool was used to transfer the final reagent mixtures (50 nL) onto the PTFE slides. For bulk HTE, the plates were heated in the customized heating block at 150 °C or 200 °C for varying times. The cover on top of the glass inserts (top of the metal block) is made by chemically resistant perfluoroalkoxy (PFA) film. Double silicone rubber mats were used on top of the PFA film, providing a tight seal that is enough to heat the solution above the boiling point with less than 5% solvent loss and no cross talk between wells. After heating, the plates were cooled to room temperature, and loaded back onto the deck of the liquid handling robot to prepare 384-well plates. The reactions mixtures were pinned onto the same DESI slide as described above before and after heating using the same transfer method.

Peak intensities data from HT screening

A)

	R1-B1	R1-B2	R1-B3	R1-B4	R1-B5	R1-B6	R1-B7	R1-B8	R1-B9	R1-B10	R1-B11	R1-B12 (S)	B12 (D)
R1-A1	5.3	3.3	6.6	281.3	12.4	6.3	3564.2	50.0	7.0	9.7	8.0	241.3	139.8
R1-A2	8.6	18.0	11.9	5.0	0.0	0.0	35.3	3.0	0.0	0.0	2.5	135.0	495.2
R1-A3	1.6	0.0	0.0	5.7	1.7	3.0	12.8	3.6	0.5	1.6	2.0	6.2	131.5
R1-A4	90.3	21.0	36.5	1213.7	30.0	15.4	38.9	7.5	511.1	117.4	5.1	286.8	3939.0
R1-A5	3.7	1.1	2.9	17.5	18.1	22.6	15.5	0.6	0.0	1.4	8.0	14.0	35.3
R1-A6	4.3	5.0	9.7	27.4	13.1	6.0	6.5	1.8	2.3	7.0	24.6	159.7	22.7
R1-A7	23.4	21.5	8.8	1080.1	8.3	8.7	5302.0	79.4	69.2	11.2	13.9	2787.1	91.9
R1-A8	19.8	7.6	5.8	4.0	9.2	4.7	11.5	4.7	7.5	2.6	3.4	2.5	33.6

B)

	R1-B1	R1-B2	R1-B3	R1-B4	R1-B5	R1-B6	R1-B7	R1-B8	R1-B9	R1-B10	R1-B11	R1-B12 (S)	B12 (D)
R1-A1	1094.1	25.5	24.1	1194.2	656.6	585.0	2243.6	197.7	1392.9	374.1	10.4	16.0	181.9
R1-A2	185.4	18.6	30.0	1058.7	68.8	76.5	49.6	64.6	508.6	56.1	6.0	256.4	431.4
R1-A3	113.6	6.4	10.2	69.2	324.5	154.8	6.3	6.2	5.9	14.0	24.0	7.7	548.2
R1-A4	999.1	312.1	1226.1	1367.7	4597.2	4515.4	2765.5	18.4	1112.3	4002.5	13.4	20.3	1296.5
R1-A5	32.8	18.6	13.4	25.1	14.2	16.9	1794.2	2.6	6.6	9.8	9.6	10.3	129.3
R1-A6	13.6	10.2	7.9	97.6	20.5	27.4	380.3	7.6	42.3	3.9	31.9	98.4	26.7
R1-A7	3534.2	166.5	200.2	5661.2	2939.8	2234.9	12713.1	203.8	1446.7	1292.6	11.9	18.5	2074.6
R1-A8	117.7	51.2	28.9	144.9	18.3	10.1	744.7	3.9	66.3	6.6	4.5	1.2	24.3

C)

	R1-B1	R1-B2	R1-B3	R1-B4	R1-B5	R1-B6	R1-B7	R1-B8	R1-B9	R1-B10	R1-B11	R1-B12 (S)	B12 (D)
R1-A1	3190.2	96.7	184.1	5502.0	1555.6	1730.2	4618.4	1363.4	7221.4	1584.5	31.3	27.0	243.1
R1-A2	277.5	56.9	56.2	1978.4	93.7	120.0	123.8	226.0	759.2	63.5	24.2	357.7	605.4
R1-A3	826.1	11.7	24.6	667.0	522.0	219.5	8.0	34.2	17.4	16.8	44.6	8.9	1069.7
R1-A4	3499.9	641.3	3345.7	4973.7	7199.4	10005.9	1267.5	63.9	2467.0	5317.5	25.8	27.5	893.9
R1-A5	1226.0	26.4	79.7	347.5	113.6	137.4	5435.5	17.2	488.3	54.4	44.4	67.8	431.9
R1-A6	61.7	31.2	37.1	209.2	53.4	93.1	684.4	35.6	110.5	29.3	31.5	757.1	62.0
R1-A7	6125.1	342.7	826.9	9886.8	4780.8	5175.7	15343.0	229.0	11798.2	2489.6	37.4	34.3	2467.7
R1-A8	703.4	145.3	113.3	5357.4	69.5	72.8	360.8	68.8	1975.1	40.1	14.8	17.0	110.5

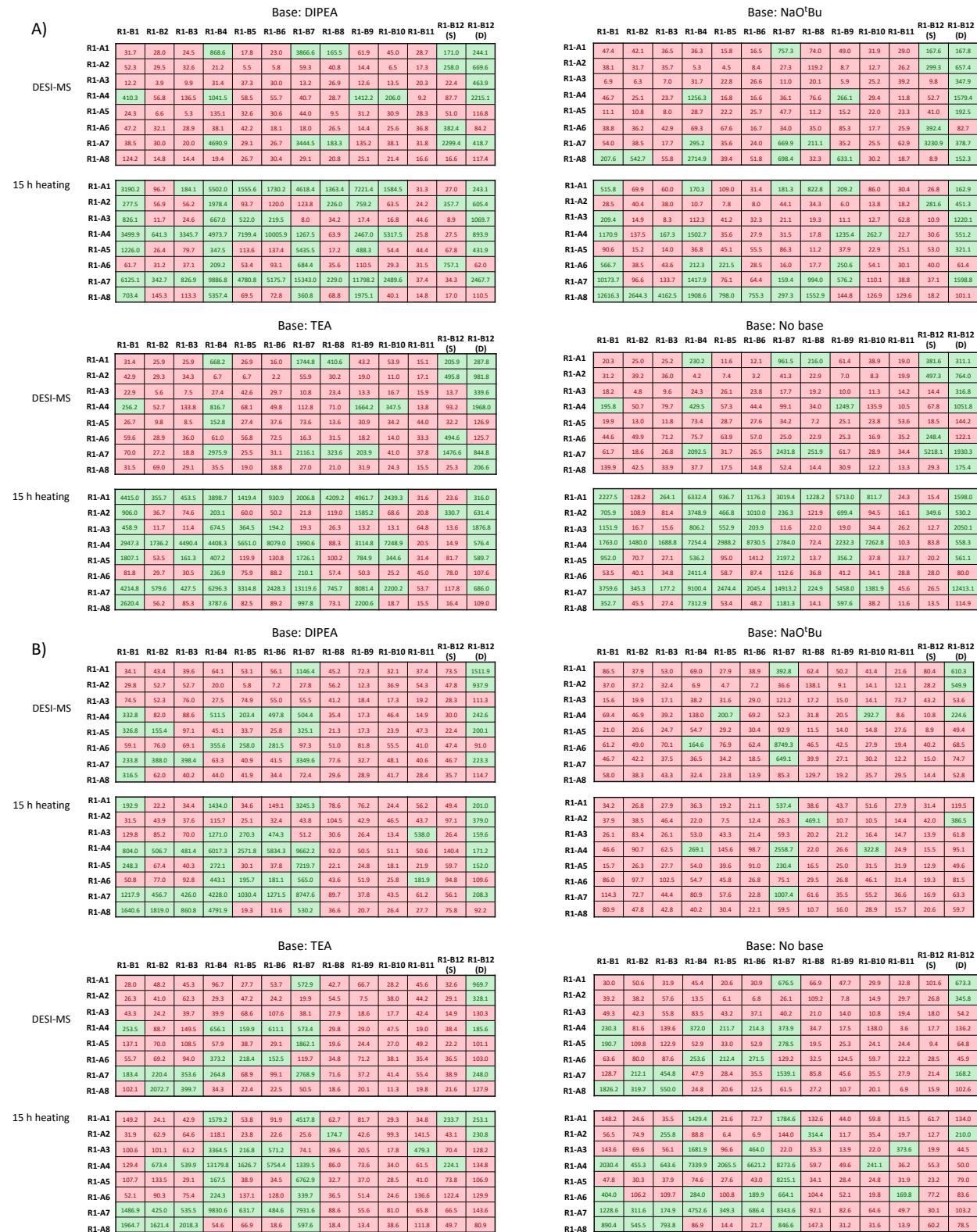
D)

	R1-B1	R1-B2	R1-B3	R1-B4	R1-B5	R1-B6	R1-B7	R1-B8	R1-B9	R1-B10	R1-B11	R1-B12 (S)	B12 (D)
R1-A1	192.9	22.2	34.4	1434.0	34.6	149.1	3245.3	78.6	76.2	24.4	56.2	49.4	201.0
R1-A2	31.5	43.9	37.6	115.7	25.1	32.4	43.8	104.5	42.9	46.5	43.7	97.1	379.0
R1-A3	129.8	85.2	70.0	1271.0	270.3	474.3	51.2	30.6	26.4	13.4	538.0	26.4	159.6
R1-A4	804.0	506.7	481.4	6017.3	2571.8	5834.3	9662.2	92.0	50.5	51.1	50.6	140.4	171.2
R1-A5	248.3	67.4	40.3	272.1	30.1	37.8	7219.7	22.1	24.8	18.1	21.9	59.7	152.0
R1-A6	50.8	77.0	92.8	443.1	195.7	181.1	565.0	43.6	51.9	25.8	181.9	94.8	109.6
R1-A7	1217.9	456.7	426.0	4228.0	1030.4	1271.5	8747.6	89.7	37.8	43.5	61.2	56.1	208.3
R1-A8	1640.6	1819.0	860.8	4791.9	19.3	11.6	530.2	36.6	20.7	26.4	27.7	75.8	92.2

Figure S1: Direct comparison of S_NAr reactions using droplet/thin film and microtiter approach

A) The droplet/thin film and B) bulk microtiter results for the same set of reaction conditions.

Experimental conditions: solvent; methanol; reaction solvent using NMP; base; DIPEA. C) Same as B, but the spray solvent was MeOH+ 1% FA D) Same as C, but the reaction solvent was 1,4 dioxane. Each cell is an average of two data points. Green cells represent "yes" reactions (product ion intensity > 150 counts). Red cells represent "no" reactions (product ion intensity < 150 counts). B12 can form both single and double addition products; the double addition product can form multiple ions. B12 (S) is the singly charged ion of the single addition product; B12 (D) is the sum of the average intensities of all the double addition ions.



Base: DIPEA

A)

	R1-B1	R1-B2	R1-B3	R1-B4	R1-B5	R1-B6	R1-B7	R1-B8	R2-B9	R1-B10	R1-B11	R1-B12 (S)	R1-B12 (D)	
DESI-MS	R2-A1	4.2	1.6	0.0	4.9	1.1	2.0	59.6	3.5	1.8	3.2	5.0	11.1	111.0
	R2-A2	5.5	3.6	7.5	12.7	7.9	12.4	0.6	9.7	8.8	11.8	5.0	146.2	239.2
	R2-A3	3.4	3.7	3.3	14.3	6.9	15.2	5.8	7.5	8.5	15.7	4.7	37.5	57.0
	R2-A4	1.6	1.7	1.9	5.4	2.7	2.5	609.9	3.9	1.4	2.1	77.6	8.9	34.5
	R2-A5	1.4	0.0	0.5	15.0	14.7	10.7	44.9	5.5	33.4	7.0	13.0	29.5	59.5
	R2-A6	20.1	4.6	2.0	284.7	1.1	6.4	879.2	4.5	3.9	3.2	4.3	55.3	325.5
	R2-A7	1.4	0.8	0.7	3.6	5.8	5.1	0.8	1.6	0.0	2.1	9.1	4.3	45.0
	R2-A8	10.8	9.5	16.1	9.1	4.2	5.1	9.3	15.8	15.1	15.5	5.5	9.6	25.0
1 h heating	R2-A1	7.0	4.2	1.7	13.8	3.0	11.1	56.7	4.4	5.1	4.0	3.8	7.7	72.8
	R2-A2	2.0	5.0	4.7	16.4	7.6	10.4	21.0	9.8	9.2	11.0	23.2	78.1	194.3
	R2-A3	5.1	6.8	3.7	13.0	5.5	10.6	18.4	23.1	41.6	16.5	2.8	20.0	43.7
	R2-A4	2.5	3.7	4.0	8.7	3.3	2.4	682.1	5.5	5.1	4.7	52.3	6.6	22.5
	R2-A5	18.8	2.0	6.9	26.6	9.9	18.7	1216.9	6.6	7.9	3.6	22.9	15.4	78.4
	R2-A6	530.9	27.4	98.9	895.2	180.6	264.4	4688.6	5.5	12.8	6.1	9.4	13.7	210.3
	R2-A7	2.2	1.8	2.9	6.6	4.4	12.9	7.6	11.3	2.2	1.3	4.0	4.4	48.6
	R2-A8	11.3	14.8	9.0	14.5	12.5	17.4	311.9	13.7	13.2	13.5	17.1	4.5	86.1
4 h heating	R2-A1	4.6	7.0	3.2	18.8	4.0	3.6	45.1	5.7	3.1	8.0	4.1	13.8	93.5
	R2-A2	2.3	5.6	4.4	15.4	8.9	13.5	26.9	10.2	13.7	7.2	34.0	100.1	189.3
	R2-A3	2.1	4.5	3.2	10.7	14.3	11.6	7.7	13.7	20.7	26.4	1.1	19.0	89.4
	R2-A4	1.3	3.1	2.8	8.5	2.0	4.3	595.4	3.7	2.7	4.2	50.0	15.9	33.5
	R2-A5	33.3	2.3	2.3	28.2	14.8	15.4	652.0	6.4	6.1	6.9	32.5	24.8	161.1
	R2-A6	612.2	30.4	65.6	1260.8	273.0	202.6	3237.5	12.1	10.4	5.5	6.8	6.4	305.5
	R2-A7	2.6	5.5	2.6	12.7	12.1	11.2	3.8	2.7	4.7	2.0	6.5	11.3	49.2
	R2-A8	10.2	10.3	13.7	18.3	8.8	13.3	250.1	10.4	13.1	14.1	10.4	3.0	72.6
15 h heating	R2-A1	1.6	11.4	13.1	21.7	4.9	7.3	38.5	4.5	2.6	5.5	6.1	19.2	58.4
	R2-A2	5.3	5.0	10.3	13.8	10.6	6.9	8.8	7.7	10.4	10.6	4.2	101.5	153.6
	R2-A3	5.2	2.7	3.9	14.4	9.8	10.2	10.4	13.4	17.2	9.8	4.5	21.8	74.9
	R2-A4	2.4	3.2	4.5	13.9	3.5	2.6	553.0	8.9	2.9	3.0	14.2	15.6	25.9
	R2-A5	63.3	1.9	4.3	32.5	12.1	14.5	971.1	11.4	7.7	4.0	26.3	15.5	49.7
	R2-A6	692.2	39.0	82.1	1208.8	24.2	123.6	3852.7	49.3	6.8	9.4	6.1	10.9	77.1
	R2-A7	1.7	1.6	3.4	9.0	10.4	12.2	9.8	3.9	4.0	1.1	4.3	15.6	83.5
	R2-A8	12.0	10.2	9.8	22.9	10.0	20.5	575.2	12.3	12.6	12.3	13.3	2.4	34.3

Base: NaO^tBu

B)

	R1-B1	R1-B2	R1-B3	R1-B4	R1-B5	R1-B6	R1-B7	R1-B8	R2-B9	R1-B10	R1-B11	R1-B12 (S)	R1-B12 (D)	
DESI-MS	R2-A1	6.8	5.1	13.9	10.5	5.5	9.4	54.7	4.1	2.9	4.3	7.8	18.2	165.8
	R2-A2	11.1	6.6	12.0	94.9	8.6	12.4	1.6	49.7	36.2	19.3	7.1	217.0	299.0
	R2-A3	14.5	8.9	13.8	9.2	10.4	18.0	8.4	12.0	7.6	18.8	4.1	17.9	80.8
	R2-A4	1.8	2.1	3.5	3.6	15.5	4.7	742.8	4.0	2.8	2.8	71.7	7.6	27.2
	R2-A5	0.6	2.7	3.3	12.8	27.9	12.4	40.0	8.7	13.8	8.8	31.2	28.4	115.5
	R2-A6	6.1	3.5	3.4	32.5	8.1	6.3	51.4	15.4	28.8	6.4	1.2	54.5	405.7
	R2-A7	1.5	18.8	13.5	10.3	42.3	39.7	8.0	6.2	5.2	1.7	10.7	6.0	38.2
	R2-A8	11.5	11.2	9.3	82.5	36.9	8.3	2.6	16.0	10.6	12.9	4.2	30.1	131.6
1 h heating	R2-A1	78.7	3.3	13.8	28.7	8.5	10.8	92.9	22.6	4.9	3.4	19.1	11.8	91.7
	R2-A2	29.2	8.0	10.9	114.6	24.1	29.9	15.7	19.3	25.0	29.4	5.6	227.4	280.7
	R2-A3	1.9	6.5	11.1	11.1	7.8	17.9	17.6	34.7	67.8	20.9	3.2	20.4	148.8
	R2-A4	3.8	4.4	4.2	13.5	19.3	17.6	734.7	7.7	8.4	26.6	13.5	6.5	44.5
	R2-A5	1.6	2.9	5.8	13.1	15.7	31.1	273.6	12.4	17.4	7.2	41.6	14.0	209.5
	R2-A6	183.8	18.7	21.9	315.7	37.8	13.5	23.5	13.5	13.7	10.6	5.5	63.1	545.6
	R2-A7	6.2	12.6	14.7	5.7	9.7	14.5	5.0	4.3	6.4	4.4	6.1	9.7	38.6
	R2-A8	67.5	55.1	60.8	72.3	49.3	15.9	103.7	21.2	15.7	18.5	15.6	12.9	102.8
4 h heating	R2-A1	169.5	4.7	8.7	15.6	6.5	14.6	17.7	22.3	9.9	8.5	18.2	14.0	147.5
	R2-A2	22.2	8.0	9.0	41.2	10.3	19.0	15.3	22.2	28.9	24.5	17.4	206.8	302.9
	R2-A3	3.5	4.2	10.5	11.0	10.3	16.8	17.6	15.9	35.1	13.6	3.7	20.2	85.7
	R2-A4	2.9	3.1	3.6	8.8	17.1	12.7	821.4	11.8	4.7	23.4	16.2	7.3	55.1
	R2-A5	1.2	6.0	3.5	10.2	14.7	25.8	171.8	18.0	17.1	11.6	34.3	31.4	178.6
	R2-A6	149.5	14.3	14.7	227.0	45.1	12.5	29.8	20.9	12.3	15.0	5.5	60.6	484.5
	R2-A7	1.3	19.6	6.9	9.6	11.2	17.3	8.7	2.9	3.7	4.6	8.9	5.8	57.2
	R2-A8	78.7	49.3	42.3	71.2	50.6	19.1	76.1	30.5	21.1	17.7	12.0	18.0	58.1
15 h heating	R2-A1	41.0	6.9	8.7	18.2	14.6	15.6	18.4	13.8	1.8	7.8	12.9	15.9	83.4
	R2-A2	12.4	8.5	12.5	22.2	15.3	12.7	8.3	19.6	12.4	7.5	4.8	187.5	239.2
	R2-A3	2.4	5.1	8.0	11.2	8.2	16.0	14.2	13.7	27.1	14.5	3.9	18.4	75.6
	R2-A4	3.1	4.3	5.5	10.9	14.4	14.3	867.5	8.6	5.2	19.8	12.7	5.6	33.4
	R2-A5	7.5	2.1	5.8	21.7	17.1	24.6	445.0	9.5	9.4	11.6	41.9	27.0	77.3
	R2-A6	496.3	17.1	30.1	356.2	53.2	9.1	70.0	16.7	3.4	9.2	6.8	10.2	307.6
	R2-A7	0.7	10.0	13.3	2.9	8.2	9.5	8.3	7.6	2.9	5.9	5.0	13.3	55.6
	R2-A8	84.8	45.3	47.9	57.2	31.5	14.6	94.3	17.8	25.4	30.7	12.8	23.6	30.7

Base: TEA

C)

	R1-B1	R1-B2	R1-B3	R1-B4	R1-B5	R1-B6	R1-B7	R1-B8	R2-B9	R1-B10	R1-B11	R1-B12 (S)	R1-B12 (D)	
DESI-MS	R2-A1	9.6	1.2	1.8	1.7	1.9	0.0	42.5	4.3	2.5	2.2	2.1	13.0	120.7
	R2-A2	4.6	3.5	4.9	9.5	7.5	11.2	0.5	9.2	10.9	13.5	2.3	150.8	238.1
	R2-A3	1.4	3.1	1.8	12.6	16.5	15.1	2.9	7.4	5.0	8.4	3.1	34.8	151.0
	R2-A4	0.0	3.4	2.8	5.1	4.4	1.5	555.8	0.7	2.5	0.0	33.5	8.4	32.5
	R2-A5	2.6	0.6	0.0	144.1	92.5	153.5	86.3	12.5	9.1	8.1	23.6	45.3	66.9
	R2-A6	27.3	4.6	4.5	180.8	10.8	3.9	328.4	15.5	4.0	5.7	4.8	66.1	294.0
	R2-A7	2.0	1.1	1.3	9.3	2.6	2.0	1.8	1.9	1.9	0.6	9.7	4.5	43.6
	R2-A8	11.2	13.5	10.4	9.5	9.4	3.6	13.2	13.7	15.3	14.5	12.5	11.9	39.2
1 h heating	R2-A1	4.6	1.0	6.1	7.0	1.4	5.9	69.6	3.2	0.7	1.8	5.5	11.4	140.6
	R2-A2	2.7	4.1	5.6	16.4	6.3	7.1	1.4	10.7	20.2	18.9	3.1	178.0	188.7
	R2-A3	1.3	3.6	1.8	13.3	13.7	8.4	5.8	19.3	30.3	16.9	3.8	26.3	58.7
	R2-A4	0.6	6.9	3.7	5.0	1.3	3.5	557.5	3.7	3.0	2.7	23.8	4.7	25.5
	R2-A5	16.9	0.6	2.4	34.8	15.6	13.9	967.8	9.0	14.5	7.7	17.7	34.5	168.3
	R2-A6	256.9	26.8	46.2	1107.0	264.2	340.3	2758.4	14.3	4.4	4.7	3.7	5.4	795.6
	R2-A7	1.4	1.4	2.7	11.5	6.9	9.0	1.1	6.6	5.2	1.9	7.9	5.0	44.7
	R2-A8	6.8	11.8	8.3	9.6	13.1	10.8	123.1	11.5	12.6	14.3	9.3	4.5	106.2
4 h heating	R2-A1	2.4	0.6	3.1	13.7	0.5	4.5	44.8	0.0	1.5	2.8	5.9	12.4	110.7
	R2-A2	3.3	3.3	4.0	9.2	9.1	10.6	3.4	11.8	9.3	6.6	6.5	127.7	209.9
	R2-A3	2.2	2.2	1.7	12.8	11.6	9.9	9.1	26.0	35.5	13.9	3.9	13.2	61.9
	R2-A4	2.7	7.2	2.6	4.7	2.3	3.9	533.8	5.8	4.8	1.8	15.7	6.9	32.3
	R2-A5	25.9	4.0	4.1	36.3	17.7	16.1	404.2	9.2	10.7	14.9	26.5	20.5	174.7
	R2-A6	354.1	29.6	45.8	1285.1	277.9	249.2	2767.3	14.9	9.4	3.7	4.1	11.5	770.0
	R2-A7	2.4	2.9	2.1	11.2	17.4	10.6	2.8	5.7	3.5	4.6	10.5	4.3	47.1
	R2-A8	7.3	8.1	10.0	17.0	18.7	11.3	293.9	18.2	11.4	12.6	8.4	7.2	134.9
15 h heating	R2-A1	5.2	3.3	4.8	11.4	1.1	2.5	74.8	2.8	2.7	4.0	5.3	24.0	72.8
	R2-A2	2.1	3.0	5.9	14.0	5.6	8.4	1.9	14.6	13.7	9.2	6.1	139.4	255.2
	R2-A3	3.1	1.4	1.3	18.0	12.1	9.8	12.8	15.9	14.0	18.0	3.6	25.8	108.5
	R2-A4	1.2	2.3	3.5	11.4	3.7	4.3	547.7	2.0	8.1	3.1	29.3	6.8	22.1
	R2-A5	7.7	1.1	2.9	37.1	22.0	21.3	479.9	11.5	16.7	6.6	19.4	39.8	103.2
	R2-A6	366.9	33.1	67.0	1216.9	127.7	320.2	3017.0	63.6	6.6	6.0	7.7	4.2	239.0
	R2-A7	4.1	1.6	3.5	10.1	15.9	13.2	4.8	7.5	3.1	1.5	11.0	8.7	43.9
	R2-A8	16.4	12.0	13.7	19.6	17.2	20.8	620.3	14.4	11.6	13.8	18.4	5.7	83.3

Base: No base

D)

	R1-B1	R1-B2	R1-B3	R1-B4	R1-B5	R1-B6	R1-B7	R1-B8	R2-B9	R1-B10	R1-B11	R1-B12 (S)	R1-B12 (D)	
DESI-MS	R2-A1	3.6	1.3	1.2	1.2	2.0	1.8	56.9	4.1	3.8	1.9	4.5	16.3	132.6
	R2-A2	1.9	7.7	4.1	5.5	13.0	12.0	0.6	13.0	10.4	11.6	3.4	244.6	451.9
	R2-A3	0.7	3.6	1.7	7.4	7.8	15.2	7.1	12.2	6.6	12.0	4.4	37.1	90.8
	R2-A4	1.2	3.0	1.4	4.5	3.2	4.6	844.5	5.1	0.7	0.8	44.1	5.2	24.2
	R2-A5	0.0	3.5	0.5	10.7	14.1	14.0	21.8	19.4	16.5	6.5	17.3	32.7	53.6
	R2-A6	8.4	7.5	3.4	48.8	3.5	4.7	50.0	7.8	2.6	4.1	2.8	43.3	115.3
	R2-A7	1.1	1.8	1.1	3.3	2.8	3.1	4.6	3.6	1.3	0.5	11.5	3.6	40.7
	R2-A8	8.4	8.3	9.8	5.2	4.2	2.4	9.8	21.2	14.2	17.5	8.3	11.3	39.7
1 h heating	R2-A1	0.0	1.1	5.9	5.6	1.2	3.8	63.9	8.4	1.7	4.0	1.9	14.0	142.8
	R2-A2	4.4	1.4	8.8	12.4	9.1	11.8	5.0	12.3	8.1	13.4	4.1	137.4	290.9
	R2-A3	0.0	4.8	7.6	11.1	6.6	23.3	6.7	16.1	16.5	14.5	2.7	10.4	87.2
	R2-A4	2.4	3.8	5.2	3.1	3.6	2.5	816.5	1.6	2.0	0.0	18.9	8.1	30.3
	R2-A5	1.8	1.7	0.0	19.6	12.6	19.4	514.2	8.1	8.3	3.5	20.7	17.5	140.9
	R2-A6	190.7	18.4	46.1	700.6	247.6	360.2	1515.5	4.4	5.7	2.5	3.8	5.0	715.0
	R2-A7	2.8	1.3	0.0	4.4	6.7	10.7	2.2	1.6	3.5	1.3	11.6	6.3	39.8
	R2-A8	5.9	10.3	12.3	7.5	16.2	8.2	241.4	14.2	18.4	13.9	9.0	6.1	113.7
4 h heating	R2-A1	1.2	1.0	3.4	11.1	0.6	5.3	43.4	2.7	3.6	2.6	5.7	17.1	147.2
	R2-A2	3.2	5.7	9.0	16.0	7.2	8.8	1.2	22.0	9.8	10.6	6.5	196.5	264.1
	R2-A3	8.0	3.6	6.6	11.0	7.4	14.2	9.3	39.8	38.1	17.3	4.8	12.6	122.6
	R2-A4	4.7	7.5	8.3	3.7	3.3	5.9	759.6	1.9	1.5	1.1	36.7	5.9	22.5
	R2-A5	34.5	2.6	4.8	12.4	11.0	16.0	1415.5	6.9	10.1	5.1	16.7	13.7	90.2
	R2-A6	242.2	36.1	48.9	982.0	138.9	211.7	1977.9	12.0	8.6	4.3	4.8	6.0	180.8
	R2-A7	1.3	1.4	1.6	2.8	5.9	5.6	12.8	4.0	1.7	5.2	6.6	3.6	49.2
	R2-A8	10.4	10.4	12.9	25.3	7.9	7.2	1112.9	16.4	14.7	15.5	17.5	11.7	92.8
15 h heating	R2-A1	1.1	1.8	2.4	20.5	2.4	5.0	11.1	3.9	2.7	1.8	2.0	27.0	98.4
	R2-A2	3.2	4.7	6.2	11.7	9.3	10.5	4.9	13.9	7.5	8.3	6.5	144.0	149.4
	R2-A3	0.0	8.0	3.0	6.3	8.0	17.9	8.2	30.5	21.4	17.0	4.4	8.0	124.8
	R2-A4	3.5	4.6	9.0	8.5	3.7	3.9	782.2	2.6	2.0	0.0	23.2	2.2	16.7
	R2-A5	38.8	3.0	4.9	13.9	10.8	9.5	1294.9	13.0	7.5	2.3	25.6	18.1	68.5
	R2-A6	266.0	70.4	112.4	850.7	67.6	138.9	3468.2	26.7	5.0	1.7	4.6	6.6	56.9
	R2-A7	3.3	2.3	2.7	4.0	4.8	9.0	32.9	3.8	5.5	5.4	8.2	3.4	40.4
	R2-A8	13.5	15.5	12.2	16.9	8.8	11.8	901.3	14.3	14.7	16.2	18.4	4.2	83.5

Figure S3: Heat map of 1,536 round 2 SnAr HTE reactions using MeOH with 1% FA as spray solvent at 150 °C using NMP as the reaction solvent. The four basic conditions are A) DIPEA B) NaOtBu C) TEA D) No base.

Base: DIPEA

A)

	R1-B1	R1-B2	R1-B3	R1-B4	R1-B5	R1-B6	R1-B7	R1-B8	R2-B9	R1-B10	R1-B11	R1-B12 (S)	R1-B12 (D)	
DESI-MS	R2-A1	7.1	3.7	6.1	9.9	8.6	8.9	235.5	4.3	6.6	3.1	9.6	16.2	112.7
	R2-A2	13.2	3.0	5.3	30.9	32.1	29.9	3.7	5.4	21.9	10.8	4.1	32.1	79.6
	R2-A3	497.9	8.4	142.1	15.3	16.7	11.4	47.0	16.7	30.6	20.8	1.9	18.9	53.1
	R2-A4	24.4	4.0	9.6	3.1	2.6	2.2	49.6	14.4	15.4	10.2	30.0	9.3	22.0
	R2-A5	50.1	11.4	19.6	18.7	11.3	10.0	281.1	10.3	16.1	10.8	15.0	13.8	122.3
	R2-A6	90.5	8.2	11.8	320.0	4.9	2.7	584.1	21.4	11.9	12.2	3.6	252.0	346.2
	R2-A7	24.9	15.8	11.2	27.1	26.9	26.2	7.7	4.5	7.8	4.8	8.5	12.1	16.8
	R2-A8	19.5	53.1	11.7	10.9	18.1	19.2	23.0	7.6	13.1	6.0	9.5	34.5	79.8
1 h heating	R2-A1	55.7	36.7	45.2	26.6	14.4	16.6	141.3	7.6	12.4	10.6	4.8	13.4	47.7
	R2-A2	12.5	6.0	5.5	25.8	38.6	27.1	24.1	8.1	17.4	9.5	35.5	19.4	59.6
	R2-A3	27.2	11.3	15.6	14.5	12.3	9.8	10.8	21.2	23.4	28.5	3.0	21.5	36.6
	R2-A4	26.6	9.3	21.9	7.8	4.0	4.3	64.4	10.8	18.3	12.6	30.4	13.0	25.2
	R2-A5	153.2	7.2	27.6	39.4	18.9	17.8	1135.6	8.5	24.5	9.2	62.1	7.2	36.4
	R2-A6	3765.1	107.0	321.1	1438.5	196.3	142.4	4023.1	21.7	14.8	13.4	10.0	10.6	74.2
	R2-A7	26.8	14.8	13.5	25.7	23.5	25.9	8.1	7.8	6.8	9.1	7.0	13.9	33.5
	R2-A8	30.4	15.6	18.0	43.7	29.6	32.2	1123.6	10.4	11.4	7.4	35.9	5.7	65.5
4 h heating	R2-A1	21.7	15.5	16.4	32.6	15.8	20.5	68.8	6.8	10.2	7.6	6.2	15.8	48.9
	R2-A2	13.6	3.7	6.5	21.5	24.8	35.2	11.0	5.7	16.8	8.5	13.8	19.0	72.9
	R2-A3	22.4	12.0	11.1	17.3	13.9	13.8	21.3	17.8	18.5	21.7	2.6	22.1	56.2
	R2-A4	21.7	8.2	8.1	13.5	6.9	7.0	50.0	12.4	20.3	17.8	24.5	12.1	20.9
	R2-A5	318.1	8.9	13.8	28.4	17.9	18.8	910.8	6.9	9.7	10.9	24.3	8.2	35.6
	R2-A6	4585.7	171.0	272.4	340.5	38.8	38.5	2951.8	117.3	19.2	12.9	5.3	9.2	42.5
	R2-A7	31.0	11.1	10.0	24.8	35.5	23.8	12.8	4.9	7.3	6.0	9.4	14.9	39.4
	R2-A8	30.6	13.4	20.4	42.8	27.4	24.2	846.6	11.0	12.8	8.7	29.3	8.2	85.3
15 h heating	R2-A1	24.3	7.4	8.7	21.8	18.2	10.2	53.6	3.9	29.7	6.6	9.5	10.4	41.1
	R2-A2	23.2	11.4	21.9	26.4	30.1	24.2	48.5	4.8	11.2	10.7	13.7	21.0	49.9
	R2-A3	24.2	17.1	9.7	22.2	15.2	13.4	54.7	24.9	21.9	27.7	4.8	17.2	43.3
	R2-A4	24.3	5.6	7.9	28.0	13.0	11.0	81.2	13.9	18.8	14.9	12.8	9.3	17.5
	R2-A5	136.1	14.9	8.8	17.7	17.7	16.0	1120.3	7.6	13.4	10.5	11.4	14.7	25.8
	R2-A6	2838.4	225.7	334.8	25.1	14.3	10.7	1631.1	218.9	33.2	21.6	4.6	24.1	108.4
	R2-A7	40.5	15.8	14.1	38.7	36.1	30.6	7.4	2.4	3.0	3.6	29.1	15.7	17.5
	R2-A8	58.4	24.2	21.2	37.2	40.5	26.8	230.8	12.7	13.0	8.1	23.3	10.1	85.0

Base: NaO^tBu

	R1-B1	R1-B2	R1-B3	R1-B4	R1-B5	R1-B6	R1-B7	R1-B8	R2-B9	R1-B10	R1-B11	R1-B12 (S)	R1-B12 (D)	
DESI-MS	R2-A1	24.6	25.4	18.7	40.7	17.8	7.8	14.1	5.1	7.8	7.8	6.5	16.9	137.2
	R2-A2	5.4	7.8	5.0	43.1	38.9	35.2	8.7	315.4	237.8	142.3	9.2	41.8	99.3
	R2-A3	48.7	34.4	52.0	18.3	20.5	15.6	5.1	19.6	28.4	19.0	5.6	26.4	88.7
	R2-A4	5.1	2.1	7.7	11.2	6.6	12.1	107.3	17.4	11.7	13.0	39.3	12.7	38.7
	R2-A5	2.8	8.3	6.5	47.3	11.2	12.7	26.7	8.6	13.7	6.9	39.1	15.9	90.7
	R2-A6	28.0	7.0	5.8	45.0	4.8	3.5	212.7	27.9	17.1	12.8	4.0	12.1	225.5
	R2-A7	44.0	40.8	31.2	25.7	24.2	32.5	5.3	7.2	9.8	4.0	1.7	17.6	27.1
	R2-A8	11.4	9.3	10.6	12.8	8.8	7.8	7.3	17.7	13.6	3.5	8.0	22.7	93.4
1 h heating	R2-A1	27.3	10.7	15.5	11.3	7.0	9.3	32.2	6.5	8.1	2.4	21.8	16.9	67.6
	R2-A2	37.2	19.1	25.5	19.6	23.3	26.1	9.6	24.5	18.6	8.1	14.9	36.4	68.1
	R2-A3	19.8	30.7	14.0	11.4	12.2	15.8	10.3	20.6	53.1	17.8	3.3	18.2	53.7
	R2-A4	11.8	6.7	7.0	11.9	11.6	8.4	108.3	18.8	13.9	10.8	5.2	11.6	30.6
	R2-A5	2.6	1.8	6.6	196.2	56.2	42.1	36.2	14.3	18.1	5.5	32.3	7.5	37.4
	R2-A6	100.3	31.9	31.3	162.2	13.3	9.6	628.2	20.4	15.8	5.1	7.8	18.8	87.8
	R2-A7	21.4	25.2	26.4	24.8	19.9	25.6	4.6	5.5	5.3	1.9	4.9	17.6	27.6
	R2-A8	45.2	25.4	26.3	17.2	15.5	13.3	22.8	22.2	11.6	10.7	3.4	8.0	82.8
4 h heating	R2-A1	6.6	8.6	11.9	18.2	12.4	18.2	37.6	10.5	6.4	6.8	14.5	16.9	52.2
	R2-A2	40.1	30.2	29.5	28.8	25.8	21.8	10.1	22.9	41.0	14.7	12.2	33.9	70.5
	R2-A3	16.5	29.7	19.0	14.4	9.7	11.0	9.9	21.7	42.7	17.9	3.0	21.9	70.6
	R2-A4	5.0	7.8	10.9	10.3	7.8	10.4	104.5	13.6	20.2	17.2	10.4	13.4	35.5
	R2-A5	5.7	3.9	6.8	18.8	14.0	16.0	26.7	15.4	20.8	12.9	27.2	10.1	33.9
	R2-A6	197.8	33.2	45.4	43.3	13.8	10.4	426.2	25.9	34.7	14.4	3.0	15.7	86.0
	R2-A7	21.5	21.8	28.5	25.5	16.8	31.6	8.4	9.8	7.2	4.5	5.3	20.9	39.4
	R2-A8	56.2	33.8	24.0	16.9	18.7	17.8	12.5	18.4	17.5	8.0	8.1	11.2	103.0
15 h heating	R2-A1	6.3	10.5	3.0	37.2	19.5	23.6	19.1	12.6	8.3	6.2	15.8	24.0	52.9
	R2-A2	42.0	30.7	26.7	26.5	15.7	20.4	13.3	29.2	40.7	7.5	10.7	28.6	68.6
	R2-A3	7.9	15.6	18.0	16.3	10.7	16.9	7.4	21.4	19.0	15.5	4.6	22.7	57.1
	R2-A4	13.0	12.5	11.3	9.3	5.4	9.5	103.3	14.6	15.2	11.4	13.5	7.2	29.7
	R2-A5	10.4	7.1	5.2	15.4	15.1	18.4	204.3	11.5	12.7	7.9	9.0	11.0	33.1
	R2-A6	245.5	25.2	31.8	15.2	9.9	7.2	713.3	89.0	76.7	9.7	5.5	31.3	105.1
	R2-A7	17.4	23.0	18.7	23.1	30.3	26.3	13.4	10.7	10.2	5.7	6.6	21.8	38.5
	R2-A8	39.8	18.4	29.6	18.7	23.9	24.1	32.8	26.0	30.1	16.0	30.0	10.4	87.6

Base: TEA

C)

	R1-B1	R1-B2	R1-B3	R1-B4	R1-B5	R1-B6	R1-B7	R1-B8	R2-B9	R1-B10	R1-B11	R1-B12 (S)	R1-B12 (D)	
DESI-MS	R2-A1	8.0	2.5	5.1	8.1	9.0	5.5	290.3	6.1	42.4	7.1	5.1	9.1	75.5
	R2-A2	7.9	2.0	7.4	25.5	29.1	31.0	4.2	5.2	21.5	9.1	2.2	19.8	75.8
	R2-A3	132.9	5.6	9.8	17.5	18.0	13.4	26.5	21.0	27.3	29.8	1.8	29.3	59.6
	R2-A4	15.1	4.7	6.1	4.5	6.3	3.5	82.2	10.5	17.6	15.3	27.3	8.6	27.3
	R2-A5	38.5	4.7	8.9	139.5	58.8	147.0	434.3	12.7	16.4	26.2	7.9	13.2	123.7
	R2-A6	199.8	12.6	18.9	66.0	7.2	6.4	829.5	45.4	14.5	7.4	2.9	83.0	607.0
	R2-A7	34.9	14.3	16.7	31.9	25.3	20.8	2.9	4.8	6.7	5.2	3.2	21.7	23.2
	R2-A8	69.2	15.1	35.8	12.5	14.2	8.9	58.7	12.0	9.1	12.0	14.1	127.1	97.8
1 h heating	R2-A1	41.9	34.9	26.5	18.9	11.7	17.0	125.6	2.3	7.3	7.2	3.4	10.8	38.2
	R2-A2	22.4	3.7	10.1	22.0	29.3	23.4	4.1	3.0	12.8	11.2	27.1	18.6	52.5
	R2-A3	38.5	6.4	6.7	18.2	12.1	7.6	7.8	21.1	25.2	19.8	1.1	21.0	64.5
	R2-A4	15.3	4.2	7.2	8.0	7.2	6.0	57.5	13.5	12.0	15.0	51.5	8.0	28.5
	R2-A5	219.4	7.0	24.1	64.1	23.1	13.0	907.4	15.1	11.4	12.1	15.6	13.2	138.6
	R2-A6	3741.6	92.5	352.3	1544.5	256.6	191.2	3062.2	37.3	13.5	9.4	8.1	5.5	40.2
	R2-A7	24.9	14.4	13.2	30.2	24.4	23.6	8.3	18.9	25.6	19.6	4.2	15.0	55.7
	R2-A8	26.4	12.8	12.7	61.4	43.0	23.1	389.2	9.9	12.0	8.9	15.5	7.6	92.2
4 h heating	R2-A1	18.5	11.5	13.2	33.5	26.0	23.9	75.5	8.0	8.2	6.2	6.2	11.7	39.7
	R2-A2	13.1	6.2	6.2	28.6	29.7	27.1	9.0	4.2	7.7	6.8	10.2	22.1	66.6
	R2-A3	22.4	5.4	7.7	15.5	15.8	10.6	11.9	23.9	21.4	18.1	4.3	17.8	72.6
	R2-A4	19.8	4.8	6.7	24.8	13.0	8.7	71.9	10.5	18.8	14.2	20.4	9.2	22.9
	R2-A5	425.2	10.4	20.0	61.5	29.2	12.3	970.3	12.1	14.8	15.7	27.4	14.5	36.5
	R2-A6	2943.3	182.9	284.7	689.8	60.4	60.1	2932.4	93.4	17.8	11.3	25.9	4.1	37.4
	R2-A7	33.5	10.6	10.8	34.8	25.5	38.1	7.3	13.5	16.3	11.2	5.9	22.0	29.1
	R2-A8	26.9	4.9	9.0	32.2	16.8	8.1	121.8	5.5	7.9	4.8	15.1	10.5	112.4
15 h heating	R2-A1	13.9	6.6	6.5	59.3	22.8	18.2	36.1	2.6	26.3	6.3	4.0	10.7	46.0
	R2-A2	51.0	12.9	10.8	33.7	20.7	28.4	12.9	6.5	12.5	15.0	10.6	17.8	37.8
	R2-A3	27.7	6.3	22.7	19.3	15.7	7.7	29.6	22.8	23.4	23.1	4.5	15.0	88.3
	R2-A4	23.9	7.1	13.5	60.0	14.3	18.1	58.4	11.7	15.8	13.1	16.1	6.5	19.4
	R2-A5	332.7	9.8	32.9	13.6	16.4	18.7	965.4	10.1	12.5	11.5	23.2	11.6	29.0
	R2-A6	3186.7	172.9	428.9	72.2	18.1	14.8	2577.8	247.0	37.6	15.9	12.5	11.0	43.2
	R2-A7	45.1	13.4	13.8	43.4	39.1	38.3	10.1	10.6	10.8	8.1	12.5	17.0	25.7
	R2-A8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Base: No base

D)

	R1-B1	R1-B2	R1-B3	R1-B4	R1-B5	R1-B6	R1-B7	R1-B8	R2-B9	R1-B10	R1-B11	R1-B12 (S)	R1-B12 (D)	
DESI-MS	R2-A1	1.6	3.2	2.7	7.0	11.0	7.5	277.6	6.7	4.0	5.3	4.1	21.3	91.8
	R2-A2	2.8	4.3	5.0	26.0	27.1	27.5	10.2	11.5	12.6	5.6	2.5	19.4	114.0
	R2-A3	230.9	61.7	6.4	14.5	12.1	13.0	62.9	20.2	22.7	17.4	3.6	47.7	115.1
	R2-A4	6.9	6.6	10.7	2.9	2.0	3.4	37.9	15.6	21.2	12.5	46.8	8.3	22.0
	R2-A5	8.5	35.8	6.8	11.7	7.4	7.4	160.3	13.7	15.0	9.7	29.1	18.6	43.4
	R2-A6	68.4	16.0	16.1	74.2	6.1	4.4	317.8	31.8	12.7	7.8	4.6	84.7	240.1
	R2-A7	14.8	14.1	22.3	26.0	27.1	25.2	3.2	6.2	6.0	5.0	4.6	18.6	25.9
	R2-A8	120.9	38.7	208.1	12.1	12.4	14.0	36.2	14.9	8.5	5.4	11.5	76.3	104.0
1 h heating	R2-A1	3.2	1.6	3.7	25.8	11.3	8.3	100.2	6.2	6.7	2.6	4.2	9.0	59.4
	R2-A2	3.9	2.6	4.0	27.1	28.0	32.3	7.6	6.6	10.5	3.8	48.4	32.1	91.0
	R2-A3	17.2	26.4	18.6	14.1	10.2	11.0	4.0	25.4	19.4	14.9	4.5	17.0	95.1
	R2-A4	28.1	19.1	16.4	3.2	6.3	4.3	62.2	16.5	17.1	9.4	49.8	7.8	19.5
	R2-A5	55.0	10.6	10.2	38.5	21.7	13.3	1579.9	14.9	12.0	6.7	17.4	7.8	35.6
	R2-A6	2387.9	107.9	174.9	2328.7	198.4	224.5	2402.8	41.9	13.7	5.4	10.0	10.8	52.1
	R2-A7	18.6	12.6	15.4	29.9	41.6	22.8	11.1	10.3	11.2	8.9	8.2	14.5	29.4
	R2-A8	17.3	12.1	11.9	53.2	22.2	20.7	1801.4	11.9	9.7	9.1	38.8	6.2	88.7
4 h heating	R2-A1	10.7	4.2	4.9	42.8	11.9	9.4	34.0	6.7	6.6	4.9	4.2	10.3	68.7
	R2-A2	2.9	2.6	3.8	22.0	28.0	23.8	6.7	6.7	13.4	4.3	22.8	18.9	80.0
	R2-A3	15.2	30.2	32.4	25.1	10.4	8.0	4.5	25.0	17.1	16.6	2.6	20.0	109.8
	R2-A4	14.3	13.6	11.6	17.3	7.9	3.4	39.5	15.9	20.2	13.4	38.1	8.7	22.5
	R2-A5	93.2	13.5	12.8	29.6	16.1	9.9	575.4	12.6	13.6	6.7	13.4	12.0	25.0
	R2-A6	2237.3	172.1	280.4	1281.3	138.2	93.8	1835.6	79.0	18.1	9.9	8.3	10.7	60.0
	R2-A7	14.0	9.8	17.2	27.6	25.6	22.5	15.8	9.7	12.1	3.8	25.0	15.2	32.0
	R2-A8	14.8	5.2	10.6	16.2	15.1	9.2	932.4	9.6	6.0	6.6	37.6	8.8	102.3
15 h heating	R2-A1	4.7	3.6	2.0	36.3	9.6	9.2	17.7	6.5	6.9	1.1	4.8	11.0	52.3
	R2-A2	5.7	3.6	4.6	26.2	22.8	26.3	6.7	7.2	9.5	5.7	9.3	32.6	88.0
	R2-A3	30.6	23.9	18.2	17.1	21.0	11.0	26.7	25.3	21.9	12.0	0.6	13.3	86.5
	R2-A4	10.7	5.5	8.3	24.7	11.6	7.5	59.0	14.3	14.0	11.4	14.0	10.7	24.8
	R2-A5	90.3	13.1	20.7	23.5	9.3	6.6	663.2	14.0	13.8	5.5	14.7	15.1	29.6
	R2-A6	1733.2	133.1	223.4	571.6	29.0	10.2	2109.0	294.6	24.8	9.4	10.8	5.7	43.1
	R2-A7	16.4	16.3	20.8	27.9	29.5	35.4	5.2	9.2	9.7	3.9	20.1	14.9	27.5
	R2-A8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

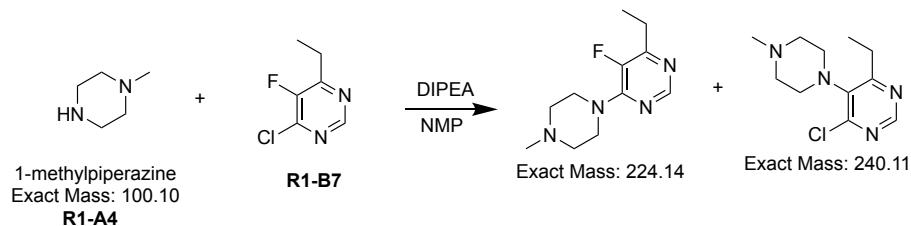
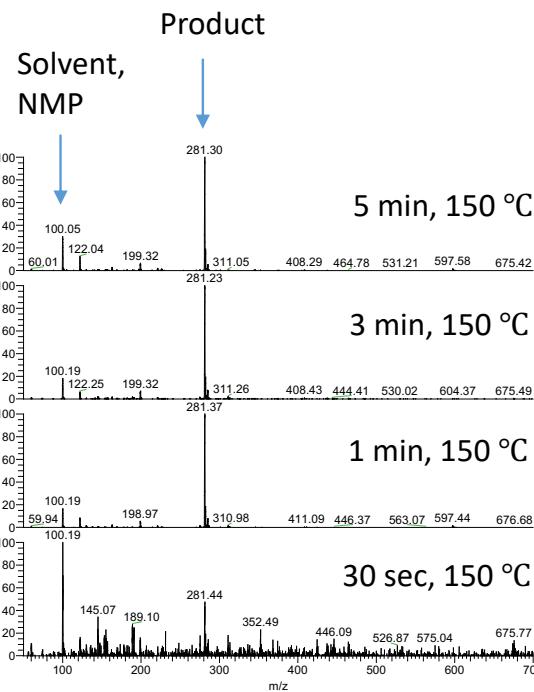
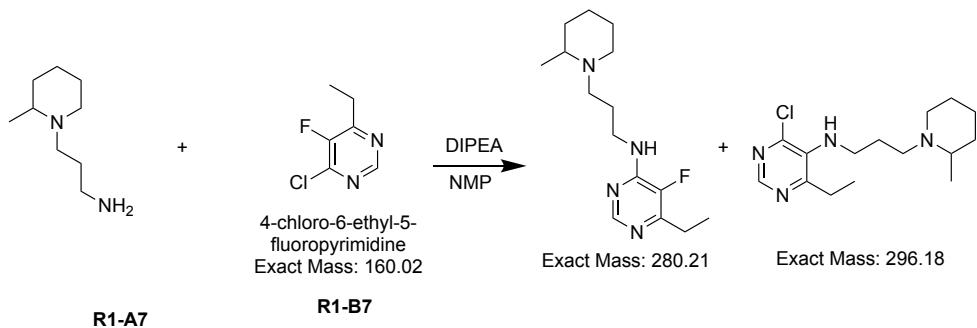
Figure S4: Heat map of 1,536 round 2 SnAr HTE reactions using MeOH with 1% FA as spray solvent at 200 °C using NMP as the reaction solvent. The four basic conditions are A) DIPEA B) NaO*t*Bu C) TEA D) No base.

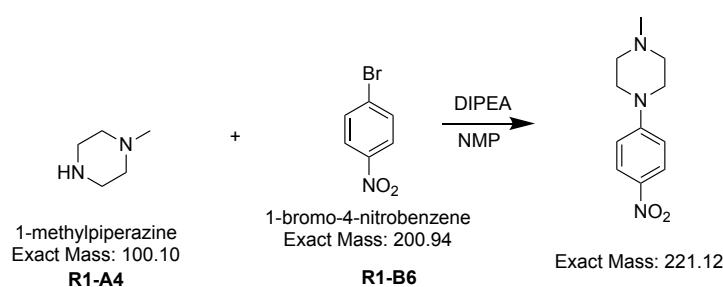
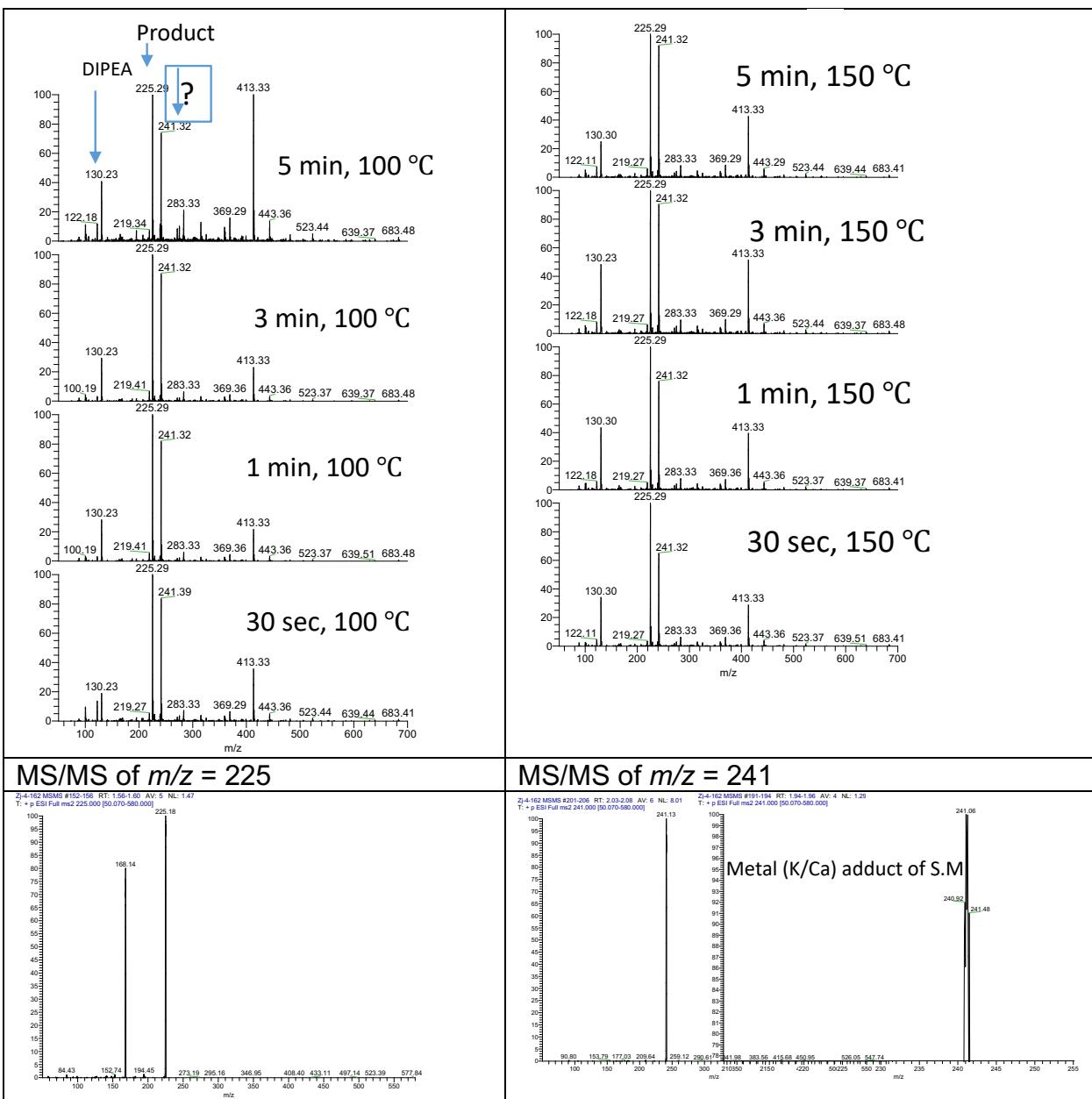
Continuous Flow Synthesis

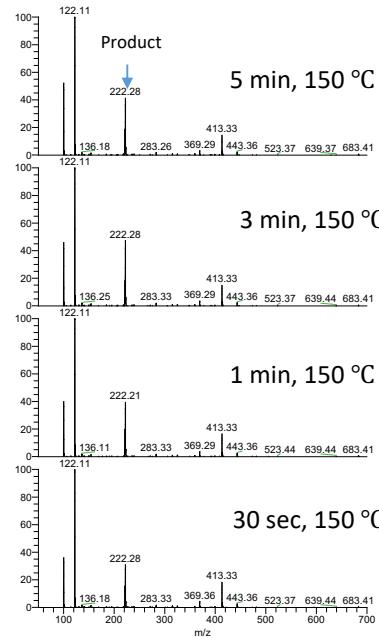
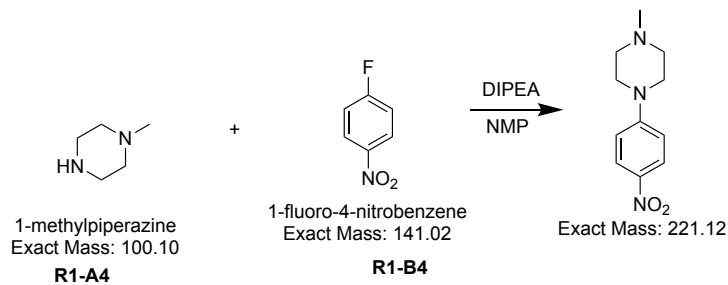
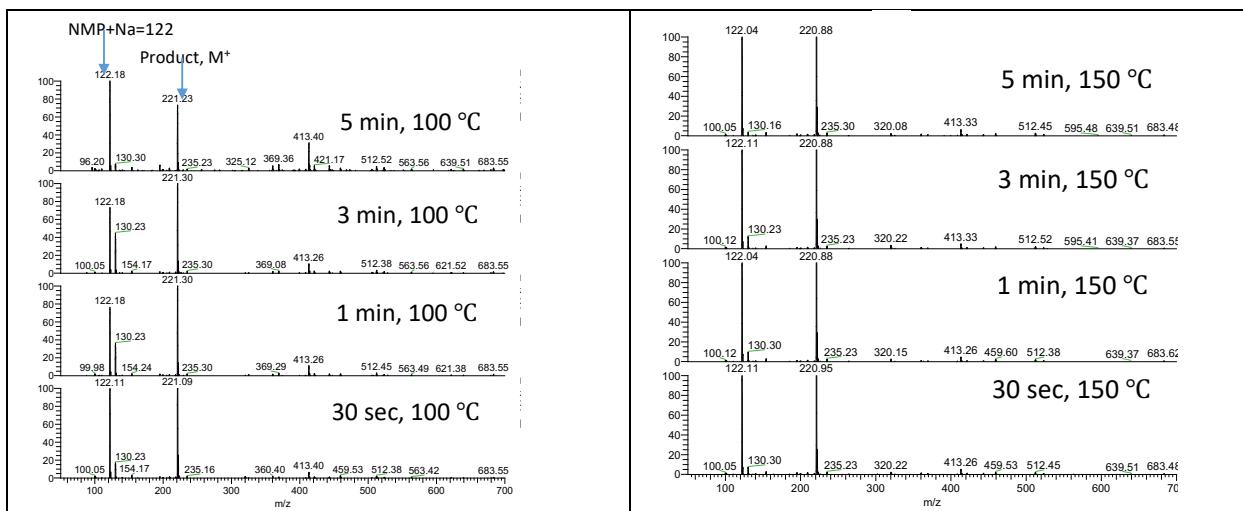
Table S1: Chemtrix reactor chip: 3225, reactor volume:10 μL , pressure: ambient pressure

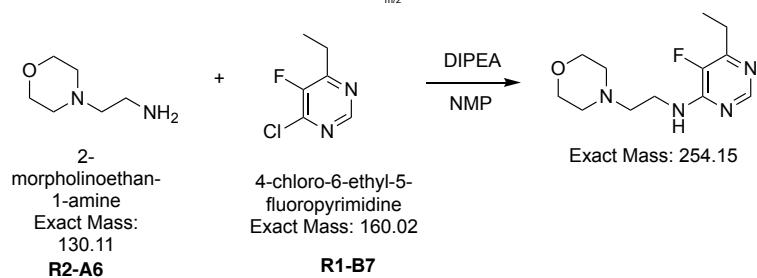
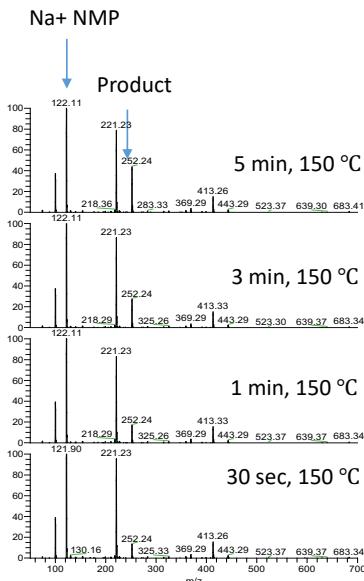
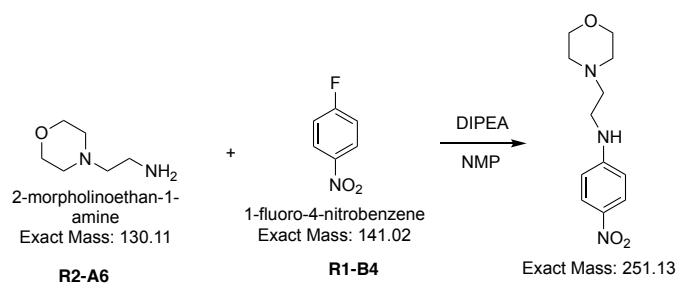
Amines $\mu\text{L}/\text{min}$	Aryl halides $\mu\text{L}/\text{min}$	Base $\mu\text{L}/\text{min}$	Residence Time T_r in Minutes	Temperature $^{\circ}\text{C}$
6.67	6.67	6.67	0.5	100/150
3.33	3.33	3.33	1	100/150
1.11	1.11	1.11	3	100/150
0.67	0.67	0.67	5	100/150

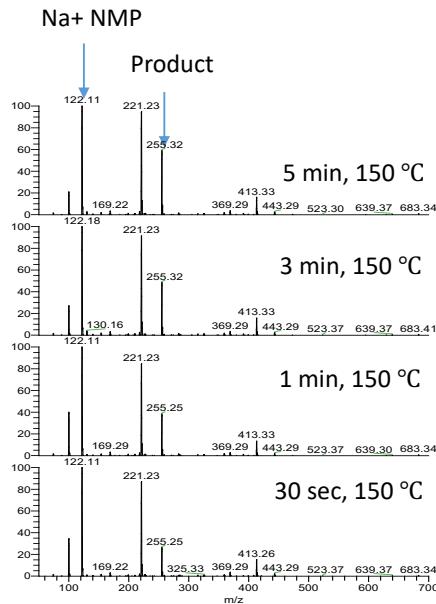
“Yes” Reaction in Flow











“No” Reaction in Flow

