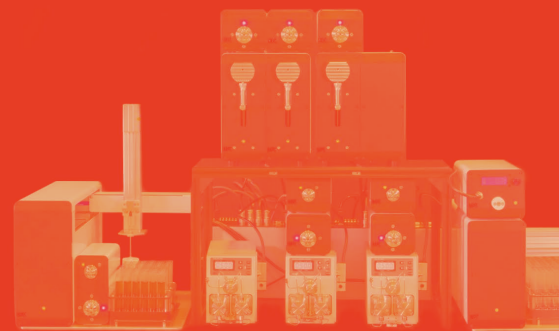
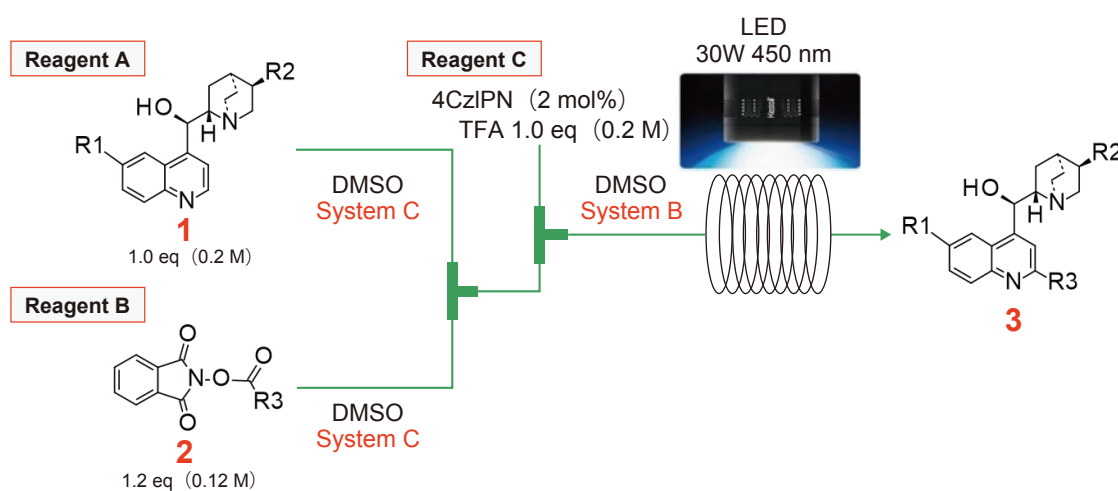


Photo Minisci reaction: 3-liquid mixture reaction



Overview

The **OptimFlow** is particularly effective for 3-liquid mixture reactions, which require more complex adjustment of reagent supply timings and flow rates than 2-liquid mixture reactions. Simple input of concentrations and mixing ratios of prepared substrates and catalysts into the **OptimFlow** can start flow synthesis without complex calculations. With multiple experimental conditions input beforehand, the system automatically performs a series of reactions, significantly reducing the workload and time taken by experimenters. The **OptimFlow** is thus useful for library synthesis and determination of experimental conditions. Below is an example of 3×2 library synthesis.



Preparation of Reagents

Reagent A1: (-)-quinine **1a** (130 mg, 0.40 mmol) was dissolved in DMSO (2 mL) and received nitrogen gas injection for about 3 min.

Reagent A2: (-)-cinchonidine **1b** (117 mg, 0.40 mmol) was dissolved in DMSO (2 mL) and received nitrogen gas injection for about 3 min.

Reagent A3: (-)-dihydroquinine **1c** (130 mg, 0.40 mmol) was dissolved in DMSO (2 mL) and received nitrogen gas injection for about 3 min.

Reagent B1: (1,3-dioxoisindolin-2-yl)cyclohexanecarboxylate **2a** (131 mg, 0.48 mmol) was dissolved in DMSO (4 mL) and received nitrogen gas injection for about 3 min.

Reagent B2: Similarly, (1,3-dioxoisindolin-2-yl)adamantane-1-carboxylate **2b** (156 mg, 0.48 mmol) was dissolved in DMSO (4 mL) and received nitrogen gas injection for about 3 min.

Reagent C: 4CzIPN(2,4,5,6-tetra(9H-carbazol-9-yl)isophthalonitrile) (6.3 mg, 0.008 mmol) as a photocatalyst and trifluoroacetic acid (61 μ L, 0.80 mmol) were dissolved in DMSO (4 mL) and received nitrogen gas injection for about 3 min.

Device Setup

Line 1, System C ver. 3.1; Line 2, System C ver. 3.1; Line 3, System B
BPR = 0.5 MPa, the 3-reagent mode with two T-shaped mixers connected with a shortest possible PTFE tube (with an inner diameter of 0.5 mm and a length of about 3 to 4 cm).

Reactors

A bundle of PTFE tubes (each with an inner diameter of 0.5 mm, a length of 10 m, and a capacity of 1.98 mL) was placed in a PhotoRedOx Box (HepatoChem, Inc.) and set in the **OptimFlow**. The light source used was an LED lamp (30 W, 450 nm).

Fraction Collector

In each experiment, the reaction solutions were collected together in a test tube with the Pre Stream Ratio set to 20% and the Post Stream Ratio to 30%.

Experiment

The parameters for each experiment were set as shown in the software input example (Experimental parameter). The reaction time (Residence Time) was 5 min, and the reference amount of Reagent A (Volume of Reagent 1) was 300 μ L. The concentrations (0.20, 0.12, and 0.20 M) of the reagents after preparation were respectively input into Conc. of Reagents 1, 2, and 3. Equivalent (1.00, 1.20, and 1.00) of the reagents were respectively input into Mol Ratio of Reagents 1, 2, and 3.

For the Fraction collector, the Pre Stream Ratio was set to 20% and the Post Stream Ratio to 30%. To collect all reaction solutions in a test tube in each experiment, the Fraction Volume was set to 10000 μ L.

The flow rates, the amounts of reagents used, and the total amount of reaction solutions in the above settings can be viewed in the Calculated value tab.

Experimental parameter	Calculated value										Procedure & details									
	Expt1	Expt2	Expt3	Expt4	Expt5	Expt6	Expt7	Expt8	Expt9	Expt10	1A1	1A2	1A3	1A4	1A5	1A6	1A7	1A8	1A9	1A10
Reagent1	1A1	1A1	1A2	1A2	1A3	1A3	1A4	1A4	1A5	1A5	2A1	2A1	2A2	2A2	2A1	2A1	2A2	2A2	2A1	2A1
Reagent2	2A1	2A2	2A1	2A2	2A1	2A2	2A1	2A2	2A1	2A2										
Reagent3																				
Residence Time (min)	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000	5.0000										
Volume of Reagent1 (μ L)	300	300	300	300	300	300	300	300	300	300										
Conc of Reagent1 (M)	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20										
Conc of Reagent2 (M)	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12										
Conc of Reagent3 (M)	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20										
MolRatio of Reagent1	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00										
MolRatio of Reagent2	1.20	1.20	1.20	1.20	1.20	1.20	1.20	1.20	1.20	1.20										
MolRatio of Reagent3	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00										
Pre StreamRatio (%)	20	20	20	20	20	20	20	20	20	20										
Post StreamRatio (%)	30	30	30	30	30	30	30	30	30	30										
Fraction Volume (μ L)	10000	10000	10000	10000	10000	10000	10000	10000	10000	10000										
Set BP1 (MPa)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5										
Upper limit of Pressure (MPa)	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50										

Experimental Parameter

Experimental parameter	Calculated value										Procedure & details									
	Expt1	Expt2	Expt3	Expt4	Expt5	Expt6	Expt7	Expt8	Expt9	Expt10	Expt1	Expt2	Expt3	Expt4	Expt5	Expt6	Expt7	Expt8	Expt9	Expt10
Flow rate of PP-1 (mL/min)	0.099	0.099	0.099	0.099	0.099	0.099	0.099	0.099	0.099	0.099										
Flow rate of PP-2 (mL/min)	0.198	0.198	0.198	0.198	0.198	0.198	0.198	0.198	0.198	0.198										
Flow rate of PP-3 (mL/min)	0.099	0.099	0.099	0.099	0.099	0.099	0.099	0.099	0.099	0.099										
Flow rate of reactor1 (mL/min)	0.396	0.396	0.396	0.396	0.396	0.396	0.396	0.396	0.396	0.396										
Flow rate of reactor2 (mL/min)																				
Volume of Reagent1 (μ L)	300	300	300	300	300	300	300	300	300	300										
Volume of Reagent2 (μ L)	600	600	600	600	600	600	600	600	600	600										
Volume of Reagent3 (μ L)	300	300	300	300	300	300	300	300	300	300										
Main stream (μ L)	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200										
Pre stream (μ L)	240	240	240	240	240	240	240	240	240	240										
Post stream (μ L)	360	360	360	360	360	360	360	360	360	360										
Total collection Vol. (μ L)	1800	1800	1800	1800	1800	1800	1800	1800	1800	1800										

Calculated value

After the reactions, 5 μ L of each resulting reaction solution was diluted with 200 μ L of DMF and analyzed with a UHPLC-MS. The conversion ratio was calculated as the ratio to the product 3 and an unreacted raw material 1 using area normalization with the ELSD area value.

1a : Quinine R1=MeO, R2=vinyl

run	Sub2:R3	3 (%)	1 (%)	2 (%)	Conv. (%)
1	c-Hex 2a	45	35	19	56
2	ADA 2b	69	16	-	81

1b : Cinchonidine R1=H, R2=vinyl

run	Sub2:R3	3 (%)	1 (%)	2 (%)	Conv. (%)
3	c-Hex 2a	25	47	25	35
4	ADA 2b	38	28	33	58

1c : Dihydroquinine R1=MeO, R2=Et

run	Sub2:R3	3 (%)	1 (%)	2 (%)	Conv. (%)
5	c-Hex 2a	37	38	22	49
6	ADA 2b	63	17	18	79