Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.
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Accelerating Reaction Optimization Through Data-Rich Experimentation and Machine-Assisted Process Development

Supplemental Information

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Analytical Information

UPLC method for Methoxylation

Analytical information around the UPLC method to monitor the methoxylation reaction is provided below:

Column: Acquity UPLC BEH C18 1.7 uM 2.1 x 100 mm Column Part no: 186002352
Solvent A : Water with 0.1 wt. % Phosphoric Acid
Solvent B: Acetonitrile
Flow rate: 0.5 mL/min
Injection volume: 1 uL
Detector: 210 nm
Run time: 6 min
Post-run time: 2 min

Table S1: UPLC gradient table for LC method.

Time (min)	%A	%B
0	90	10
4	5	95
6	5	95
6.1	90	10

UPLC method for Bromination

Analytical information around the UPLC method to monitor the bromination reaction is provided below:

Column: Acquity UPLC BEH C18 1.7 uM 2.1 x 100 mm Column Part no: 186002352
Solvent A : Water with 0.1% Formic Acid
Solvent B: Acetonitrile with 0.1% Formic Acid
Flow rate: 0.8 mL/min
Injection volume: 1 uL
Detector: 200 nm
Run time: 5 min

Table S2: UPLC gradient table for LC method.

Time (min)	%A	%B
0	90	10
0.5	90	10
3.0	10	90
3.5	10	90
3.6	90	10
5.0	90	10

Input to SNOBFIT Algorithm

Coded variable definition for Methoxylation case study

Coded variables were used to normalize search variables. Coded variables were calculated via Eq. S1 using terms from Table S3, where x_i corresponds to the coded variable for reaction variable, w_i, indexed by i, u_i is the lower bound for that reaction variable, and v_i is the upper bound of that reaction variable.

Table S3: Bounds for reaction variables in methoxylation optimization case study.

	Lower bound	Upper bound
Temperature (deg. C)	60	(80)[a] 85
CuBr (mol%)	1	10
DMF (eq.)	0	3
NaOMe (eq.)	2.5	5.0
Time (h)	2	(24)[a] 30

a – Initial bound on variable before adjusting after round 1 results

$$x_i = \frac{w_i - u_i}{v_i - u_i} \qquad \text{Eq. S1}$$

Input to SNOBFIT Algorithm for Methoxylation case study

Parameters used in the SNOBFIT algorithm for the optimization of the methoxylation case study are provided in Table S4.

Table S4: SNOBFIT parameters used in optimization methoxylation case study.

Parameter	Value	Description
N	5	Dimensionality of the optimization problem.
u	[0 0 0 0 0]	Vector containing lower bounds for coded variables.
v	[1.25 1 1 1 1.25]	Vector containing upper bounds for coded variables.
dx	$[5\ 11\ 8\ 4\ 1] \cdot 10^{-2}$	Resolution vector to define experimental space between lower and upper bounds.
N_{point}	10	Number of space-filling start experiments to be generated
N_{req}	10	Number of experiments to generated in each call to SNOBFIT
N_{call}	40	Limit on number of function calls
P	0.3	Probability of generating an experiment of class 4 (e.g., an experiment in unexplored space)
ΔF	3%	Assumed error in experimental data

Input to SNOBFIT Algorithm for Bromination

Coded variable definition for bromination case study

Coded variables were used to normalize search variables. Coded variables were calculated via Eq. S1 using terms from Table S5Table S4, where x_i corresponds to the coded variable for reaction variable, w_i, indexed by i, u_i is the lower bound for that reaction variable, and v_i is the upper bound of that reaction variable.

Table S5: Bounds for reaction variables in bromination optimization case study.

	Lower bound	Upper bound
Temperature (deg. C)	40	90
DMF (Vol)	1	10
4(eq.)	12	24
Time (h)	2	20

Input to SNOBFIT Algorithm for bromination case study

Parameters used in the SNOBFIT algorithm for the optimization of the bromination case study are provided in Table S6.

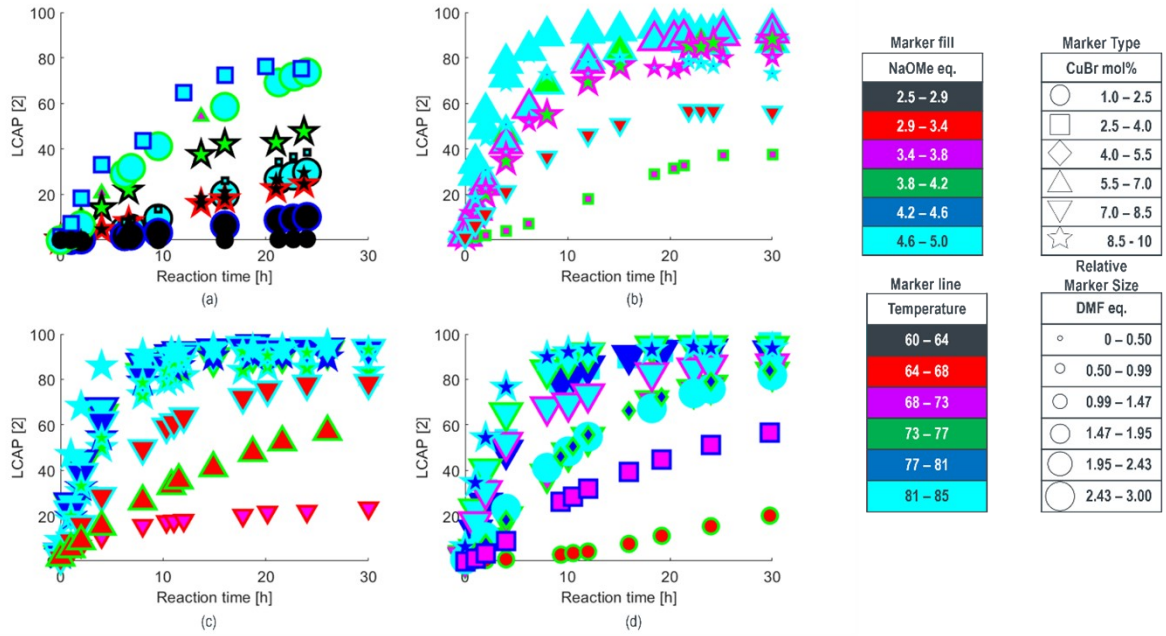
Table S6: SNOBFIT parameters used in the optimization of the bromination case study.

Parameter	Value	Description
N	4	Dimensionality of the optimization problem.
u	[0 0 0 0]	Vector containing lower bounds for coded variables.
v	[1 1 1 1]	Vector containing upper bounds for coded variables.
dx	$[2\ 4\ 4\ 10] \cdot 10^{-2}$	Resolution vector to define experimental space between lower and upper bounds.
N_{point}	10	Number of space-filling start experiments to be generated
N_{req}	10	Number of experiments to generated in each call to SNOBFIT
N_{call}	40	Limit on number of function calls
P	0.3	Probability of generating an experiment of class 4 (e.g., an experiment in unexplored space)
ΔF	3%	Assumed error in experimental data

Reaction and Optimization Results

Reaction and Optimization Results for Methoxylation

The reaction product profiles collected during optimization experiments are provided in Figures S1.



Figures S1: Product **2** profiles collected during SNOBFIT optimization, with input factors denoted by marker properties.

The complete reaction optimization data set is enumerated in Table S7.

Table S7: Optimization data collected for methoxylation case study with blue highlighted rows indicating experimental conditions requested by the SNOBFIT algorithm and grey rows corresponding to additional points inputted into the SNOBFIT algorithm by the scientist.

		Coded Experimental Factors					Reaction Results	
Round	Reaction No.	Temperature	CuBr	DMF	NaOMe	Time	2 LCAP	Obj. Fun.
1	1	0.815	0.631	0.255	0.380	0.00	0.27	3.958
1	1	0.815	0.631	0.255	0.380	0.04	5.64	9.328
1	1	0.815	0.631	0.255	0.380	0.08	10.91	14.598
1	1	0.815	0.631	0.255	0.380	0.17	20.58	24.268
1	1	0.815	0.631	0.255	0.380	0.28	31.25	34.938
1	1	0.815	0.631	0.255	0.380	0.57	54.24	57.928
1	1	0.815	0.631	0.255	0.380	0.67	59.65	63.338
1	1	0.815	0.631	0.255	0.380	0.88	67.36	71.048
1	1	0.815	0.631	0.255	0.380	0.99	70.56	74.248
1	2	0.050	0.061	0.970	0.884	0.00	0	9.394
1	2	0.050	0.061	0.970	0.884	0.04	0	9.394
1	2	0.050	0.061	0.970	0.884	0.08	0.48	9.874
1	2	0.050	0.061	0.970	0.884	0.26	4.26	13.654
1	2	0.050	0.061	0.970	0.884	0.29	5.1	14.494
1	2	0.050	0.061	0.970	0.884	0.40	9.5	18.894
1	2	0.050	0.061	0.970	0.884	0.67	19.96	29.354
1	2	0.050	0.061	0.970	0.884	0.88	26.61	36.004
1	2	0.050	0.061	0.970	0.884	0.95	28.23	37.624
1	2	0.050	0.061	0.970	0.884	1.00	29.73	39.124
1	3	0.000	0.906	0.950	0.645	0.00	0.3	1.236
1	3	0.000	0.906	0.950	0.645	0.04	3.36	4.296
1	3	0.000	0.906	0.950	0.645	0.08	7.22	8.156
1	3	0.000	0.906	0.950	0.645	0.17	14.15	15.086
1	3	0.000	0.906	0.950	0.645	0.28	21.81	22.746
1	3	0.000	0.906	0.950	0.645	0.57	37.45	38.386
1	3	0.000	0.906	0.950	0.645	0.67	42.13	43.066
1	3	0.000	0.906	0.950	0.645	0.88	42.79	43.726
1	3	0.000	0.906	0.950	0.645	0.99	47.55	48.486
1	4	0.235	0.923	0.877	0.015	0.00	0	0.773
1	4	0.235	0.923	0.877	0.015	0.04	1.12	1.893
1	4	0.235	0.923	0.877	0.015	0.08	2.05	2.823
1	4	0.235	0.923	0.877	0.015	0.17	4.66	5.433
1	4	0.235	0.923	0.877	0.015	0.28	8	8.773
1	4	0.235	0.923	0.877	0.015	0.57	15.98	16.753
1	4	0.235	0.923	0.877	0.015	0.67	17.99	18.763
1	4	0.235	0.923	0.877	0.015	0.88	22.47	23.243
1	4	0.235	0.923	0.877	0.015	0.99	24.61	25.383

		Coded Experimental Factors					Reaction Results	
Round	Reaction No.	Temperature	CuBr	DMF	NaOMe	Time	2 LCAP	Obj. Fun.
1	5	0.960	0.025	0.949	0.074	0.00	0	9.749
1	5	0.960	0.025	0.949	0.074	0.04	0	9.749
1	5	0.960	0.025	0.949	0.074	0.08	0.22	9.969
1	5	0.960	0.025	0.949	0.074	0.26	1.67	11.419
1	5	0.960	0.025	0.949	0.074	0.29	1.93	11.679
1	5	0.960	0.025	0.949	0.074	0.40	3.21	12.959
1	5	0.960	0.025	0.949	0.074	0.67	6.42	16.169
1	5	0.960	0.025	0.949	0.074	0.88	8.85	18.599
1	5	0.960	0.025	0.949	0.074	0.95	9.52	19.269
1	5	0.960	0.025	0.949	0.074	1.00	10.19	19.939
1	6	0.770	0.113	0.931	0.861	0.00	0	8.874
1	6	0.770	0.113	0.931	0.861	0.04	2.26	11.134
1	6	0.770	0.113	0.931	0.861	0.08	6.57	15.444
1	6	0.770	0.113	0.931	0.861	0.26	29.08	37.954
1	6	0.770	0.113	0.931	0.861	0.29	31.68	40.554
1	6	0.770	0.113	0.931	0.861	0.40	41.19	50.064
1	6	0.770	0.113	0.931	0.861	0.67	58.47	67.344
1	6	0.770	0.113	0.931	0.861	0.88	69.16	78.034
1	6	0.770	0.113	0.931	0.861	0.95	71.73	80.604
1	6	0.770	0.113	0.931	0.861	1.00	73.62	82.494
1	7	0.110	0.241	0.007	0.910	0.00	0	7.589
1	7	0.110	0.241	0.007	0.910	0.04	0.45	8.039
1	7	0.110	0.241	0.007	0.910	0.08	1.78	9.369
1	7	0.110	0.241	0.007	0.910	0.26	7.92	15.509
1	7	0.110	0.241	0.007	0.910	0.29	9.05	16.639
1	7	0.110	0.241	0.007	0.910	0.40	13.55	21.139
1	7	0.110	0.241	0.007	0.910	0.67	25.94	33.529
1	7	0.110	0.241	0.007	0.910	0.88	34.45	42.039
1	7	0.110	0.241	0.007	0.910	0.95	36.45	44.039
1	7	0.110	0.241	0.007	0.910	1.00	38.57	46.159
1	8	0.030	0.973	0.031	0.601	0.00	0	0.273
1	8	0.030	0.973	0.031	0.601	0.04	0.61	0.883
1	8	0.030	0.973	0.031	0.601	0.08	1.65	1.923
1	8	0.030	0.973	0.031	0.601	0.17	4.79	5.063
1	8	0.030	0.973	0.031	0.601	0.28	8.93	9.203
1	8	0.030	0.973	0.031	0.601	0.57	18.52	18.793
1	8	0.030	0.973	0.031	0.601	0.67	21.14	21.413
1	8	0.030	0.973	0.031	0.601	0.88	26.58	26.853
1	8	0.030	0.973	0.031	0.601	0.99	29.62	29.893

		Coded Experimental Factors					Reaction Results	
Round	Reaction No.	Temperature	CuBr	DMF	NaOMe	Time	2 LCAP	Obj. Fun.
1	9	0.950	0.242	0.571	0.995	0.00	1.52	9.105
1	9	0.950	0.242	0.571	0.995	0.04	7.18	14.765
1	9	0.950	0.242	0.571	0.995	0.08	18.28	25.865
1	9	0.950	0.242	0.571	0.995	0.17	33.05	40.635
1	9	0.950	0.242	0.571	0.995	0.33	43.57	51.155
1	9	0.950	0.242	0.571	0.995	0.50	64.77	72.355
1	9	0.950	0.242	0.571	0.995	0.67	72.38	79.965
1	9	0.950	0.242	0.571	0.995	0.83	76.31	83.895
1	9	0.950	0.242	0.571	0.995	0.98	75.25	82.835
1	10	0.085	0.149	0.442	0.073	0.00	0	8.511
1	10	0.085	0.149	0.442	0.073	0.04	0	8.511
1	10	0.085	0.149	0.442	0.073	0.08	0	8.511
1	10	0.085	0.149	0.442	0.073	0.26	0	8.511
1	10	0.085	0.149	0.442	0.073	0.29	0	8.511
1	10	0.085	0.149	0.442	0.073	0.40	0	8.511
1	10	0.085	0.149	0.442	0.073	0.67	0	8.511
1	10	0.085	0.149	0.442	0.073	0.88	0.33	8.841
1	10	0.085	0.149	0.442	0.073	0.95	0.4	8.911
1	10	0.085	0.149	0.442	0.073	1.00	0.47	8.981
2	1	1.250	1.000	0.240	1.000	0.00	3.37	3.37
2	1	1.250	1.000	0.240	1.000	0.04	25.02	25.02
2	1	1.250	1.000	0.240	1.000	0.08	44.49	44.49
2	1	1.250	1.000	0.240	1.000	0.17	68.58	68.58
2	1	1.250	1.000	0.240	1.000	0.26	81.31	81.31
2	1	1.250	1.000	0.240	1.000	0.50	88.82	88.82
2	1	1.250	1.000	0.240	1.000	0.77	89.13	89.13
2	1	1.250	1.000	0.240	1.000	0.85	89.46	89.46
2	1	1.250	1.000	0.240	1.000	0.89	89.15	89.15
2	1	1.250	1.000	0.240	1.000	1.05	88.87	88.87
2	1	1.250	1.000	0.240	1.000	1.25	87.48	87.48
2	2	1.250	0.667	0.880	1.000	0.00	4.65	7.98
2	2	1.250	0.667	0.880	1.000	0.04	33.61	36.94
2	2	1.250	0.667	0.880	1.000	0.08	56.02	59.35
2	2	1.250	0.667	0.880	1.000	0.17	77.57	80.90
2	2	1.250	0.667	0.880	1.000	0.33	89.59	92.92
2	2	1.250	0.667	0.880	1.000	0.50	90.89	94.22
2	2	1.250	0.667	0.880	1.000	0.63	91.75	95.08
2	2	1.250	0.667	0.880	1.000	0.91	90.76	94.09
2	2	1.250	0.667	0.880	1.000	0.96	90.41	93.74
2	2	1.250	0.667	0.880	1.000	1.01	90.53	93.86
2	2	1.250	0.667	0.880	1.000	1.25	92.14	95.47

		Coded Experimental Factors					Reaction Results	
Round	Reaction No.	Temperature	CuBr	DMF	NaOMe	Time	**2** LCAP	Obj. Fun.
2	3	1.150	0.556	0.960	1.000	0.00	3.61	8.05
2	3	1.150	0.556	0.960	1.000	0.04	28.4	32.84
2	3	1.150	0.556	0.960	1.000	0.08	48.84	53.28
2	3	1.150	0.556	0.960	1.000	0.17	71.53	75.97
2	3	1.150	0.556	0.960	1.000	0.26	83.26	87.70
2	3	1.150	0.556	0.960	1.000	0.50	92.6	97.04
2	3	1.150	0.556	0.960	1.000	0.77	92.96	97.40
2	3	1.150	0.556	0.960	1.000	0.85	92.77	97.21
2	3	1.150	0.556	0.960	1.000	0.89	92.88	97.32
2	3	1.150	0.556	0.960	1.000	1.05	92.77	97.21
2	3	1.150	0.556	0.960	1.000	1.25	92.97	97.41
2	4	1.250	0.556	0.960	0.520	0.00	2.19	6.63
2	4	1.250	0.556	0.960	0.520	0.04	14.05	18.49
2	4	1.250	0.556	0.960	0.520	0.08	25.99	30.43
2	4	1.250	0.556	0.960	0.520	0.17	46.43	50.87
2	4	1.250	0.556	0.960	0.520	0.33	68.51	72.95
2	4	1.250	0.556	0.960	0.520	0.50	79.32	83.76
2	4	1.250	0.556	0.960	0.520	0.63	83.22	87.66
2	4	1.250	0.556	0.960	0.520	0.91	86.74	91.18
2	4	1.250	0.556	0.960	0.520	0.96	86.82	91.26
2	4	1.250	0.556	0.960	0.520	1.01	85.84	90.28
2	4	1.250	0.556	0.960	0.520	1.25	86.59	91.03
2	5	0.500	0.556	0.960	1.000	0.00	1.75	6.19
2	5	0.500	0.556	0.960	1.000	0.04	13.06	17.50
2	5	0.500	0.556	0.960	1.000	0.08	24.05	28.49
2	5	0.500	0.556	0.960	1.000	0.17	42.27	46.71
2	5	0.500	0.556	0.960	1.000	0.26	57.78	62.22
2	5	0.500	0.556	0.960	1.000	0.50	77.58	82.02
2	5	0.500	0.556	0.960	1.000	0.77	87.48	91.92
2	5	0.500	0.556	0.960	1.000	0.85	87.94	92.38
2	5	0.500	0.556	0.960	1.000	0.89	88.36	92.80
2	5	0.500	0.556	0.960	1.000	1.05	89.72	94.16
2	5	0.500	0.556	0.960	1.000	1.25	90.9	95.34
2	6	0.600	1.000	0.960	0.520	0.00	1.56	1.56
2	6	0.600	1.000	0.960	0.520	0.04	11.09	11.09
2	6	0.600	1.000	0.960	0.520	0.08	20.05	20.05
2	6	0.600	1.000	0.960	0.520	0.17	34.6	34.60
2	6	0.600	1.000	0.960	0.520	0.33	54.95	54.95
2	6	0.600	1.000	0.960	0.520	0.50	69.45	69.45
2	6	0.600	1.000	0.960	0.520	0.63	76.39	76.39
2	6	0.600	1.000	0.960	0.520	0.91	85.07	85.07
2	6	0.600	1.000	0.960	0.520	0.96	84.7	84.70
2	6	0.600	1.000	0.960	0.520	1.01	86.6	86.60
2	6	0.600	1.000	0.960	0.520	1.25	88.21	88.21

		Coded Experimental Factors					Reaction Results	
Round	Reaction No.	Temperature	CuBr	DMF	NaOMe	Time	**2** LCAP	Obj. Fun.
2	7	0.500	1.000	0.480	0.880	0.00	1.06	1.06
2	7	0.500	1.000	0.480	0.880	0.04	11.85	11.85
2	7	0.500	1.000	0.480	0.880	0.08	22.72	22.72
2	7	0.500	1.000	0.480	0.880	0.17	38.77	38.77
2	7	0.500	1.000	0.480	0.880	0.26	51.67	51.67
2	7	0.500	1.000	0.480	0.880	0.50	73.08	73.08
2	7	0.500	1.000	0.480	0.880	0.77	75.6	75.60
2	7	0.500	1.000	0.480	0.880	0.85	74.75	74.75
2	7	0.500	1.000	0.480	0.880	0.89	76.42	76.42
2	7	0.500	1.000	0.480	0.880	1.05	79.83	79.83
2	7	0.500	1.000	0.480	0.880	1.25	80.17	80.17
2	8	1.200	0.889	0.240	0.680	0.00	2.6	3.71
2	8	1.200	0.889	0.240	0.680	0.04	18.31	19.42
2	8	1.200	0.889	0.240	0.680	0.08	30.77	31.88
2	8	1.200	0.889	0.240	0.680	0.17	50.71	51.82
2	8	1.200	0.889	0.240	0.680	0.33	72.66	73.77
2	8	1.200	0.889	0.240	0.680	0.50	78.23	79.34
2	8	1.200	0.889	0.240	0.680	0.63	80.4	81.51
2	8	1.200	0.889	0.240	0.680	0.91	78.51	79.62
2	8	1.200	0.889	0.240	0.680	0.96	77.61	78.72
2	8	1.200	0.889	0.240	0.680	1.01	76.37	77.48
2	8	1.200	0.889	0.240	0.680	1.25	73.15	74.26
2	9	0.650	0.222	0.240	0.400	0.00	0.79	8.57
2	9	0.650	0.222	0.240	0.400	0.04	1.33	9.11
2	9	0.650	0.222	0.240	0.400	0.08	2.06	9.84
2	9	0.650	0.222	0.240	0.400	0.17	4.15	11.93
2	9	0.650	0.222	0.240	0.400	0.26	7.2	14.98
2	9	0.650	0.222	0.240	0.400	0.50	18.11	25.89
2	9	0.650	0.222	0.240	0.400	0.77	28.79	36.57
2	9	0.650	0.222	0.240	0.400	0.85	31.55	39.33
2	9	0.650	0.222	0.240	0.400	0.89	32.78	40.56
2	9	0.650	0.222	0.240	0.400	1.05	37.1	44.88
2	9	0.650	0.222	0.240	0.400	1.25	37.54	45.32
2	10	1.050	0.778	0.480	0.200	0.00	1.1	3.32
2	10	1.050	0.778	0.480	0.200	0.04	6.38	8.60
2	10	1.050	0.778	0.480	0.200	0.08	11.44	13.66
2	10	1.050	0.778	0.480	0.200	0.17	21.18	23.40
2	10	1.050	0.778	0.480	0.200	0.33	36.34	38.56
2	10	1.050	0.778	0.480	0.200	0.50	46.06	48.28
2	10	1.050	0.778	0.480	0.200	0.63	50.65	52.87
2	10	1.050	0.778	0.480	0.200	0.91	56.84	59.06
2	10	1.050	0.778	0.480	0.200	0.96	56.81	59.03
2	10	1.050	0.778	0.480	0.200	1.01	56.76	58.98
2	10	1.050	0.778	0.480	0.200	1.25	56.06	58.28

		Coded Experimental Factors					Reaction Results	
Round	Reaction No.	Temperature	CuBr	DMF	NaOMe	Time	**2** LCAP	Obj. Fun.
2	7	0.500	1.000	0.480	0.880	0.00	1.06	1.06
2	7	0.500	1.000	0.480	0.880	0.04	11.85	11.85
2	7	0.500	1.000	0.480	0.880	0.08	22.72	22.72
2	7	0.500	1.000	0.480	0.880	0.17	38.77	38.77
2	7	0.500	1.000	0.480	0.880	0.26	51.67	51.67
2	7	0.500	1.000	0.480	0.880	0.50	73.08	73.08
2	7	0.500	1.000	0.480	0.880	0.77	75.6	75.60
2	7	0.500	1.000	0.480	0.880	0.85	74.75	74.75
2	7	0.500	1.000	0.480	0.880	0.89	76.42	76.42
2	7	0.500	1.000	0.480	0.880	1.05	79.83	79.83
2	7	0.500	1.000	0.480	0.880	1.25	80.17	80.17
2	8	1.200	0.889	0.240	0.680	0.00	2.6	3.71
2	8	1.200	0.889	0.240	0.680	0.04	18.31	19.42
2	8	1.200	0.889	0.240	0.680	0.08	30.77	31.88
2	8	1.200	0.889	0.240	0.680	0.17	50.71	51.82
2	8	1.200	0.889	0.240	0.680	0.33	72.66	73.77
2	8	1.200	0.889	0.240	0.680	0.50	78.23	79.34
2	8	1.200	0.889	0.240	0.680	0.63	80.4	81.51
2	8	1.200	0.889	0.240	0.680	0.91	78.51	79.62
2	8	1.200	0.889	0.240	0.680	0.96	77.61	78.72
2	8	1.200	0.889	0.240	0.680	1.01	76.37	77.48
2	8	1.200	0.889	0.240	0.680	1.25	73.15	74.26
2	9	0.650	0.222	0.240	0.400	0.00	0.79	8.57
2	9	0.650	0.222	0.240	0.400	0.04	1.33	9.11
2	9	0.650	0.222	0.240	0.400	0.08	2.06	9.84
2	9	0.650	0.222	0.240	0.400	0.17	4.15	11.93
2	9	0.650	0.222	0.240	0.400	0.26	7.2	14.98
2	9	0.650	0.222	0.240	0.400	0.50	18.11	25.89
2	9	0.650	0.222	0.240	0.400	0.77	28.79	36.57
2	9	0.650	0.222	0.240	0.400	0.85	31.55	39.33
2	9	0.650	0.222	0.240	0.400	0.89	32.78	40.56
2	9	0.650	0.222	0.240	0.400	1.05	37.1	44.88
2	9	0.650	0.222	0.240	0.400	1.25	37.54	45.32
2	10	1.050	0.778	0.480	0.200	0.00	1.1	3.32
2	10	1.050	0.778	0.480	0.200	0.04	6.38	8.60
2	10	1.050	0.778	0.480	0.200	0.08	11.44	13.66
2	10	1.050	0.778	0.480	0.200	0.17	21.18	23.40
2	10	1.050	0.778	0.480	0.200	0.33	36.34	38.56
2	10	1.050	0.778	0.480	0.200	0.50	46.06	48.28
2	10	1.050	0.778	0.480	0.200	0.63	50.65	52.87
2	10	1.050	0.778	0.480	0.200	0.91	56.84	59.06
2	10	1.050	0.778	0.480	0.200	0.96	56.81	59.03
2	10	1.050	0.778	0.480	0.200	1.01	56.76	58.98
2	10	1.050	0.778	0.480	0.200	1.25	56.06	58.28

		Coded Experimental Factors					Reaction Results	
Round	Reaction No.	Temperature	CuBr	DMF	NaOMe	Time	**2** LCAP	Obj. Fun.
3	1	1.100	1.000	0.960	0.520	0.00	2.81	2.81
3	1	1.100	1.000	0.960	0.520	0.04	18.15	18.15
3	1	1.100	1.000	0.960	0.520	0.08	30.51	30.51
3	1	1.100	1.000	0.960	0.520	0.17	49.9	49.90
3	1	1.100	1.000	0.960	0.520	0.33	73.06	73.06
3	1	1.100	1.000	0.960	0.520	0.43	79.03	79.03
3	1	1.100	1.000	0.960	0.520	0.46	80.21	80.21
3	1	1.100	1.000	0.960	0.520	0.50	81.51	81.51
3	1	1.100	1.000	0.960	0.520	0.74	83.9	83.90
3	1	1.100	1.000	0.960	0.520	0.84	85.62	85.62
3	1	1.100	1.000	0.960	0.520	1.00	84.94	84.94
3	1	1.100	1.000	0.960	0.520	1.25	83.33	83.33
3	2	0.800	0.778	0.960	1.000	0.00	2.44	4.66
3	2	0.800	0.778	0.960	1.000	0.04	25.05	27.27
3	2	0.800	0.778	0.960	1.000	0.08	42.26	44.48
3	2	0.800	0.778	0.960	1.000	0.17	64.7	66.92
3	2	0.800	0.778	0.960	1.000	0.33	82.62	84.84
3	2	0.800	0.778	0.960	1.000	0.45	89.44	91.66
3	2	0.800	0.778	0.960	1.000	0.48	89.21	91.43
3	2	0.800	0.778	0.960	1.000	0.62	89.52	91.74
3	2	0.800	0.778	0.960	1.000	0.78	91.34	93.56
3	2	0.800	0.778	0.960	1.000	0.90	91.1	93.32
3	2	0.800	0.778	0.960	1.000	1.08	92.64	94.86
3	3	0.950	1.000	0.960	0.760	0.00	3.1	3.10
3	3	0.950	1.000	0.960	0.760	0.04	19.6	19.60
3	3	0.950	1.000	0.960	0.760	0.08	32.78	32.78
3	3	0.950	1.000	0.960	0.760	0.17	55.04	55.04
3	3	0.950	1.000	0.960	0.760	0.33	79.14	79.14
3	3	0.950	1.000	0.960	0.760	0.45	85.52	85.52
3	3	0.950	1.000	0.960	0.760	0.48	85.92	85.92
3	3	0.950	1.000	0.960	0.760	0.62	90.19	90.19
3	3	0.950	1.000	0.960	0.760	0.78	90.62	90.62
3	3	0.950	1.000	0.960	0.760	0.90	91.02	91.02
3	3	0.950	1.000	0.960	0.760	1.08	89.74	89.74
3	4	0.900	0.778	0.960	1.000	0.00	3.46	5.68
3	4	0.900	0.778	0.960	1.000	0.04	25.67	27.89
3	4	0.900	0.778	0.960	1.000	0.08	44.56	46.78
3	4	0.900	0.778	0.960	1.000	0.17	67.58	69.80
3	4	0.900	0.778	0.960	1.000	0.33	87.13	89.35
3	4	0.900	0.778	0.960	1.000	0.45	90.88	93.10
3	4	0.900	0.778	0.960	1.000	0.48	92.22	94.44
3	4	0.900	0.778	0.960	1.000	0.62	93.42	95.64
3	4	0.900	0.778	0.960	1.000	0.78	95.33	97.55
3	4	0.900	0.778	0.960	1.000	0.90	93.42	95.64
3	4	0.900	0.778	0.960	1.000	1.08	93.77	95.99

		Coded Experimental Factors					Reaction Results	
Round	Reaction No.	Temperature	CuBr	DMF	NaOMe	Time	**2** LCAP	Obj. Fun.
3	5	1.250	0.778	0.960	0.760	0.00	3.36	5.58
3	5	1.250	0.778	0.960	0.760	0.04	22.12	24.34
3	5	1.250	0.778	0.960	0.760	0.08	38.59	40.81
3	5	1.250	0.778	0.960	0.760	0.17	61.46	63.68
3	5	1.250	0.778	0.960	0.760	0.33	81.41	83.63
3	5	1.250	0.778	0.960	0.760	0.43	86.7	88.92
3	5	1.250	0.778	0.960	0.760	0.46	89.54	91.76
3	5	1.250	0.778	0.960	0.760	0.50	91.66	93.88
3	5	1.250	0.778	0.960	0.760	0.74	94.47	96.69
3	5	1.250	0.778	0.960	0.760	0.84	93.78	96.00
3	5	1.250	0.778	0.960	0.760	1.00	94.06	96.28
3	5	1.250	0.778	0.960	0.760	1.25	93.23	95.45
3	6	1.250	1.000	0.720	0.600	0.00	2.36	2.36
3	6	1.250	1.000	0.720	0.600	0.04	19.9	19.90
3	6	1.250	1.000	0.720	0.600	0.08	33.04	33.04
3	6	1.250	1.000	0.720	0.600	0.17	54.19	54.19
3	6	1.250	1.000	0.720	0.600	0.33	78.48	78.48
3	6	1.250	1.000	0.720	0.600	0.43	83.51	83.51
3	6	1.250	1.000	0.720	0.600	0.46	87.13	87.13
3	6	1.250	1.000	0.720	0.600	0.50	88.56	88.56
3	6	1.250	1.000	0.720	0.600	0.74	92.3	92.30
3	6	1.250	1.000	0.720	0.600	0.84	90.48	90.48
3	6	1.250	1.000	0.720	0.600	1.00	91.77	91.77
3	6	1.250	1.000	0.720	0.600	1.25	92.96	92.96
3	7	1.250	1.000	0.960	1.000	0.00	9.02	9.02
3	7	1.250	1.000	0.960	1.000	0.04	46.87	46.87
3	7	1.250	1.000	0.960	1.000	0.08	68.12	68.12
3	7	1.250	1.000	0.960	1.000	0.17	85.85	85.85
3	7	1.250	1.000	0.960	1.000	0.33	91.04	91.04
3	7	1.250	1.000	0.960	1.000	0.45	91.75	91.75
3	7	1.250	1.000	0.960	1.000	0.48	92.02	92.02
3	7	1.250	1.000	0.960	1.000	0.62	93.82	93.82
3	7	1.250	1.000	0.960	1.000	0.78	93.14	93.14
3	7	1.250	1.000	0.960	1.000	0.90	93.44	93.44
3	7	1.250	1.000	0.960	1.000	1.08	95.05	95.05
3	8	0.250	0.778	0.400	0.440	0.00	1.09	3.31
3	8	0.250	0.778	0.400	0.440	0.04	3.4	5.62
3	8	0.250	0.778	0.400	0.440	0.08	6.43	8.65
3	8	0.250	0.778	0.400	0.440	0.17	10.68	12.90
3	8	0.250	0.778	0.400	0.440	0.33	15.65	17.87
3	8	0.250	0.778	0.400	0.440	0.43	17.36	19.58
3	8	0.250	0.778	0.400	0.440	0.46	17.58	19.80
3	8	0.250	0.778	0.400	0.440	0.50	17.92	20.14
3	8	0.250	0.778	0.400	0.440	0.74	20.1	22.32
3	8	0.250	0.778	0.400	0.440	0.84	21.48	23.70
3	8	0.250	0.778	0.400	0.440	1.00	21.89	24.11
3	8	0.250	0.778	0.400	0.440	1.25	23.34	25.56

		Coded Experimental Factors					Reaction Results	
Round	Reaction No.	Temperature	CuBr	DMF	NaOMe	Time	**2** LCAP	Obj. Fun.
3	9	1.100	0.778	0.800	0.280	0.00	1.43	3.65
3	9	1.100	0.778	0.800	0.280	0.04	8.97	11.19
3	9	1.100	0.778	0.800	0.280	0.08	16.2	18.42
3	9	1.100	0.778	0.800	0.280	0.17	28.58	30.80
3	9	1.100	0.778	0.800	0.280	0.33	49.64	51.86
3	9	1.100	0.778	0.800	0.280	0.43	59.09	61.31
3	9	1.100	0.778	0.800	0.280	0.46	61.04	63.26
3	9	1.100	0.778	0.800	0.280	0.50	63.68	65.90
3	9	1.100	0.778	0.800	0.280	0.74	72.12	74.34
3	9	1.100	0.778	0.800	0.280	0.84	75.47	77.69
3	9	1.100	0.778	0.800	0.280	1.00	78.06	80.28
3	9	1.100	0.778	0.800	0.280	1.25	78.45	80.67
3	10	0.750	0.667	0.800	0.280	0.00	1.56	4.89
3	10	0.750	0.667	0.800	0.280	0.04	5.26	8.59
3	10	0.750	0.667	0.800	0.280	0.08	8.79	12.12
3	10	0.750	0.667	0.800	0.280	0.17	15.17	18.50
3	10	0.750	0.667	0.800	0.280	0.33	26.33	29.66
3	10	0.750	0.667	0.800	0.280	0.45	33.06	36.39
3	10	0.750	0.667	0.800	0.280	0.48	35.56	38.89
3	10	0.750	0.667	0.800	0.280	0.62	40.96	44.29
3	10	0.750	0.667	0.800	0.280	0.78	47.61	50.94
3	10	0.750	0.667	0.800	0.280	0.90	52.34	55.67
3	10	0.750	0.667	0.800	0.280	1.08	56.96	60.29
4	1	1.250	0.220	0.960	1.000	0.00	1.29	9.09
4	1	1.250	0.220	0.960	1.000	0.04	15.19	22.99
4	1	1.250	0.220	0.960	1.000	0.08	30.8	38.60
4	1	1.250	0.220	0.960	1.000	0.17	53.07	60.87
4	1	1.250	0.220	0.960	1.000	0.39	79.21	87.01
4	1	1.250	0.220	0.960	1.000	0.44	82.26	90.06
4	1	1.250	0.220	0.960	1.000	0.50	85.13	92.93
4	1	1.250	0.220	0.960	1.000	0.67	89.98	97.78
4	1	1.250	0.220	0.960	1.000	0.80	92.71	100.51
4	1	1.250	0.220	0.960	1.000	1.00	94.05	101.85
4	1	1.250	0.220	0.960	1.000	1.24	95.54	103.34
4	2	0.650	0.770	0.960	0.440	0.00	0.94	3.24
4	2	0.650	0.770	0.960	0.440	0.04	5.15	7.45
4	2	0.650	0.770	0.960	0.440	0.08	10.17	12.47
4	2	0.650	0.770	0.960	0.440	0.17	19.53	21.83
4	2	0.650	0.770	0.960	0.440	0.33	38.26	40.56
4	2	0.650	0.770	0.960	0.440	0.42	47.64	49.94
4	2	0.650	0.770	0.960	0.440	0.50	54.52	56.82
4	2	0.650	0.770	0.960	0.440	0.76	70.6	72.90
4	2	0.650	0.770	0.960	0.440	0.93	75.52	77.82
4	2	0.650	0.770	0.960	0.440	1.00	77.43	79.73
4	2	0.650	0.770	0.960	0.440	1.25	83.18	85.48

		Coded Experimental Factors					Reaction Results	
Round	Reaction No.	Temperature	CuBr	DMF	NaOMe	Time	**2** LCAP	Obj. Fun.
4	3	0.950	0.770	0.960	0.760	0.00	1.46	3.76
4	3	0.950	0.770	0.960	0.760	0.04	13.7	16.00
4	3	0.950	0.770	0.960	0.760	0.08	25.53	27.83
4	3	0.950	0.770	0.960	0.760	0.17	48.81	51.11
4	3	0.950	0.770	0.960	0.760	0.39	79.41	81.71
4	3	0.950	0.770	0.960	0.760	0.44	83.03	85.33
4	3	0.950	0.770	0.960	0.760	0.50	85.94	88.24
4	3	0.950	0.770	0.960	0.760	0.67	90.57	92.87
4	3	0.950	0.770	0.960	0.760	0.80	92.8	95.10
4	3	0.950	0.770	0.960	0.760	1.00	93.33	95.63
4	3	0.950	0.770	0.960	0.760	1.24	92.55	94.85
4	4	0.800	0.770	0.960	1.000	0.00	2.33	4.63
4	4	0.800	0.770	0.960	1.000	0.04	22.99	25.29
4	4	0.800	0.770	0.960	1.000	0.08	40.62	42.92
4	4	0.800	0.770	0.960	1.000	0.17	65.34	67.64
4	4	0.800	0.770	0.960	1.000	0.33	84.14	86.44
4	4	0.800	0.770	0.960	1.000	0.42	88.7	91.00
4	4	0.800	0.770	0.960	1.000	0.50	91.63	93.93
4	4	0.800	0.770	0.960	1.000	0.76	94.64	96.94
4	4	0.800	0.770	0.960	1.000	0.93	94.99	97.29
4	4	0.800	0.770	0.960	1.000	1.00	94.85	97.15
4	4	0.800	0.770	0.960	1.000	1.25	94.53	96.83
4	5	0.600	0.770	0.960	1.000	0.00	1.57	3.87
4	5	0.600	0.770	0.960	1.000	0.04	17.33	19.63
4	5	0.600	0.770	0.960	1.000	0.08	31.04	33.34
4	5	0.600	0.770	0.960	1.000	0.17	52.3	54.60
4	5	0.600	0.770	0.960	1.000	0.33	67.93	70.23
4	5	0.600	0.770	0.960	1.000	0.42	69.62	71.92
4	5	0.600	0.770	0.960	1.000	0.50	73.66	75.96
4	5	0.600	0.770	0.960	1.000	0.76	82.98	85.28
4	5	0.600	0.770	0.960	1.000	0.93	85	87.30
4	5	0.600	0.770	0.960	1.000	1.00	86.27	88.57
4	5	0.600	0.770	0.960	1.000	1.25	86.85	89.15
4	6	1.150	0.000	0.960	1.000	0.00	0.74	10.74
4	6	1.150	0.000	0.960	1.000	0.04	3.75	13.75
4	6	1.150	0.000	0.960	1.000	0.08	10.56	20.56
4	6	1.150	0.000	0.960	1.000	0.17	23.05	33.05
4	6	1.150	0.000	0.960	1.000	0.33	41.09	51.09
4	6	1.150	0.000	0.960	1.000	0.42	48.32	58.32
4	6	1.150	0.000	0.960	1.000	0.50	54.75	64.75
4	6	1.150	0.000	0.960	1.000	0.76	67.29	77.29
4	6	1.150	0.000	0.960	1.000	0.93	73.87	83.87
4	6	1.150	0.000	0.960	1.000	1.00	75.81	85.81
4	6	1.150	0.000	0.960	1.000	1.25	81.77	91.77

		Coded Experimental Factors					Reaction Results	
Round	Reaction No.	Temperature	CuBr	DMF	NaOMe	Time	**2** LCAP	Obj. Fun.
4	7	1.250	0.990	0.960	0.760	0.00	6.29	6.39
4	7	1.250	0.990	0.960	0.760	0.04	34.52	34.62
4	7	1.250	0.990	0.960	0.760	0.08	54.29	54.39
4	7	1.250	0.990	0.960	0.760	0.17	76.51	76.61
4	7	1.250	0.990	0.960	0.760	0.33	89.9	90.00
4	7	1.250	0.990	0.960	0.760	0.42	92.06	92.16
4	7	1.250	0.990	0.960	0.760	0.50	93.24	93.34
4	7	1.250	0.990	0.960	0.760	0.76	93.02	93.12
4	7	1.250	0.990	0.960	0.760	0.93	94.34	94.44
4	7	1.250	0.990	0.960	0.760	1.00	93.84	93.94
4	7	1.250	0.990	0.960	0.760	1.25	93.74	93.84
4	8	0.700	0.440	0.320	0.800	0.00	0	5.60
4	8	0.700	0.440	0.320	0.800	0.04	3.85	9.45
4	8	0.700	0.440	0.320	0.800	0.08	7.92	13.52
4	8	0.700	0.440	0.320	0.800	0.17	17.96	23.56
4	8	0.700	0.440	0.320	0.800	0.39	45.94	51.54
4	8	0.700	0.440	0.320	0.800	0.44	50.52	56.12
4	8	0.700	0.440	0.320	0.800	0.50	55.51	61.11
4	8	0.700	0.440	0.320	0.800	0.67	66.24	71.84
4	8	0.700	0.440	0.320	0.800	0.80	72.15	77.75
4	8	0.700	0.440	0.320	0.800	1.00	79.07	84.67
4	8	0.700	0.440	0.320	0.800	1.24	83.87	89.47
4	9	0.750	0.110	0.400	0.200	0.00	0.35	9.25
4	9	0.750	0.110	0.400	0.200	0.04	0.27	9.17
4	9	0.750	0.110	0.400	0.200	0.08	0.39	9.29
4	9	0.750	0.110	0.400	0.200	0.17	0.79	9.69
4	9	0.750	0.110	0.400	0.200	0.39	2.83	11.73
4	9	0.750	0.110	0.400	0.200	0.44	3.52	12.42
4	9	0.750	0.110	0.400	0.200	0.50	4.17	13.07
4	9	0.750	0.110	0.400	0.200	0.67	7.58	16.48
4	9	0.750	0.110	0.400	0.200	0.80	11.12	20.02
4	9	0.750	0.110	0.400	0.200	1.00	15.34	24.24
4	9	0.750	0.110	0.400	0.200	1.24	20	28.90
4	10	0.950	0.220	0.800	0.440	0.00	0	7.80
4	10	0.950	0.220	0.800	0.440	0.04	1.19	8.99
4	10	0.950	0.220	0.800	0.440	0.08	3.3	11.10
4	10	0.950	0.220	0.800	0.440	0.17	8.78	16.58
4	10	0.950	0.220	0.800	0.440	0.39	26.26	34.06
4	10	0.950	0.220	0.800	0.440	0.44	28.4	36.20
4	10	0.950	0.220	0.800	0.440	0.50	31.83	39.63
4	10	0.950	0.220	0.800	0.440	0.67	39.37	47.17
4	10	0.950	0.220	0.800	0.440	0.80	44.83	52.63
4	10	0.950	0.220	0.800	0.440	1.00	51.21	59.01
4	10	0.950	0.220	0.800	0.440	1.24	56.7	64.50

Reaction and Optimization Results for Bromination

The reaction profiles collected during the bromination optimization case study are presented Figure S2.

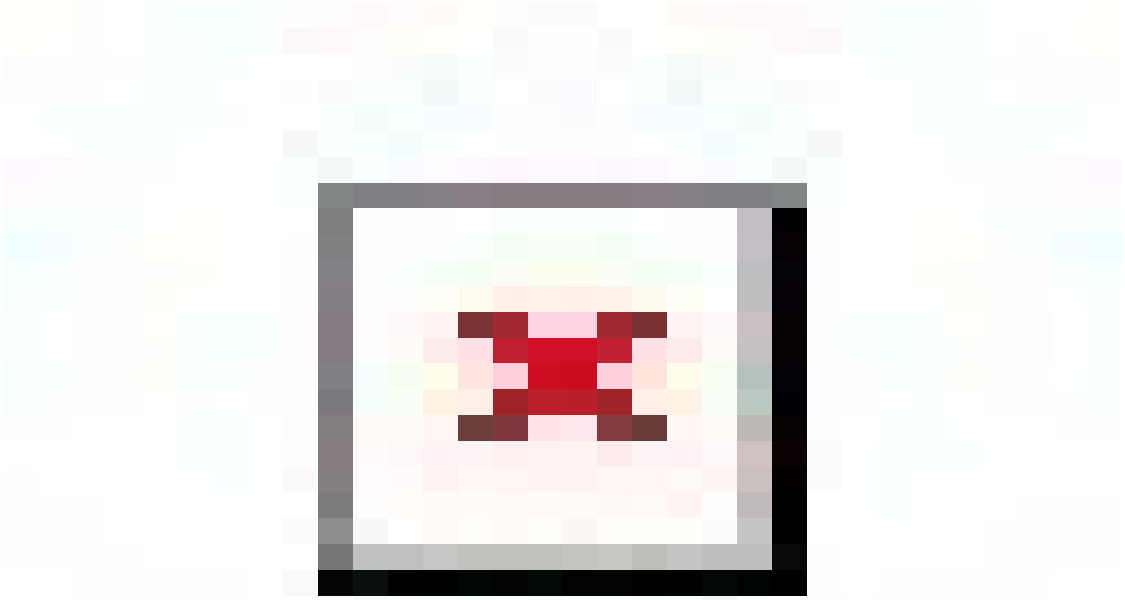


Figure S2: Optimization results for bromination investigation, highlighting assay yield and experimental conditions denoted for a) the first round, b) the second round, c) the third round, and d) the fourth round.

Results are also enumerated in Table S8.

Table S8: Optimization data collected for bromination case study with blue highlighted rows indicating experimental conditions requested by the SNOBFIT algorithm and grey rows corresponding to additional points inputted into the SNOBFIT algorithm by the scientist. Rows highlighted in orange were discarded from analysis and attributed to unrepresentative reaction sampling.

		Coded Experimental Factors				Reaction Results	
Round	Reaction No.	Temperature	DMF	Vilsmeier 4	Time	2 LCAP	Obj. Fun.
1	1	0.43	0.23	0.17	0.00	85.5%	85.5%
1	1	0.43	0.23	0.17	0.11	91.6%	91.6%
1	1	0.43	0.23	0.17	0.22	92.4%	92.4%
1	1	0.43	0.23	0.17	0.33	89.1%	89.1%
1	1	0.43	0.23	0.17	0.44	88.5%	88.5%
1	1	0.43	0.23	0.17	0.56	87.1%	87.1%
1	1	0.43	0.23	0.17	0.67	87.1%	87.1%
1	1	0.43	0.23	0.17	0.77	85.8%	85.8%
1	1	0.43	0.23	0.17	0.89	85.1%	85.1%
1	1	0.43	0.23	0.17	1.00	85.0%	85.0%
1	2	0.81	0.99	0.95	0.00	82.3%	82.3%
1	2	0.81	0.99	0.95	0.11	94.6%	94.6%
1	2	0.81	0.99	0.95	0.19	96.0%	96.0%
1	2	0.81	0.99	0.95	0.33	93.5%	93.5%
1	2	0.81	0.99	0.95	0.44	95.9%	95.9%
1	2	0.81	0.99	0.95	0.56	94.7%	94.7%
1	2	0.81	0.99	0.95	0.67	96.0%	96.0%
1	2	0.81	0.99	0.95	0.78	95.5%	95.5%
1	2	0.81	0.99	0.95	0.89	96.6%	96.6%
1	2	0.81	0.99	0.95	1.00	94.5%	94.5%
1	3	0.38	0.04	0.90	0.00	4.2%	4.2%
1	3	0.38	0.04	0.90	0.11	22.4%	22.4%
1	3	0.38	0.04	0.90	0.22	41.3%	41.3%
1	3	0.38	0.04	0.90	0.33	54.6%	54.6%
1	3	0.38	0.04	0.90	0.44	63.7%	63.7%
1	3	0.38	0.04	0.90	0.56	70.9%	70.9%
1	3	0.38	0.04	0.90	0.67	76.6%	76.6%
1	3	0.38	0.04	0.90	0.78	79.6%	79.6%
1	3	0.38	0.04	0.90	0.89	81.6%	81.6%
1	3	0.38	0.04	0.90	1.00	82.9%	82.9%
1	4	0.17	0.95	0.02	0.00	2.3%	2.3%
1	4	0.17	0.95	0.02	0.07	19.7%	19.7%
1	4	0.17	0.95	0.02	0.22	70.2%	70.2%
1	4	0.17	0.95	0.02	0.33	85.2%	85.2%
1	4	0.17	0.95	0.02	0.44	89.7%	89.7%
1	4	0.17	0.95	0.02	0.56	89.9%	89.9%
1	4	0.17	0.95	0.02	0.67	91.9%	91.9%
1	4	0.17	0.95	0.02	0.78	91.7%	91.7%
1	4	0.17	0.95	0.02	0.89	93.2%	93.2%
1	4	0.17	0.95	0.02	1.00	92.3%	92.3%

		Coded Experimental Factors				Reaction Results	
Round	Reaction No.	Temperature	DMF	Vilsmeier 4	Time	2 LCAP	Obj. Fun.
1	5	0.10	0.70	0.95	0.00	0.0%	0.0%
1	5	0.10	0.70	0.95	0.11	0.0%	0.0%
1	5	0.10	0.70	0.95	0.22	0.0%	0.0%
1	5	0.10	0.70	0.95	0.33	1.5%	1.5%
1	5	0.10	0.70	0.95	0.44	3.0%	3.0%
1	5	0.10	0.70	0.95	0.56	4.7%	4.7%
1	5	0.10	0.70	0.95	0.67	7.0%	7.0%
1	5	0.10	0.70	0.95	0.78	10.3%	10.3%
1	5	0.10	0.70	0.95	0.89	12.8%	12.8%
1	5	0.10	0.70	0.95	0.98	15.1%	15.1%
1	6	0.83	0.04	0.99	0.00	90.2%	90.2%
1	6	0.83	0.04	0.99	0.11	91.5%	91.5%
1	6	0.83	0.04	0.99	0.22	19.0%	0.0%
1	6	0.83	0.04	0.99	0.33	90.0%	90.0%
1	6	0.83	0.04	0.99	0.44	89.6%	89.6%
1	6	0.83	0.04	0.99	0.56	36.1%	0.0%
1	6	0.83	0.04	0.99	0.67	88.0%	88.0%
1	6	0.83	0.04	0.99	0.78	87.6%	87.6%
1	6	0.83	0.04	0.99	0.84	88.2%	88.2%
1	6	0.83	0.04	0.99	1.00	87.1%	87.1%
1	7	0.97	0.94	0.29	0.00	92.6%	72.6%
1	7	0.97	0.94	0.29	0.11	86.2%	66.2%
1	7	0.97	0.94	0.29	0.22	80.6%	60.6%
1	7	0.97	0.94	0.29	0.33	73.4%	53.4%
1	7	0.97	0.94	0.29	0.44	68.7%	48.7%
1	7	0.97	0.94	0.29	0.56	63.4%	43.4%
1	7	0.97	0.94	0.29	0.67	58.8%	38.8%
1	7	0.97	0.94	0.29	0.78	55.4%	35.4%
1	7	0.97	0.94	0.29	0.87	51.7%	31.7%
1	7	0.97	0.94	0.29	1.00	47.9%	27.9%
1	8	0.89	0.17	0.14	0.04	72.3%	52.3%
1	8	0.89	0.17	0.14	0.11	63.4%	43.4%
1	8	0.89	0.17	0.14	0.22	53.3%	33.3%
1	8	0.89	0.17	0.14	0.33	44.0%	24.0%
1	8	0.89	0.17	0.14	0.44	36.0%	16.0%
1	8	0.89	0.17	0.14	0.56	28.7%	8.7%
1	8	0.89	0.17	0.14	0.67	23.7%	3.7%
1	8	0.89	0.17	0.14	0.78	19.1%	-0.9%
1	8	0.89	0.17	0.14	0.89	15.9%	-4.1%
1	8	0.89	0.17	0.14	1.00	13.0%	-7.0%

		Coded Experimental Factors				Reaction Results	
Round	Reaction No.	Temperature	DMF	Vilsmeier 4	Time	2 LCAP	Obj. Fun.
1	9	0.07	0.07	0.03	0.02	0.8%	0.8%
1	9	0.07	0.07	0.03	0.11	11.2%	11.2%
1	9	0.07	0.07	0.03	0.22	35.8%	35.8%
1	9	0.07	0.07	0.03	0.33	61.3%	61.3%
1	9	0.07	0.07	0.03	0.44	76.0%	76.0%
1	9	0.07	0.07	0.03	0.56	81.9%	81.9%
1	9	0.07	0.07	0.03	0.67	84.4%	84.4%
1	9	0.07	0.07	0.03	0.78	86.5%	86.5%
1	9	0.07	0.07	0.03	0.89	87.7%	87.7%
1	9	0.07	0.07	0.03	1.00	87.1%	87.1%
1	10	0.01	0.84	0.90	0.00	0.0%	0.0%
1	10	0.01	0.84	0.90	0.11	0.0%	0.0%
1	10	0.01	0.84	0.90	0.17	0.0%	0.0%
1	10	0.01	0.84	0.90	0.33	0.0%	0.0%
1	10	0.01	0.84	0.90	0.44	0.0%	0.0%
1	10	0.01	0.84	0.90	0.56	2.1%	2.1%
1	10	0.01	0.84	0.90	0.67	2.6%	2.6%
1	10	0.01	0.84	0.90	0.78	3.0%	3.0%
1	10	0.01	0.84	0.90	0.89	4.7%	4.7%
1	10	0.01	0.84	0.90	1.00	5.5%	5.5%
2	1	0.72	0.04	0.00	0.00	81.9%	61.9%
2	1	0.72	0.04	0.00	0.11	74.5%	54.5%
2	1	0.72	0.04	0.00	0.22	67.9%	47.9%
2	1	0.72	0.04	0.00	0.33	64.9%	44.9%
2	1	0.72	0.04	0.00	0.44	59.0%	39.0%
2	1	0.72	0.04	0.00	0.56	57.0%	37.0%
2	1	0.72	0.04	0.00	0.67	53.3%	33.3%
2	1	0.72	0.04	0.00	0.78	48.7%	28.7%
2	1	0.72	0.04	0.00	0.89	46.6%	26.6%
2	1	0.72	0.04	0.00	1.00	41.8%	21.8%
2	2	0.52	0.00	0.00	0.00	82.3%	82.3%
2	2	0.52	0.00	0.00	0.11	80.9%	80.9%
2	2	0.52	0.00	0.00	0.22	79.6%	79.6%
2	2	0.52	0.00	0.00	0.33	79.7%	79.7%
2	2	0.52	0.00	0.00	0.44	77.1%	77.1%
2	2	0.52	0.00	0.00	0.56	76.3%	76.3%
2	2	0.52	0.00	0.00	0.67	74.3%	74.3%
2	2	0.52	0.00	0.00	0.78	73.4%	73.4%
2	2	0.52	0.00	0.00	0.89	71.6%	71.6%
2	2	0.52	0.00	0.00	1.00	69.9%	69.9%

		Coded Experimental Factors				Reaction Results	
Round	Reaction No.	Temperature	DMF	Vilsmeier 4	Time	2 LCAP	Obj. Fun.
2	3	1.00	0.96	1.00	0.00	93.6%	93.6%
2	3	1.00	0.96	1.00	0.11	95.7%	95.7%
2	3	1.00	0.96	1.00	0.22	97.7%	97.7%
2	3	1.00	0.96	1.00	0.33	97.0%	97.0%
2	3	1.00	0.96	1.00	0.44	97.7%	97.7%
2	3	1.00	0.96	1.00	0.56	92.2%	92.2%
2	3	1.00	0.96	1.00	0.67	94.9%	94.9%
2	3	1.00	0.96	1.00	0.78	96.4%	96.4%
2	3	1.00	0.96	1.00	0.89	93.5%	93.5%
2	3	1.00	0.96	1.00	1.00	93.0%	93.0%
2	4	0.68	0.00	0.44	0.00	85.2%	85.2%
2	4	0.68	0.00	0.44	0.11	87.6%	87.6%
2	4	0.68	0.00	0.44	0.22	86.9%	86.9%
2	4	0.68	0.00	0.44	0.33	86.6%	86.6%
2	4	0.68	0.00	0.44	0.44	86.6%	86.6%
2	4	0.68	0.00	0.44	0.56	87.6%	87.6%
2	4	0.68	0.00	0.44	0.67	87.7%	87.7%
2	4	0.68	0.00	0.44	0.78	87.8%	87.8%
2	4	0.68	0.00	0.44	0.89	88.3%	88.3%
2	4	0.68	0.00	0.44	1.00	86.7%	86.7%
2	5	0.44	1.00	0.00	0.00	84.2%	84.2%
2	5	0.44	1.00	0.00	0.11	88.2%	88.2%
2	5	0.44	1.00	0.00	0.22	91.2%	91.2%
2	5	0.44	1.00	0.00	0.33	90.5%	90.5%
2	5	0.44	1.00	0.00	0.44	90.7%	90.7%
2	5	0.44	1.00	0.00	0.56	87.9%	87.9%
2	5	0.44	1.00	0.00	0.67	87.2%	87.2%
2	5	0.44	1.00	0.00	0.78	88.1%	88.1%
2	5	0.44	1.00	0.00	0.89	87.2%	87.2%
2	5	0.44	1.00	0.00	1.00	86.6%	86.6%
2	6	1.00	0.12	1.00	0.00	91.2%	71.2%
2	6	1.00	0.12	1.00	0.11	87.5%	87.5%
2	6	1.00	0.12	1.00	0.22	90.1%	90.1%
2	6	1.00	0.12	1.00	0.33	87.8%	87.8%
2	6	1.00	0.12	1.00	0.44	88.5%	88.5%
2	6	1.00	0.12	1.00	0.56	87.7%	87.7%
2	6	1.00	0.12	1.00	0.67	82.1%	82.1%
2	6	1.00	0.12	1.00	0.78	81.7%	81.7%
2	6	1.00	0.12	1.00	0.89	81.1%	81.1%
2	6	1.00	0.12	1.00	1.00	79.8%	79.8%

		Coded Experimental Factors				Reaction Results	
Round	Reaction No.	Temperature	DMF	Vilsmeier 4	Time	2 LCAP	Obj. Fun.
2	7	0.48	0.52	0.00	0.00	88.6%	88.6%
2	7	0.48	0.52	0.00	0.11	86.9%	86.9%
2	7	0.48	0.52	0.00	0.22	86.8%	86.8%
2	7	0.48	0.52	0.00	0.33	84.3%	84.3%
2	7	0.48	0.52	0.00	0.44	84.1%	84.1%
2	7	0.48	0.52	0.00	0.50	86.1%	86.1%
2	7	0.48	0.52	0.00	0.67	80.5%	80.5%
2	7	0.48	0.52	0.00	0.78	81.9%	81.9%
2	7	0.48	0.52	0.00	0.89	81.0%	81.0%
2	7	0.48	0.52	0.00	1.00	78.8%	78.8%
2	8	0.72	0.40	0.40	0.00	89.7%	89.7%
2	8	0.72	0.40	0.40	0.11	87.9%	87.9%
2	8	0.72	0.40	0.40	0.22	91.4%	91.4%
2	8	0.72	0.40	0.40	0.33	89.5%	89.5%
2	8	0.72	0.40	0.40	0.44	96.9%	96.9%
2	8	0.72	0.40	0.40	0.56	90.5%	70.5%
2	8	0.72	0.40	0.40	0.60	88.7%	88.7%
2	8	0.72	0.40	0.40	0.78	88.9%	88.9%
2	8	0.72	0.40	0.40	0.89	88.6%	88.6%
2	8	0.72	0.40	0.40	1.00	88.4%	88.4%
2	9	0.78	0.76	0.44	0.00	91.1%	91.1%
2	9	0.78	0.76	0.44	0.11	91.0%	91.0%
2	9	0.78	0.76	0.44	0.22	92.3%	92.3%
2	9	0.78	0.76	0.44	0.33	95.5%	95.5%
2	9	0.78	0.76	0.44	0.40	90.6%	90.6%
2	9	0.78	0.76	0.44	0.56	90.1%	90.1%
2	9	0.78	0.76	0.44	0.67	91.8%	91.8%
2	9	0.78	0.76	0.44	0.78	93.1%	93.1%
2	9	0.78	0.76	0.44	0.89	91.8%	91.8%
2	9	0.78	0.76	0.44	1.00	92.0%	92.0%
2	10	0.54	0.52	0.76	0.00	20.0%	20.0%
2	10	0.54	0.52	0.76	0.11	52.2%	52.2%
2	10	0.54	0.52	0.76	0.22	67.3%	67.3%
2	10	0.54	0.52	0.76	0.33	78.3%	78.3%
2	10	0.54	0.52	0.76	0.44	83.2%	83.2%
2	10	0.54	0.52	0.76	0.56	85.9%	85.9%
2	10	0.54	0.52	0.76	0.67	86.5%	86.5%
2	10	0.54	0.52	0.76	0.80	88.4%	88.4%
2	10	0.54	0.52	0.76	0.89	87.9%	87.9%
2	10	0.54	0.52	0.76	1.00	88.5%	88.5%

		Coded Experimental Factors				Reaction Results	
Round	Reaction No.	Temperature	DMF	Vilsmeier 4	Time	2 LCAP	Obj. Fun.
3	1	1.00	0.04	1.00	0.00	85.6%	85.6%
3	1	1.00	0.04	1.00	0.11	83.8%	83.8%
3	1	1.00	0.04	1.00	0.22	81.1%	81.1%
3	1	1.00	0.04	1.00	0.33	84.4%	84.4%
3	1	1.00	0.04	1.00	0.40	80.7%	60.7%
3	1	1.00	0.04	1.00	0.56	77.0%	77.0%
3	1	1.00	0.04	1.00	0.67	77.3%	77.3%
3	1	1.00	0.04	1.00	0.78	74.9%	74.9%
3	1	1.00	0.04	1.00	0.89	73.1%	73.1%
3	1	1.00	0.04	1.00	1.00	71.5%	71.5%
3	2	0.54	0.00	0.72	0.00	42.0%	42.0%
3	2	0.54	0.00	0.72	0.11	68.9%	68.9%
3	2	0.54	0.00	0.72	0.22	78.6%	78.6%
3	2	0.54	0.00	0.72	0.33	84.4%	84.4%
3	2	0.54	0.00	0.72	0.44	82.8%	82.8%
3	2	0.54	0.00	0.72	0.56	84.3%	84.3%
3	2	0.54	0.00	0.72	0.67	86.3%	86.3%
3	2	0.54	0.00	0.72	0.80	87.3%	87.3%
3	2	0.54	0.00	0.72	0.89	82.5%	82.5%
3	2	0.54	0.00	0.72	1.00	85.7%	85.7%
3	3	0.28	0.00	0.52	0.00	1.7%	1.7%
3	3	0.28	0.00	0.52	0.11	14.8%	14.8%
3	3	0.28	0.00	0.52	0.22	32.1%	32.1%
3	3	0.28	0.00	0.52	0.33	46.1%	46.1%
3	3	0.28	0.00	0.52	0.44	58.0%	58.0%
3	3	0.28	0.00	0.52	0.56	64.2%	64.2%
3	3	0.28	0.00	0.52	0.60	66.2%	66.2%
3	3	0.28	0.00	0.52	0.78	73.4%	73.4%
3	3	0.28	0.00	0.52	0.89	75.3%	75.3%
3	3	0.28	0.00	0.52	1.00	79.2%	79.2%
3	4	0.58	0.76	0.64	0.00	83.7%	83.7%
3	4	0.58	0.76	0.64	0.11	90.3%	90.3%
3	4	0.58	0.76	0.64	0.20	90.5%	90.5%
3	4	0.58	0.76	0.64	0.33	92.5%	92.5%
3	4	0.58	0.76	0.64	0.44	91.6%	91.6%
3	4	0.58	0.76	0.64	0.56	91.9%	91.9%
3	4	0.58	0.76	0.64	0.67	90.6%	90.6%
3	4	0.58	0.76	0.64	0.78	91.2%	91.2%
3	4	0.58	0.76	0.64	0.89	87.8%	87.8%
3	4	0.58	0.76	0.64	1.00	92.7%	92.7%

		Coded Experimental Factors				Reaction Results	
Round	Reaction No.	Temperature	DMF	Vilsmeier 4	Time	2 LCAP	Obj. Fun.
3	5	0.60	0.40	0.60	0.00	67.6%	67.6%
3	5	0.60	0.40	0.60	0.11	85.1%	85.1%
3	5	0.60	0.40	0.60	0.22	89.4%	89.4%
3	5	0.60	0.40	0.60	0.30	87.9%	87.9%
3	5	0.60	0.40	0.60	0.44	89.3%	89.3%
3	5	0.60	0.40	0.60	0.56	89.2%	89.2%
3	5	0.60	0.40	0.60	0.67	88.6%	88.6%
3	5	0.60	0.40	0.60	0.78	92.7%	92.7%
3	5	0.60	0.40	0.60	0.89	86.3%	86.3%
3	5	0.60	0.40	0.60	1.00	88.5%	88.5%
3	6	0.40	0.00	0.44	0.00	36.5%	36.5%
3	6	0.40	0.00	0.44	0.11	73.5%	73.5%
3	6	0.40	0.00	0.44	0.22	79.0%	79.0%
3	6	0.40	0.00	0.44	0.33	84.6%	84.6%
3	6	0.40	0.00	0.44	0.44	84.8%	84.8%
3	6	0.40	0.00	0.44	0.56	84.1%	84.1%
3	6	0.40	0.00	0.44	0.67	87.1%	87.1%
3	6	0.40	0.00	0.44	0.80	87.2%	87.2%
3	6	0.40	0.00	0.44	0.89	82.9%	82.9%
3	6	0.40	0.00	0.44	1.00	86.7%	86.7%
3	7	0.44	0.00	1.00	0.00	24.9%	24.9%
3	7	0.44	0.00	1.00	0.11	54.6%	54.6%
3	7	0.44	0.00	1.00	0.22	65.9%	65.9%
3	7	0.44	0.00	1.00	0.33	76.2%	76.2%
3	7	0.44	0.00	1.00	0.44	81.9%	81.9%
3	7	0.44	0.00	1.00	0.56	83.4%	83.4%
3	7	0.44	0.00	1.00	0.67	85.0%	85.0%
3	7	0.44	0.00	1.00	0.80	83.7%	83.7%
3	7	0.44	0.00	1.00	0.89	83.4%	83.4%
3	7	0.44	0.00	1.00	1.00	83.5%	83.5%
3	8	0.30	0.00	0.32	0.00	19.4%	19.4%
3	8	0.30	0.00	0.32	0.11	66.3%	66.3%
3	8	0.30	0.00	0.32	0.22	80.9%	80.9%
3	8	0.30	0.00	0.32	0.33	82.1%	82.1%
3	8	0.30	0.00	0.32	0.44	85.6%	85.6%
3	8	0.30	0.00	0.32	0.56	85.1%	85.1%
3	8	0.30	0.00	0.32	0.67	82.1%	82.1%
3	8	0.30	0.00	0.32	0.80	84.5%	84.5%
3	8	0.30	0.00	0.32	0.89	83.5%	83.5%
3	8	0.30	0.00	0.32	1.00	84.4%	84.4%

		Coded Experimental Factors				Reaction Results	
Round	Reaction No.	Temperature	DMF	Vilsmeier 4	Time	2 LCAP	Obj. Fun.
3	9	0.68	0.20	0.76	0.00	71.9%	71.9%
3	9	0.68	0.20	0.76	0.11	86.8%	86.8%
3	9	0.68	0.20	0.76	0.20	88.7%	88.7%
3	9	0.68	0.20	0.76	0.33	88.7%	88.7%
3	9	0.68	0.20	0.76	0.44	95.6%	95.6%
3	9	0.68	0.20	0.76	0.56	90.7%	70.7%
3	9	0.68	0.20	0.76	0.67	89.9%	89.9%
3	9	0.68	0.20	0.76	0.78	89.7%	89.7%
3	9	0.68	0.20	0.76	0.89	92.1%	92.1%
3	9	0.68	0.20	0.76	1.00	90.5%	90.5%
3	10	0.62	0.68	0.76	0.00	53.2%	53.2%
3	10	0.62	0.68	0.76	0.11	77.8%	77.8%
3	10	0.62	0.68	0.76	0.22	84.5%	84.5%
3	10	0.62	0.68	0.76	0.33	90.7%	90.7%
3	10	0.62	0.68	0.76	0.40	91.5%	91.5%
3	10	0.62	0.68	0.76	0.56	93.9%	93.9%
3	10	0.62	0.68	0.76	0.67	93.2%	93.2%
3	10	0.62	0.68	0.76	0.78	91.5%	91.5%
3	10	0.62	0.68	0.76	0.89	92.6%	92.6%
3	10	0.62	0.68	0.76	1.00	90.2%	90.2%
4	1	0.78	1.00	0.68	0.00	84.7%	84.7%
4	1	0.78	1.00	0.68	0.11	91.3%	91.3%
4	1	0.78	1.00	0.68	0.22	93.6%	93.6%
4	1	0.78	1.00	0.68	0.33	91.6%	91.6%
4	1	0.78	1.00	0.68	0.44	94.0%	94.0%
4	1	0.78	1.00	0.68	0.56	94.1%	94.1%
4	1	0.78	1.00	0.68	0.67	94.1%	94.1%
4	1	0.78	1.00	0.68	0.78	91.6%	91.6%
4	1	0.78	1.00	0.68	0.89	93.6%	93.6%
4	1	0.78	1.00	0.68	1.00	92.9%	92.9%
4	2	0.40	0.28	0.36	0.00	57.2%	57.2%
4	2	0.40	0.28	0.36	0.11	84.3%	84.3%
4	2	0.40	0.28	0.36	0.22	88.5%	88.5%
4	2	0.40	0.28	0.36	0.33	90.9%	90.9%
4	2	0.40	0.28	0.36	0.44	89.7%	89.7%
4	2	0.40	0.28	0.36	0.56	88.2%	88.2%
4	2	0.40	0.28	0.36	0.67	90.4%	90.4%
4	2	0.40	0.28	0.36	0.78	92.3%	92.3%
4	2	0.40	0.28	0.36	0.89	90.8%	90.8%
4	2	0.40	0.28	0.36	1.00	89.8%	89.8%

		Coded Experimental Factors				Reaction Results	
Round	Reaction No.	Temperature	DMF	Vilsmeier 4	Time	2 LCAP	Obj. Fun.
4	3	0.84	0.40	1.00	0.00	88.4%	88.4%
4	3	0.84	0.40	1.00	0.11	90.8%	90.8%
4	3	0.84	0.40	1.00	0.22	90.5%	90.5%
4	3	0.84	0.40	1.00	0.33	91.1%	91.1%
4	3	0.84	0.40	1.00	0.44	90.0%	90.0%
4	3	0.84	0.40	1.00	0.56	90.6%	90.6%
4	3	0.84	0.40	1.00	0.67	89.8%	89.8%
4	3	0.84	0.40	1.00	0.78	88.7%	88.7%
4	3	0.84	0.40	1.00	0.89	89.7%	89.7%
4	3	0.84	0.40	1.00	1.00	88.5%	88.5%
4	4	0.68	0.24	1.00	0.00	73.4%	73.4%
4	4	0.68	0.24	1.00	0.10	86.7%	86.7%
4	4	0.68	0.24	1.00	0.22	91.0%	91.0%
4	4	0.68	0.24	1.00	0.33	90.7%	90.7%
4	4	0.68	0.24	1.00	0.44	91.3%	91.3%
4	4	0.68	0.24	1.00	0.56	93.8%	93.8%
4	4	0.68	0.24	1.00	0.67	92.1%	92.1%
4	4	0.68	0.24	1.00	0.78	91.4%	91.4%
4	4	0.68	0.24	1.00	0.89	92.3%	92.3%
4	4	0.68	0.24	1.00	1.00	91.0%	91.0%
4	5	0.30	0.28	0.28	0.00	32.5%	32.5%
4	5	0.30	0.28	0.28	0.11	79.7%	79.7%
4	5	0.30	0.28	0.28	0.22	88.8%	88.8%
4	5	0.30	0.28	0.28	0.33	89.0%	89.0%
4	5	0.30	0.28	0.28	0.44	90.5%	90.5%
4	5	0.30	0.28	0.28	0.56	88.0%	88.0%
4	5	0.30	0.28	0.28	0.67	89.5%	89.5%
4	5	0.30	0.28	0.28	0.78	93.8%	93.8%
4	5	0.30	0.28	0.28	0.89	89.1%	89.1%
4	5	0.30	0.28	0.28	1.00	90.8%	90.8%
4	6	0.60	0.20	0.68	0.00	61.0%	61.0%
4	6	0.60	0.20	0.68	0.11	84.1%	84.1%
4	6	0.60	0.20	0.68	0.22	88.3%	88.3%
4	6	0.60	0.20	0.68	0.33	89.0%	89.0%
4	6	0.60	0.20	0.68	0.44	90.7%	90.7%
4	6	0.60	0.20	0.68	0.56	91.0%	91.0%
4	6	0.60	0.20	0.68	0.67	90.1%	90.1%
4	6	0.60	0.20	0.68	0.78	89.2%	89.2%
4	6	0.60	0.20	0.68	0.89	89.5%	89.5%
4	6	0.60	0.20	0.68	1.00	90.0%	90.0%

		Coded Experimental Factors				Reaction Results	
Round	Reaction No.	Temperature	DMF	Vilsmeier 4	Time	2 LCAP	Obj. Fun.
4	7	0.80	0.32	1.00	0.00	92.8%	92.8%
4	7	0.80	0.32	1.00	0.11	94.6%	94.6%
4	7	0.80	0.32	1.00	0.22	92.8%	92.8%
4	7	0.80	0.32	1.00	0.33	93.3%	93.3%
4	7	0.80	0.32	1.00	0.44	92.6%	92.6%
4	7	0.80	0.32	1.00	0.56	88.7%	88.7%
4	7	0.80	0.32	1.00	0.67	90.0%	90.0%
4	7	0.80	0.32	1.00	0.78	90.1%	90.1%
4	7	0.80	0.32	1.00	0.90	89.3%	89.3%
4	7	0.80	0.32	1.00	1.00	86.2%	66.2%
4	8	0.20	0.20	0.52	0.00	1.7%	1.7%
4	8	0.20	0.20	0.52	0.11	6.3%	6.3%
4	8	0.20	0.20	0.52	0.22	19.2%	19.2%
4	8	0.20	0.20	0.52	0.33	32.8%	32.8%
4	8	0.20	0.20	0.52	0.44	43.8%	43.8%
4	8	0.20	0.20	0.52	0.56	53.5%	53.5%
4	8	0.20	0.20	0.52	0.67	59.4%	59.4%
4	8	0.20	0.20	0.52	0.78	66.5%	66.5%
4	8	0.20	0.20	0.52	0.90	71.0%	71.0%
4	8	0.20	0.20	0.52	1.00	75.3%	75.3%
4	9	0.90	0.88	0.24	0.00	96.1%	76.1%
4	9	0.90	0.88	0.24	0.11	92.2%	72.2%
4	9	0.90	0.88	0.24	0.20	90.9%	70.9%
4	9	0.90	0.88	0.24	0.33	86.0%	86.0%
4	9	0.90	0.88	0.24	0.44	85.7%	65.7%
4	9	0.90	0.88	0.24	0.56	80.3%	80.3%
4	9	0.90	0.88	0.24	0.67	80.8%	80.8%
4	9	0.90	0.88	0.24	0.78	75.6%	75.6%
4	9	0.90	0.88	0.24	0.89	77.4%	77.4%
4	9	0.90	0.88	0.24	1.00	74.0%	54.0%
4	10	0.78	0.76	0.88	0.00	88.1%	88.1%
4	10	0.78	0.76	0.88	0.11	97.7%	97.7%
4	10	0.78	0.76	0.88	0.22	96.8%	96.8%
4	10	0.78	0.76	0.88	0.33	97.1%	97.1%
4	10	0.78	0.76	0.88	0.44	95.5%	95.5%
4	10	0.78	0.76	0.88	0.56	96.6%	96.6%
4	10	0.78	0.76	0.88	0.70	97.1%	97.1%
4	10	0.78	0.76	0.88	0.78	96.3%	96.3%
4	10	0.78	0.76	0.88	0.89	96.8%	96.8%
4	10	0.78	0.76	0.88	1.00	96.2%	96.2%

Details Regarding Data-Driven Modeling of Methoxylation

k-Nearest Neighbor Algorithm applied to Methoxylation Reaction Data

In order to determine which experimental data were in the local vicinity of the optimal reaction conditions in experiment 34, a k-nearest neighbor algorithm was utilized. The Matlab function knnsearch was employed using the Mahalanobis distance as a metric. The distances were sorted in ascending order and plotted in Figure S3 to visualize if a natural break in neighbor distance existed. Based on this visual, 15 experiments were selected to be in the local neighborhood of the optimal conditions and considered for additional data analysis.

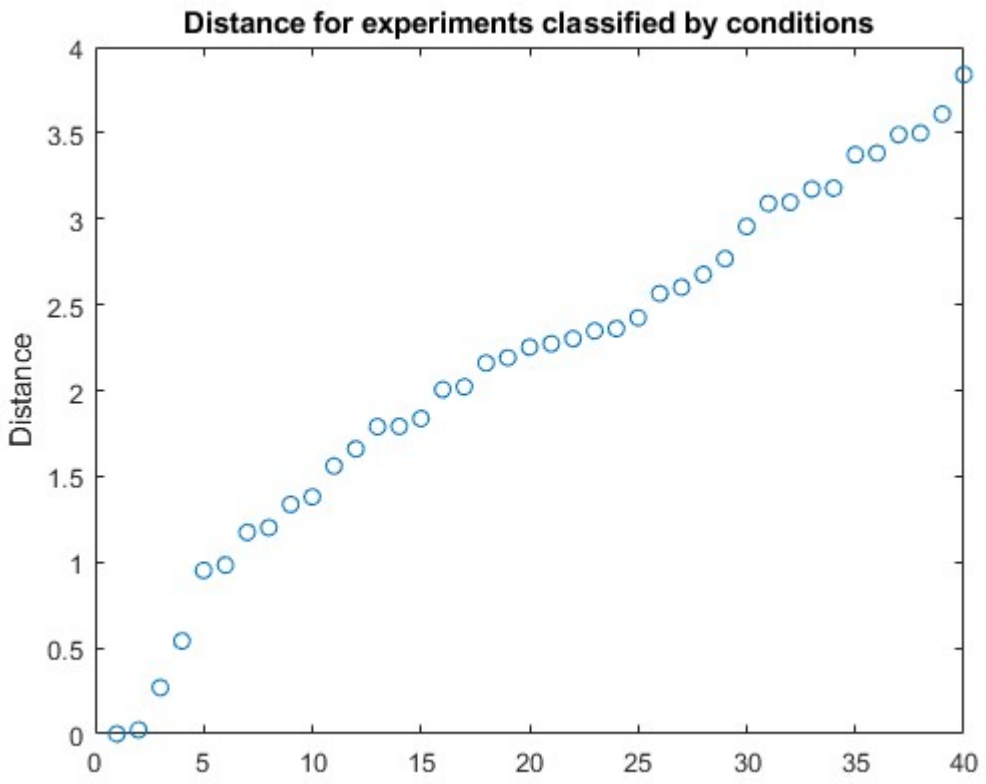


Figure S3: Mahalanobis distance of all experimental conditions from the optimal conditions in experiment 34.

The reaction profile for these 15 experiments are provided in Figure S4, and the corresponding experimental conditions are provided in Table S9 below.

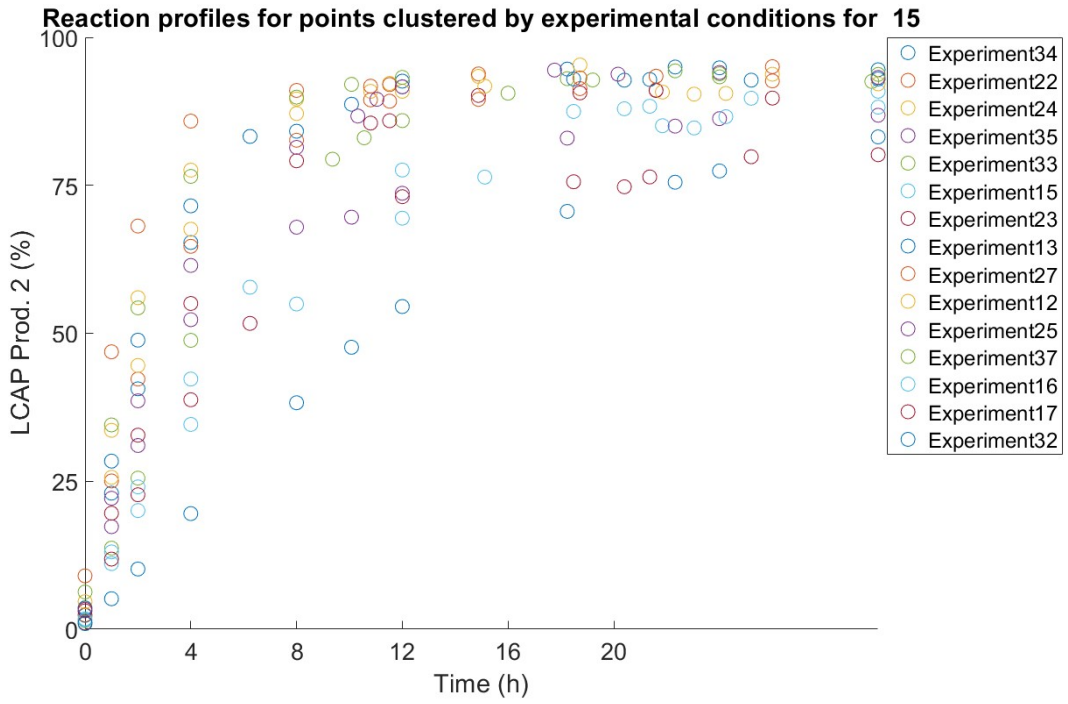


Figure S4: Plot of reaction profiles for experiments identified in the local neighborhood of optimal reaction conditions.

Relevant background on FPCA methodology applied to Methoxylation

The first step in the FPCA methodology is to pool the reaction time-series data for a given response across all experiments. Next, the mean function, μ(t), is estimated from this collective, longitudinal dataset through a local linear scatterplot smoother to give a smooth curve estimate of the mean function (Eq. S2). This smoothing plays an important role as it permits modeling with a range of features, such as datasets that are sparse or dense, datasets that have uniform or disparate sample time measurements, and datasets that contain noise or measurement errors. Similar to a Taylor series expansion, it is assumed that μ(t) can be approximated as a local linear approximation within neighborhood around a measurement time point, t_j, such that

$$\mu(t_j) \approx \hat{\mu}(t_j) = \beta_0 + \beta_1(t - t_j) \qquad \text{Eq. S2}$$

where $\hat{\mu}(t)$ is the linear approximation function of mean curve, and β_0 and β_1 are constants. To generate a smoothed estimator function over the range of measurement times in the dataset, β_0 and β_1 were computed through a local linear scatterplot smoother, a one-dimensional local weighted least square estimate, given by Eq. S3.

$$(\beta_0(t), \quad \beta_1(t)) = \arg\min \sum_{i=1}^{n} \sum_{j}^{N_i} \kappa_\mu\left(\frac{T_{ij} - t}{h_\mu}\right)\{Y_{ij} - \beta_0 - \beta_1(t - T_{ij})\}^2 \qquad \text{Eq. S3}$$

where i is an index for experiments, j is an index for the measurement in experiment i, $\kappa_\mu = \kappa_\mu(T_{ij}, t, h_\mu)$ is a kernel smoothing function, h_μ is the bandwidth, Y_{ij} is response for the measurement data point, and T_{ij} is corresponds to the

measurement time of the data point. The kernel function acts as weighting factor in the squared error calculation, providing estimates for β_0 and β_1 that lead to lower residual error for the data where t is near t_j. A bandwidth is used to scale the time by the Euclidean distance for the regression. A variety of kernel functions and methods to determine an appropriate bandwidth can be used in the smoothing procedure. In this work, a Gaussian kernel function (e.g., $\kappa_\mu \sim exp(-(T_{ij} - t)/h_\mu)$ and an adjusted generalized cross-validation bandwidth, one that calculates the geometric mean of the minimum bandwidth choice for a local window and the optimal bandwidth choice using the generalized cross-validation method, were implemented.

As Eq. S2 indicates, the solution to the local least square problem is time dependent. A unique solution for the best fit parameters, β_0 and β_1, will exist for a given measurement time, $t=t_j$. Therefore, the estimates themselves become functions of time, such that $\beta_0 = \beta_0(t)$ and $\beta_1 = \beta_1(t)$, and the mean function estimate is then defined as:

$$\hat{\mu}(t) = \beta_0(t) \qquad \text{Eq. S4}$$

A plot of the methoxylation reaction profiles used in the FPCA modeling along with the associated functional mean is provided in Figure S5.

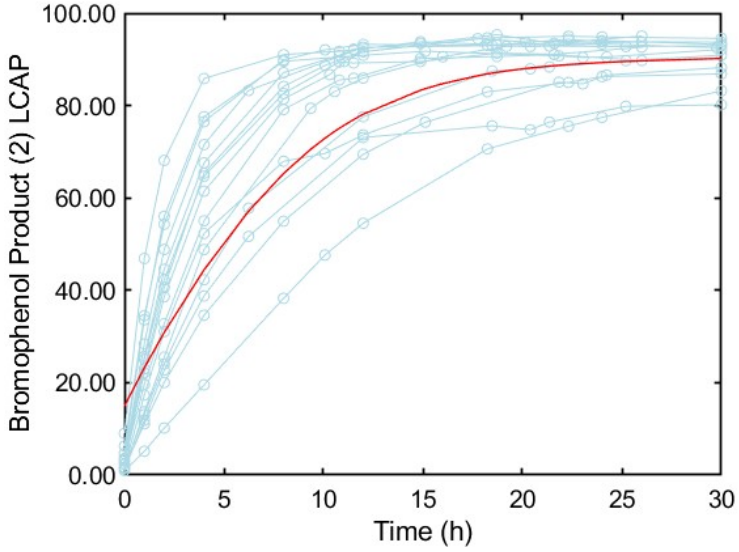


Figure S5: Plot of Methoxylation experimental reaction profiles (o) selected through nearest neighbor algorithm along with functional mean estimate (-).

The mean function estimate can then be used to compute the raw covariances.

$$G_i(T_{ij},T_{il}) = \left(Y_{ij} - \hat{\mu}(T_{ij})\right)\left(Y_{il} - \hat{\mu}(T_{il})\right);\ j \neq l \qquad \text{Eq. S5}$$

Here again, a smoothing operation is performed to convert the pointwise data of raw covariances to a smoothed surface for the covariance estimate. The estimate of the covariance surface, $\hat{G}(s,t)$, is approximated through linear expansion around a local neighborhood of time points defined by s_j and t_l (Eq. S6), with smoothed parameters determined by the two-dimensional scatterplot smoother provide in Eq. S7.

$$G(s_j,t_l) \approx \hat{G}(s_j,t_l) = \alpha_0 + \alpha_{11}(s - s_j) + \alpha_{12}(t - t_l);\ j \neq l \qquad \text{Eq. S6}$$

$$\begin{pmatrix}\alpha_0(s,t) & \alpha_{11}(s,t) & \alpha_{12}(s,t)\end{pmatrix} = \arg\min \sum_{i=1}^{n} \sum_{1 \le j \ne l \le N_i} \kappa_G\left(\frac{T_{ij}-s}{h_G}\right)\kappa_G\left(\frac{T_{il}-t}{h_G}\right)\left\{G_i(t_{ij},t_{il}) - \alpha_0 - \alpha_{11}(s-T_{ij}) - \alpha_{12}(t-T_{il})\right\}^2$$

Eq. S7

where α_0, α_{11}, and α_{12} are constants in the linear expansion of $\hat{G}(s,t)$, $\kappa_G = \kappa_G(T_{ij}, t, h_G)$ is a smoothing kernel function, and h_G is the bandwidth. In this work, a Gaussian kernel function (e.g., $\kappa_G \sim exp(-(T_{ij} - t)/h_G)$ and an adjusted generalized cross-validation bandwidth, one that calculates the geometric mean of the minimum bandwidth choice for a local window and the optimal bandwidth choice using the generalized cross-validation method, were applied. Similar to the calculations above, the solution to Eq. S7 is unique for a given pair of measurement time points, s_j and t_l, so the estimates themselves are functions of time, yielding the covariance estimate in Eq. S8.

$$\hat{G}(s,t) = \alpha_0(s,t)$$

Eq. S8

The functional principal components, or eigenfunctions, and the associated FPC scores can be calculated once estimates of the mean function and the covariance surface are available. The judicious selection of the number of principal components *K* can be determined through the pseudo-Akaike Information Criteria, the pseudo-Bayesian Information Criteria, or through the Fraction of Variance Explained (FVE) method. In this work, the FVE method was selected as it provided the most parsimonious FPCA models for the datasets that were considered. Here, eigenvalue decomposition of the estimated covariance matrix is performed to obtain the eigenvalues (λ) and corresponding eigenvectors. The resulting positive eigenvalues are sorted in decreasing order, and the number *K* of included functional principal components corresponds to the smallest *J* for which the fraction of variance is greater than the threshold, which was 0.90 in this work. See Eq. S9.

$$FVE_J = \frac{\sum_{k=1}^{J} \lambda_k}{\sum \lambda_k}$$

Eq. S9

As shown in the scree plot of Figure S6, only one principal component was required to model the set of reaction profiles selected by the nearest neighbor algorithm.

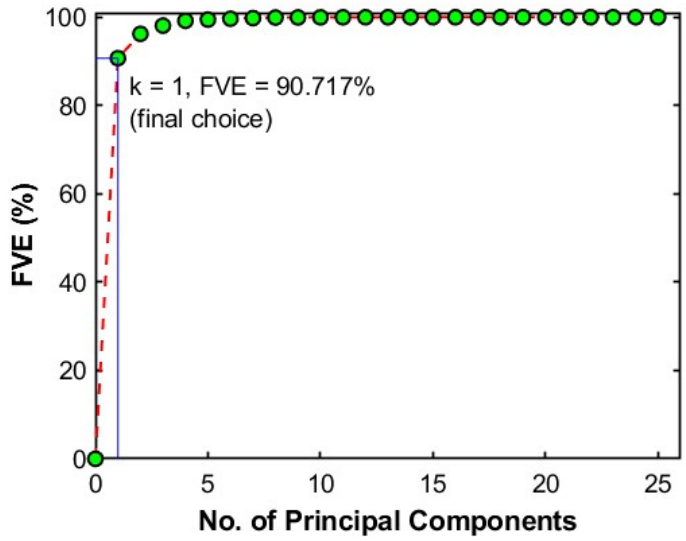


Figure S6: Scree plot for fraction of variance (FVE) explained to select number of functional principal components.

The corresponding normalized eigenvectors for the eigenvalues selected through FVE correspond to the functional principal components, ϕ_k. Lastly, estimates of the FPC scores for functional principal component *k* in experiment *i* can be calculated through Eq. S10.

$$\xi_{ik} \approx \hat{\xi}_{ik} = \lambda_k \hat{\phi}_{ik}^T \hat{\Sigma}_{Y_i}^{-1} \left(\bar{Y}_i - \hat{\mu}_i\right) \qquad \text{Eq. S10}$$

where bold terms indicate a vector or matrix with elements corresponding to sample times t_j, with $\hat{\phi}_{ik}$ = [$\varphi_k(T_{i,1})$, $\varphi k(T_{i,2})$, … , $\varphi k(T_{i,Ni})$]T, $\bar{Y}_i$=[$Y_{i,1}$, $Y_{i,2}$, … , $Y_{i,Ni}$]T, $\hat{\mu}_i$ = [$\hat{\mu}(T_{i,1})$, $\hat{\mu}(T_{i,2})$, … , $\hat{\mu}(T_{i,Ni})$]T, $\hat{\Sigma}_{Y_i}|_{jl} = \hat{G}(T_{ij}, T_{il}) + \hat{\sigma}^2 \delta_{jl}$ with $\hat{G}(T_{ij}, T_{il}) = \sum_{k=1}^{K} \lambda_k \phi_k(T_{ij}) \phi_k(T_{il})$ is a fitted estimate of covariance surface, with elements (j, l) corresponding to . FPC Scores for the associated experiments are provided in Table S9.

Table S9: Estimated FPC Scores (Eq. S9) for Methoxylation reaction data used in FPCA modelling along with associated experimental conditions.

Experiment	Coded Variables				FPC Score
	Temperature	CuBr	DMF	NaOMe	
	x_1	x_2	x_3	x_4	
34	0.80	0.77	0.96	1.00	62.83
22	0.80	0.78	0.96	1.00	58.00
24	0.90	0.78	0.96	1.00	70.93
35	0.60	0.77	0.96	1.00	1.09
33	0.95	0.77	0.96	0.76	22.41
15	0.50	0.56	0.96	1.00	-6.56
23	0.95	1.00	0.96	0.76	36.74
13	1.15	0.56	0.96	1.00	81.01
27	1.25	1.00	0.96	1.00	104.76
12	1.25	0.67	0.96	1.00	87.21
25	1.25	0.78	0.88	0.76	54.78
37	1.25	0.99	0.96	0.76	88.19
16	0.60	1.00	0.96	0.52	-38.79
17	0.50	1.00	0.48	0.88	-34.91
32	0.65	0.77	0.96	0.44	-97.28

Combining these terms in Eq. S11 leads to the final model form.

$$\hat{y}(t) = \mu(t) + \sum_{k=1}^{\infty} \xi_{ik} \phi_k(t) \approx \hat{\mu}(t) + \sum_{k=1}^{K} \hat{\xi}_{ik} \hat{\phi}_k(t) \qquad \text{Eq. S11}$$

As one may note, the notation above does not match Eq. 1 in the corresponding manuscript exactly. Specifically, the estimators of terms (denoted by "^") were not included in Eq. 1 of the manuscript to streamline the numerical discussion and allow the general reader to more smoothly to the results and model application to more fully appreciate the impact of FPCA modeling in drug substance datasets.

FPC Score Regression Results

To generate a predictive model, the FPC scores from Table S9 were regressed against the experimental conditions. The stepwise linear regression was performed in Matlab using the "stepwiselm" routine, specifying a quadratic model and the p value of 0.05 to enter the model. The resulting regression equation is provided in Eq. S12 and the associated statistics are provided in Table S10.

$$\hat{\xi}(x) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 + \beta_{12} x_1 x_2 + \beta_{14} x_1 x_4 + \beta_{24} x_2 x_4 + \beta_{11} x_1^2 + \beta_{22} x_2^2 + \beta_{33} x_3^2 \qquad \text{Eq. S12}$$

Table S10: FPC Score regression results.

Coefficient	Value	p-value
β_0	-582.5	0.01
β_1	-46.5	0.70
β_2	1878.0	<0.01
β_3	-1978.1	0.02
β_4	993.1	<0.01
β_{12}	384.9	0.01
β_{14}	209.1	0.04
β_{24}	-1199.5	<0.01
β_{11}	-144.66	0.02
β_{22}	-718.29	0.01
β_{33}	1272.5	0.02

Using these coefficients, regressed FPC scores were plotted against calculated results to provide the parity plot in Figure S7. As

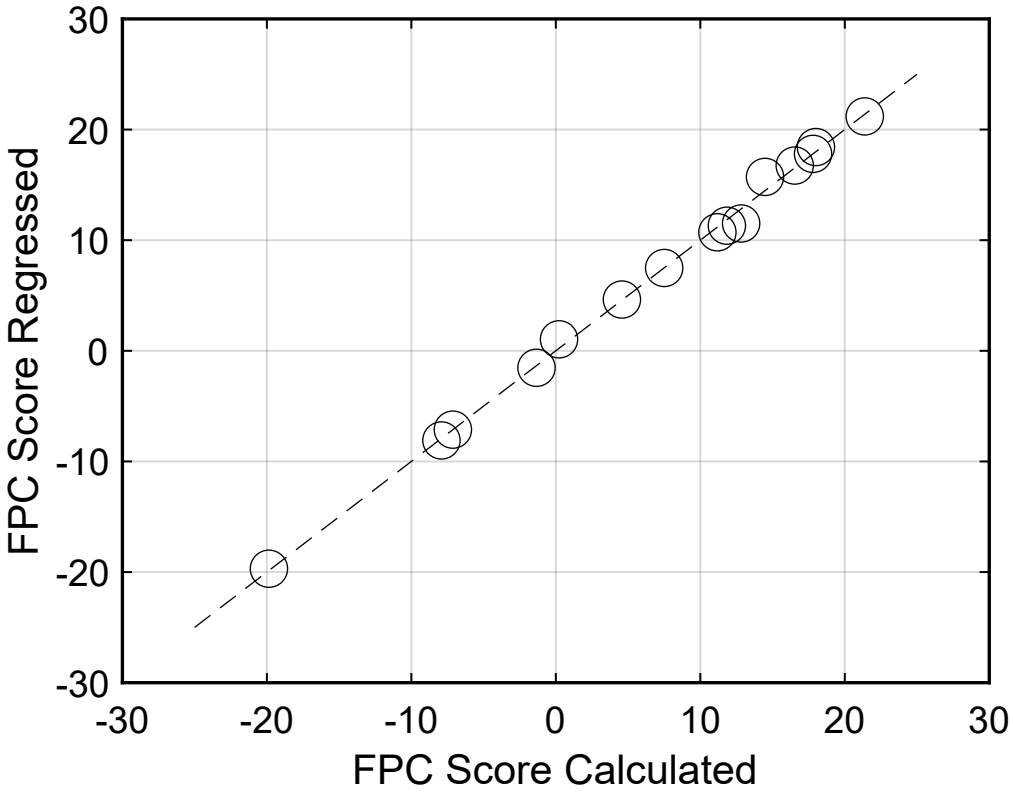


Figure S7: Parity plot of calculated FPC score and regressed FPC scores using linear regression of Eq. 2 in the manuscript.

this plot shows, there was excellent agreement between regressed and calculated FPC scores.

Details Regarding Data-Driven Modeling of Bromination

k-Nearest Neighbor Algorithm applied to Bromination Reaction Data

The reaction optimization data from the bromination reaction was leveraged to build a data-driven model to exemplify how the data could influence future process development. Because the reaction profiles contained limited dynamic data, a response surface model was established for a selected for single measurement time. A time of 8 h was selected because it showed ideal features for a stationary model – the kinetics for product formation slowed for many experiments at this time, and conditions with significant product degradation were easy to identify at this time point. The optimal conditions of experiment served as the center point for distance measurements.

Using a similar k-nearest neighbor method as described above, 20 experiments were categorized as being suitability close for data-driven modelling purposes. The reaction profiles for these experiments are provided in Figure S8.

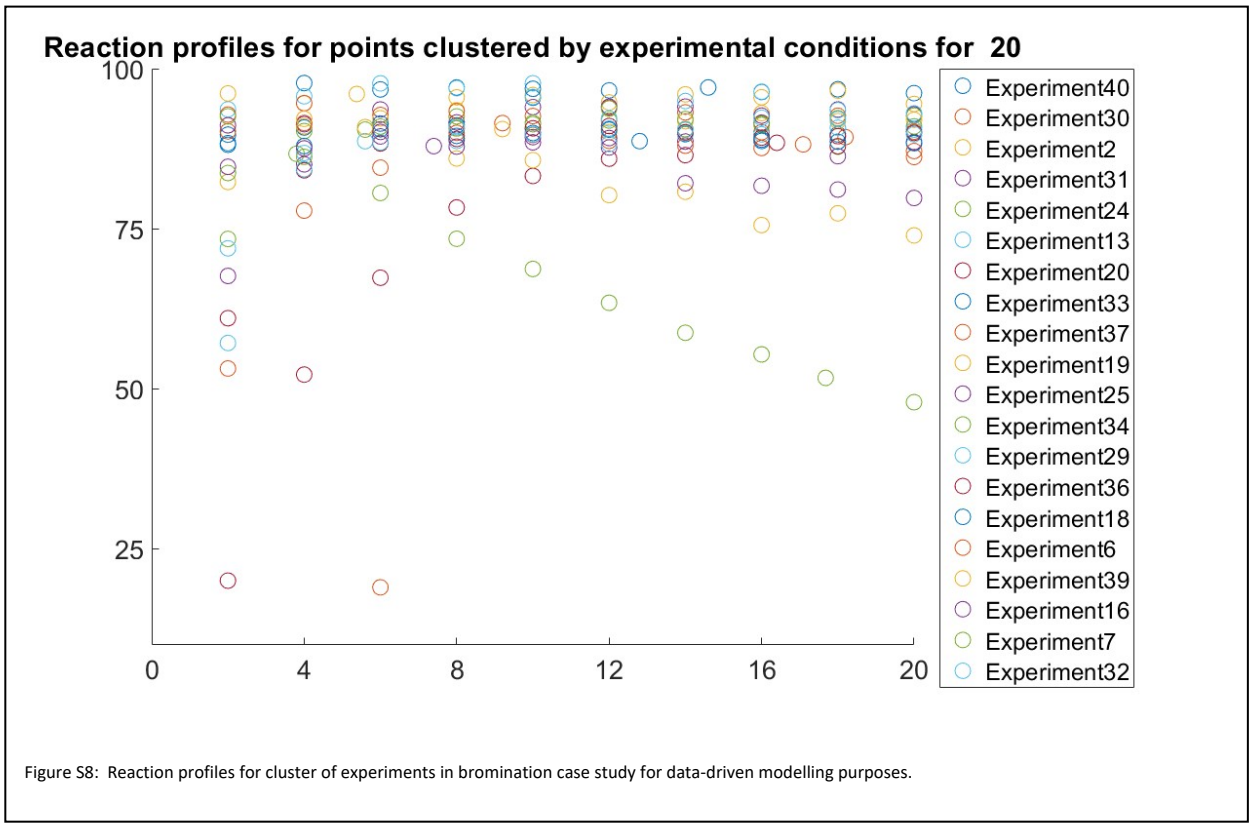


Figure S8: Reaction profiles for cluster of experiments in bromination case study for data-driven modelling purposes.

Linear Regression of Bromination Reaction Data

The assay yield for the 8 h samples, Y(x), in the profiles given in were fit to a quadratic model through stepwise linear regression. The regression was done with real reaction variables (vs. coded variables). The stepwise linear regression was performed in Matlab using the "stepwiselm" routine, specifying a quadratic model and the p value of 0.05 to enter the model (Eq. S13). The resulting model is given below.

$$Y(x) = \beta_0 + \beta_1 Temperature + \beta_2 DMF + \beta_3 Vilsmeier\ 4 + \beta_{13} Temperature\ Vilsmeier\ 4 + \beta_{11} Temper$$

Eq. S13

Table S11: Regression results for data-driven model developed in Bromination case study.

Coefficient	Value	p-value
β_0	83.9	0.18
β_1	4.7	0.01
β_2	0.63	0.03
β_3	-17.6	<0.01
β_{13}	0.22	<0.01
β_{11}	-0.06	<0.01