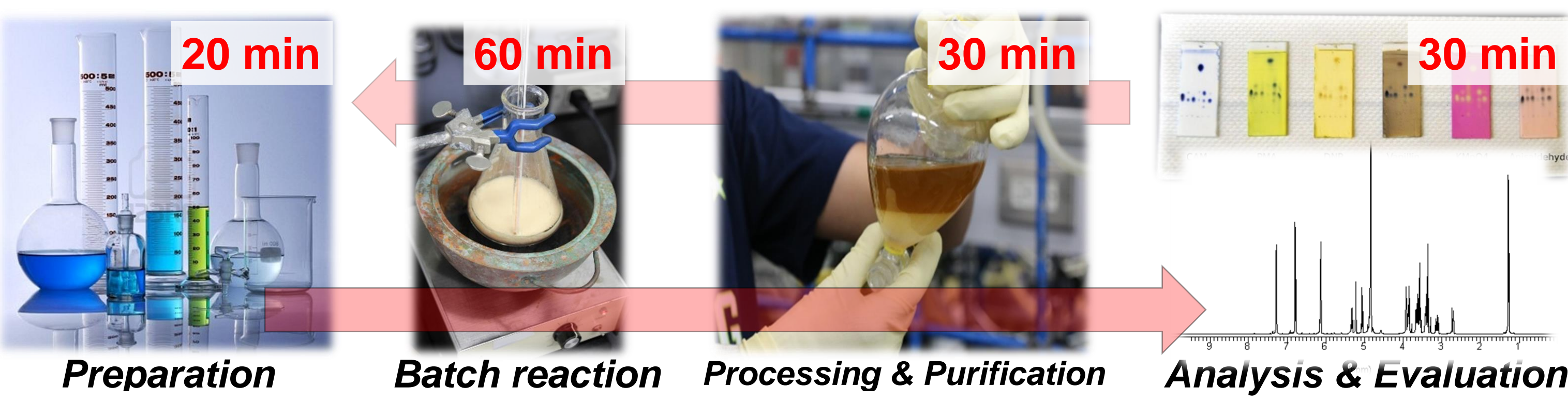




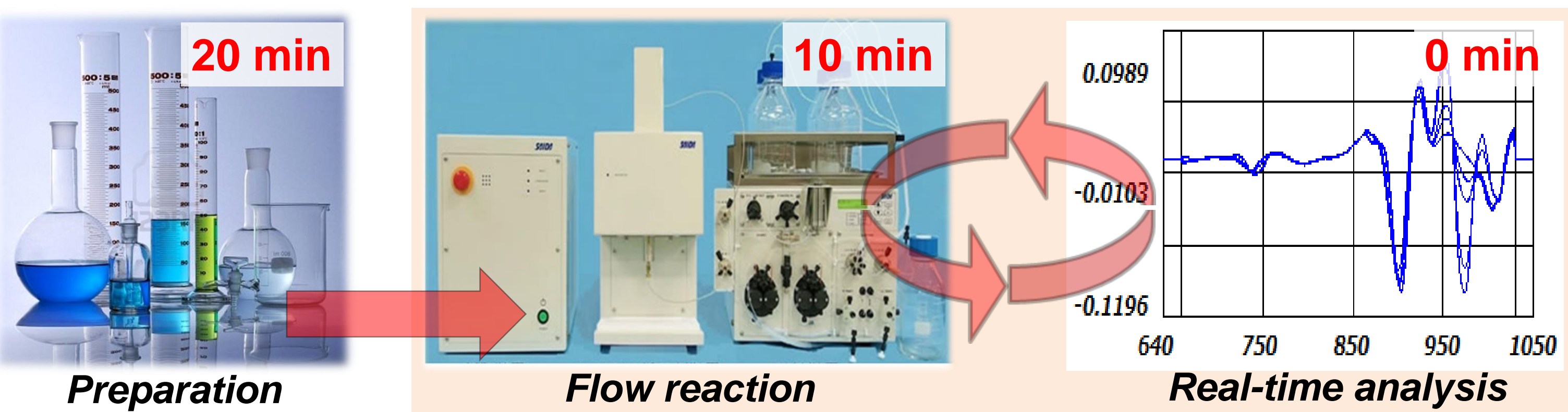
1. Introduction / Previous Works

1-1. Research Background

Batch reaction (Total: N × 140 min)



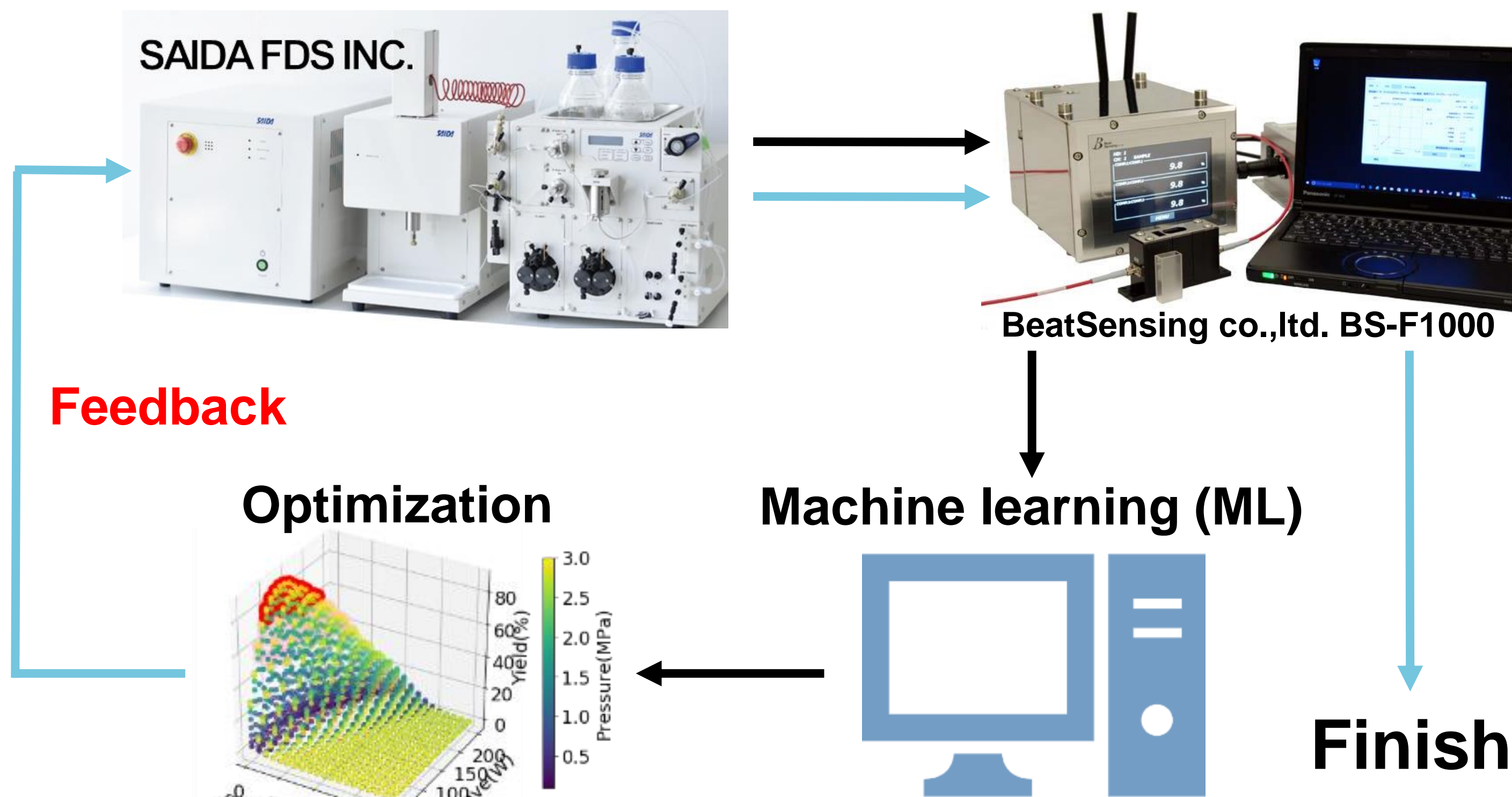
Flow reaction (Total: 20 + N × 10 min)



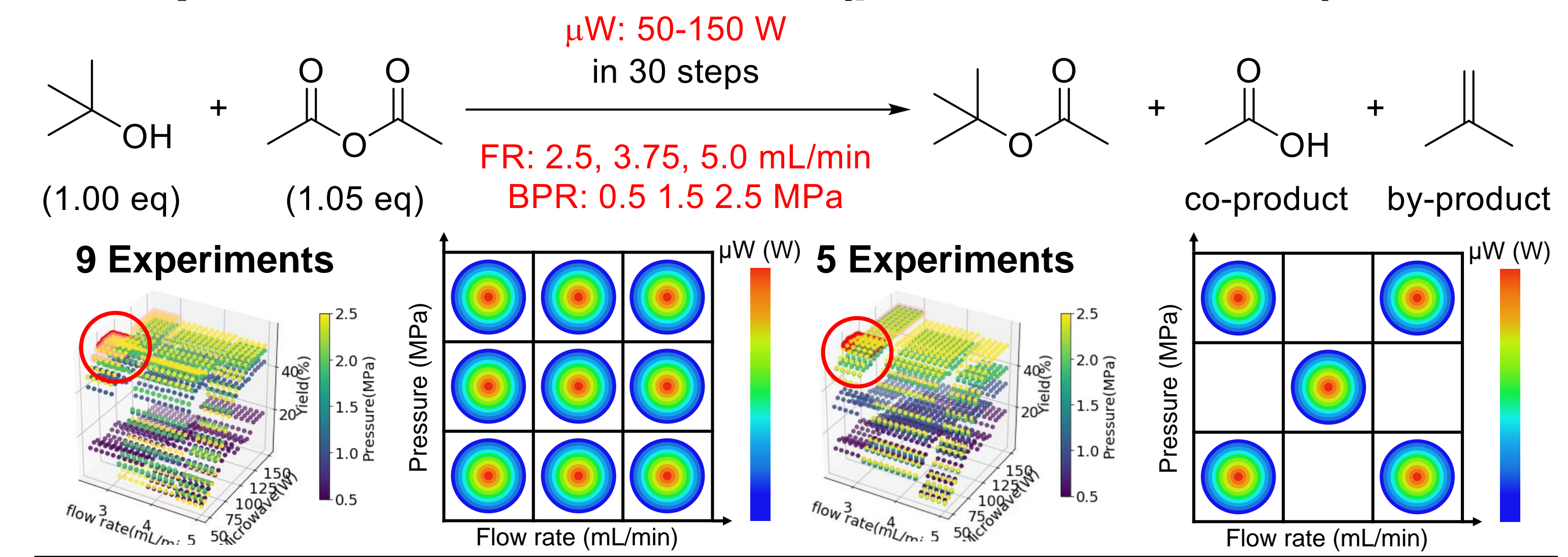
1-2. Optimization of Continuous Variables by ML

Microwave-assisted flow reaction

In-line analysis by NIR



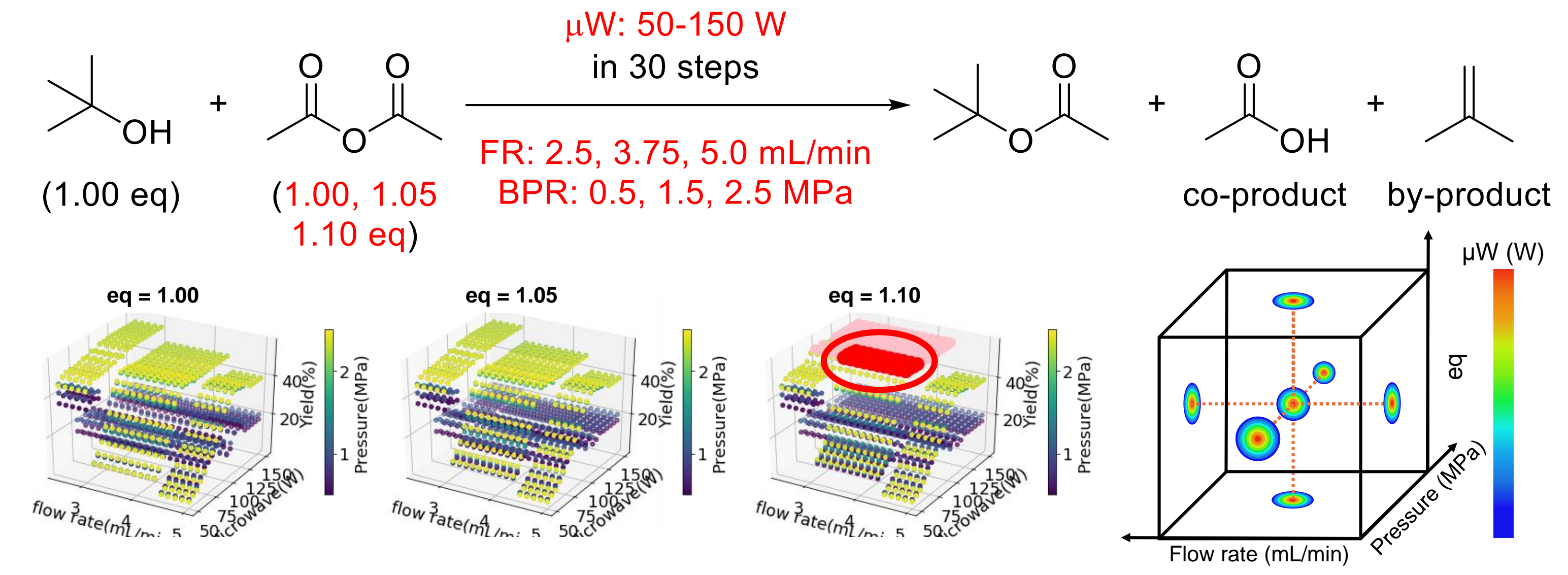
1-3. Optimization of 3 Factors (μW, FR, Pressure)



No. of Exp. ^a	μW (W) ^b	Temp. (°C) ^c	Flow rate (mL/min) ^b	Pressure (MPa) ^b	Yield (opt. / mea. ^d) (%)	RRMSE ^f (%)
9	76	215	2.5	2.5	56.0 / 57.0 (63.3) ^e	1.75
5	76	215	2.5	2.5	56.0 / 57.0 (63.3) ^e	1.75

^a Without threshold. ^b Predicted by random forest with logistic function. ^c Outlet temperature. ^d Determined by NIR analysis. ^e Determined by GC analysis using TC-17 column. ^f Relative roots mean square error.

1-4. Optimization of 4 Factors (μW, FR, Pressure, eq)

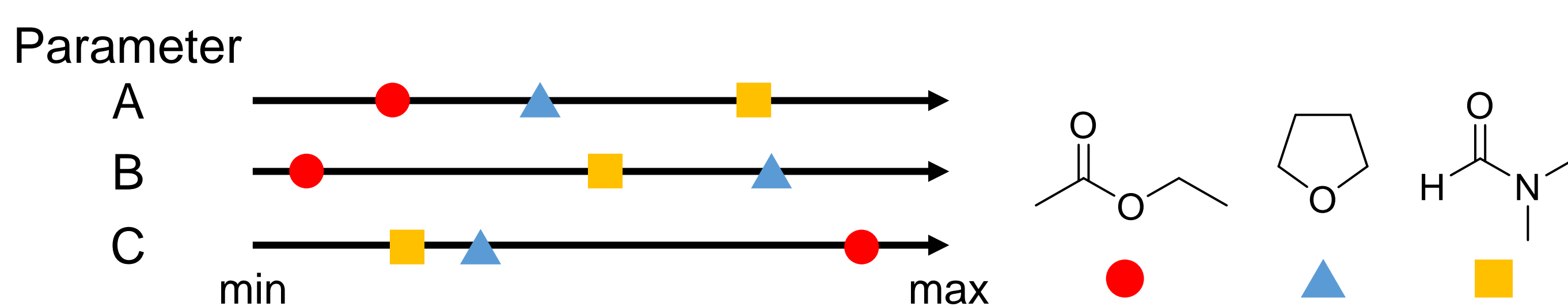


No. of Exp. ^a	μW (W) ^b	Temp. (°C) ^c	Flow rate (mL/min) ^b	Pressure (MPa) ^b	eq ^b	Yield (opt. / mea. ^d) (%)	RRMSE ^f (%)
7	92	209	3.2	1.5	1.10	56.1 / 52.2 (59.0) ^e	7.47

^a Without threshold. ^b Predicted by random forest with logistic function. ^c Outlet temperature. ^d Determined by NIR analysis. ^e Determined by GC analysis using TC-17 column. ^f Relative roots mean square error.

2. Optimization of Solvents in Acetylation

2-1. Numerous Representation of Solvents by Molecular Descriptors (5270 Parameters)



2-2. Selection of Suitable Solvents in Chemical Process (277 ⇒ 83 ⇒ 61)

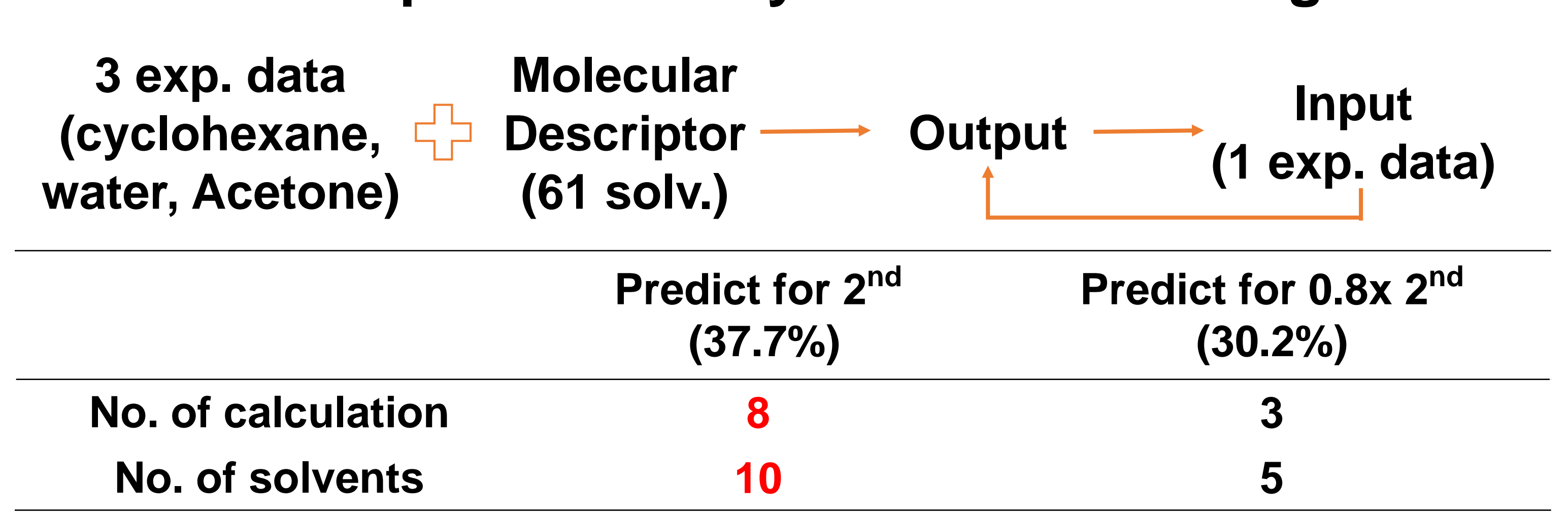
Entry	Name	Entry	Name	Entry	Name	Entry	Name	Entry	Name
1	(2,2-Dimethyl-1,3-dioxolan-4-yl)methanol	50	Acetic Anhydride	99	Diethyl Ether	148	n-Propylamine		
2	(E)-1,2-Dichloroethane	51	Acetophenone	100	Ethane-1,2-diyldiacetate	149	Octamethylcyclotrisiloxane		
3	(Trifluoromethoxy)benzene	52	Aniline	101	Ethanolamine	150	Octamethylcyclotrisiloxane		
4	(Z)-1,2-Dichloroethane	53	Benzonitrile	102	Ethoxybenzene	151	p-Cymene		
5	1,1,1,3,3,3-Hexafluoropropan-2-ol	54	Benzofuran	103	Ethyl Ethoxypropionate	152	Pentachlorobenzene		
6	1,1,2,2-Tetrachloroethane	55	Benzylamine	104	Ethyl 3-oxobutanoate	153	Perfluorodecalin		
7	1,1,2-Trichloroethane	56	Bromobenzene	105	Ethyl butyrate	154	Perfluorodecalin		
8	1,2,3,4,5-Pentafluoro-6-trifluoromethylbenzene	57	Butoxyglycol	106	Ethyl propionate	155	Pentane-3-ol		
9	1,2-Dichloropropane	58	Butyl Carbonyl	107	Ethylbenzene	156	Pentane-2,4-dione		
10	1,2-Diaminoethane	59	Butyl Carbonyl Acetate	108	Ethylcyclohexane	157	Perfluorobenzene		
11	1,2-Dichlorobenzene	60	Butyl Cellulosic Acetate	109	Fluorobenzene	158	Perfluorodecalin		
12	1,2-Dimethoxypropane	61	Butyl Cellulosic Acetate	110	Gamma-Butyrolactone	159	Perfluorodecalin		
13	1,3,2-Dioxathiolane-2-oxide	62	Furfural	111	Hexamethylcyclotrisiloxane	160	Pentane-2-ol		
14	1,3-Dichlorobenzene	63	Butylbenzene	112	Hexamethylcyclotrisiloxane	161	Propylene Glycol Ether		
15	1,3-Dioxolane	64	Butyric acid	113	Hexamethylene	162	PMMA Glycol Ether		
16	1,3-Dioxolane	65	Butyrolactone	114	Hexanenitrile	163	PrB Glycol Ether		
17	1,8-Diazabicyclo[7.2.1]heptane	66	Carbonyl	115	Hexyl Acetate	164	Propyl Cellulosic Acetate		
18	1-Butylamine	67	cis-Decalin	116	Hexyl Carbonyl	165	Propyl Cellulosic Acetate		
19	1-chloro-4-(trifluoromethyl)benzene	68	Cyclohexanone	117	HMPA	166	Propylene Glycol Ether		
20	1-Hexanol	69	Cyclohexanone	118	Indane	167	Propylene Glycol Ether		
21	1-Methoxypropan-2-ol	70	Cyclopentane	119	Iodobenzene	168	Propyl Formate		
22	1-Methylpiperazine-2-one	71	Cyclopentane	120	Cyclohexanone	169	Propylene Glycol Ether		
23	1-Nitropropane	72	Decamethylcyclotrisiloxane	121	Decamethylcyclotrisiloxane	170	Propylene Glycol Ether		
24	1-Nitropropane	73	Decamethylcyclotrisiloxane	122	Diethylamine	171	Pyridazine		
25	2,2,2-Trifluoroethanol	74	Decane	123	Diethylamine	172	Pyridine		
26	2,2,2-Trifluoroethanol	75	Diethylamine	124	Methylamine	173	Pyrimidine		
27	2,2,4-Trimethyl-1,3-pentanediol-1-isobutyrate	76	Diethyl Carbonyl	125	Methyl benzoate	174	Pyrimidine		
28	2,2,4-Trimethyl-1,3-pentanediol-1-isobutyrate	77	Diethylamine	126	Methyl Butyrate	175	Quinoline		
29	2,2-Dimethoxypropane	78	Diethylene Glycol	127	Methyl Carbonyl	176	tert-Amyl Alcohol		
30	2,2-Dimethyl-1,3-dioxolane	79	Diethylmethyl diethyl ether	128	Methyl Carbonyl	177	Tetraethylene glycol		
31	2,4-Dimethyl-3-pentanone	80	Dihydrotetra-2H-one	129	Methyl Propionate	178	Tetrahydrofuran		
32	2,6-Dimethyl-4-heptanone	81	Dihydrohexanone	130	Methylpropylamine	179	Tetrahydrofuran		
33	2,6-Dimethylpyridine	82	Dihydrohexanone	131	Methylpropylamine	180	Tetrahydrofuran		
34	2-Amino-2-methylpropan-1-ol	83	Dimethylamine	132	N,N-Dimethylamine	181	Tetrahydrofuran		
35	2-Ethoxyethanol	84	Dimethylamine	133	N,N-Dimethylamine	182	Tetrahydrofuran		
36	2-Ethoxyethyl Acetate	85	Dimethyl Acetate	134	N,N-Dimethylamine	183	Tetrahydrofuran		
37	2-Ethoxyethanol	86	Dimethyl Carbonyl	135	N-Ethyl-N-isopropylpropan-2-amine	184	Tetrahydrofuran		
38	2-Methoxy-1-(1-methoxy-2-propoxy)oxypropane	87	Dimethyl Sulfoxide	136	Nitrobenzene	185	Thiophene		
39	2-Methyl-1-propanamine	88	Dimethyl Sulfoxide	137	Nitrobenzene	186	TPA		
40	2-Methyl-1-propanamine	89	Di-n-propylether	138	N-Methylacetamide	187	TPM Glycol Ether		
41	2-Methylcyclohexane	90	Dipropylamine	139	N-Methylamine	188	TPB Glycol Ether		
42	2-Methylpyridine	91	Dipropylamine	140	N-Methylformamide	189	Triethylamine		
43	2-Nitropropane	92	DMF	141	N-methylmorpholine	190	Trichloroethane		
44	3,5-Dimethyl-2-butane	93	DMF	142	n-Nonane	191	Triethylamine		
45	3,5,5-Trimethylcyclohex-2-enone	94	DMPU	143	n-Pentyl Acetate	192	Triethylamine		
46	3-Methyl-2-butanone	95	DPM Glycol Ether	144	n-Propyl Acetate	193	Triethylene Glycol		
47	4-Hydroxy-4-methylpentan-2-one	96	DPM Glycol Ether	145	n-Propyl Acetate	194	Triethylene Glycol		
48	4-Methylcyclohexanemethanol	97	DPM Glycol Ether	146	n-Propyl Acetate	195	Triethylene Glycol		
49	5-Chloroacetone	98	DPM Glycol Ether	147	n-Propyl Acetate	196	Triethylene Glycol		

Entry	Name	Yield (%)	Entry	Name	Yield (%)	Entry	Name	Yield (%)	
196	1,1,1-Trichloroethane	217	tert-Butanol	50.7	228	Tetra	5.9	259	o-xylene
197	1,1-Dichloroethane	218	Triacetin	42.1	239	Anisole	7.6	260	DCM
198	1,1-Dichloroethane	219	5-Methylthiopyran-2(3H)-one	37.7	240	methyl 2-hydroxypropanoate	7.6	261	Methyl Acetate
199	1,2-Dichloroethane	220	DMA	34.8	241	Methylcyclohexane	7.3	262	Ethyl Formate
200	2-methylpropane	221	MIBK	33.5	242	n-Butyl Acetate	7.0	263	n-Hexane
201	Acetic Acid	222	Cyclohexanone	32.3	243	CPME	6.4	264	Benzyl alcohol
202	Benzene	223	DMF	28.9	244	Diphenyl Ether	6.3	265	1,4-Dioxane
203	Benzotrifluoride	224	NMP	28.2	245	iso-Propyl Acetate	5.8	266	3-Methylbutan-1-ol
204	Butan-1-ol	225	Hexan-2-one	24.6	246	Triethylamine	5.3	267	iso-Butanol
205	Butan-2-ol	226	MIBK	22.6	247	D-Limonene	4.9	268	n-Heptane
206	Carbon Disulfide	227	Pyridine	22.2	248	p-Xylene	4.9	269	Nitromethane
207	Diethyl Ether	228	Chloroform	22.0	249	Propanoic Acid	4.7	270	Ethanol
208	DMSO	229	Chlorobenzene	21.5	250	Acetone	4.5	271	Methanol
209	Ethyl Lactate	230	Acetonitrile	14.9	251	m-xylene	4.4	272	Formamide
210	Ethylene Glycol	231	Butanone	13.2	252	Glyme	4.1	273	IPA
211	Glycerol	232	1-chlorobutane	11.4	253	Tetrachloroethene	4.0	274	Methyl Formate
212	iso-Hexane	233	2-MeTHF	9.5	254	Ethyl Acetate	3.9	275	MTBE
213	Methyl Cellulosive	234	Pentan-3-one	9.5	255	n-Pentane	3.9	276	n-Pentane
214	n-Octane	235	Diglyme	9.3	256	Formic Acid	3.8	277	Pentane-1-ol
215	Propan-1-ol	236	Pentan-2-one	9.2	257	Cyclohexane	3.3	278	Water
216	Tetrachloromethane	237	iso-Butyl Acetate	8.9	258	Toluene	3.1	279	

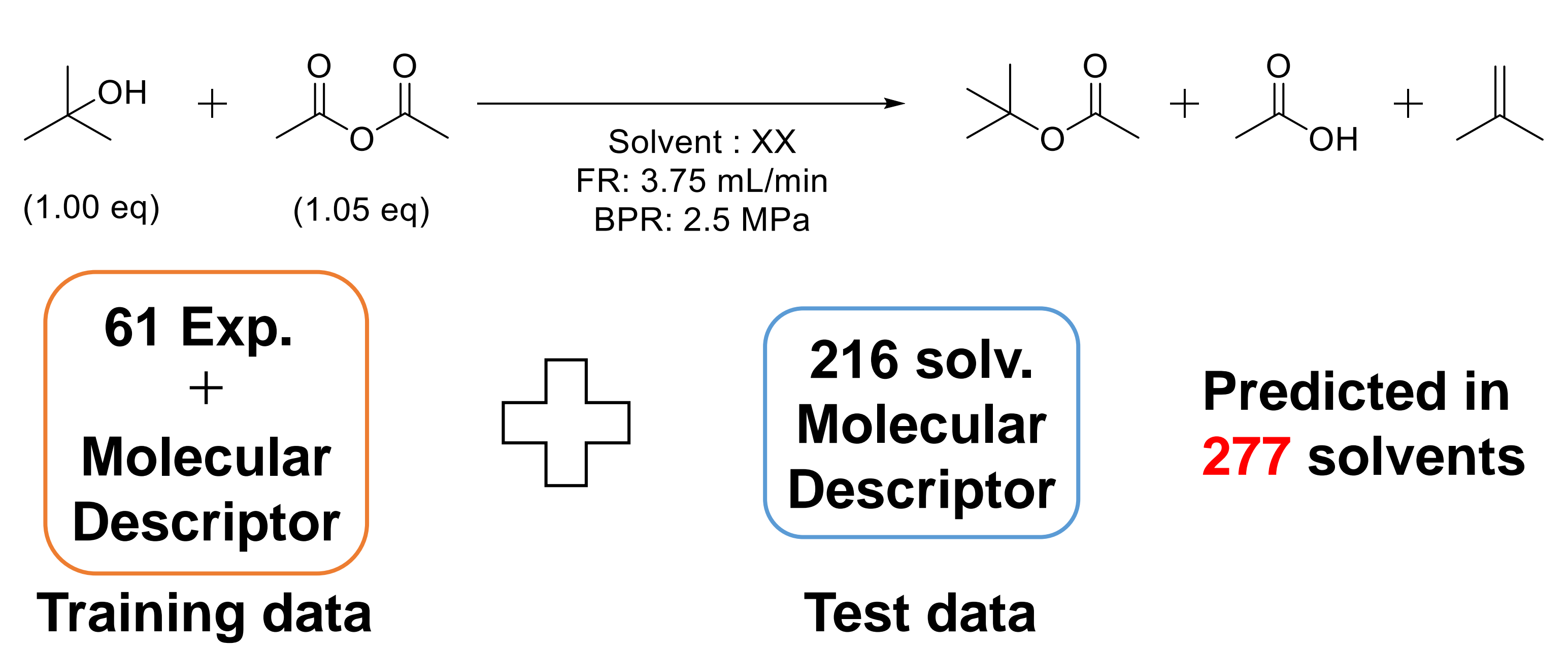
^a Not conducted. ^b Boiling or high viscosity of solvent hampered the reaction.

F. Pena-Pereira et al. Green Chem., 2015, 17, 4773.

2-3. Solvent optimization by Machine Learning



2-4. Prediction of Better Solvents



Actual Solvent Rank	Yield (%)	Predicted Solvent Rank	Yield (%)
1	42.2	Propylene Diacetate	27.9
2	37.7	DPMA Glycol Ether	48.4
3	34.8	Ethylene Glycol Diacetate	14.3

✓ Higher yielded solvent in 277 solvents