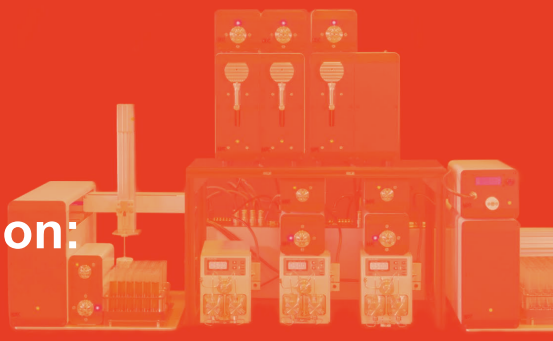
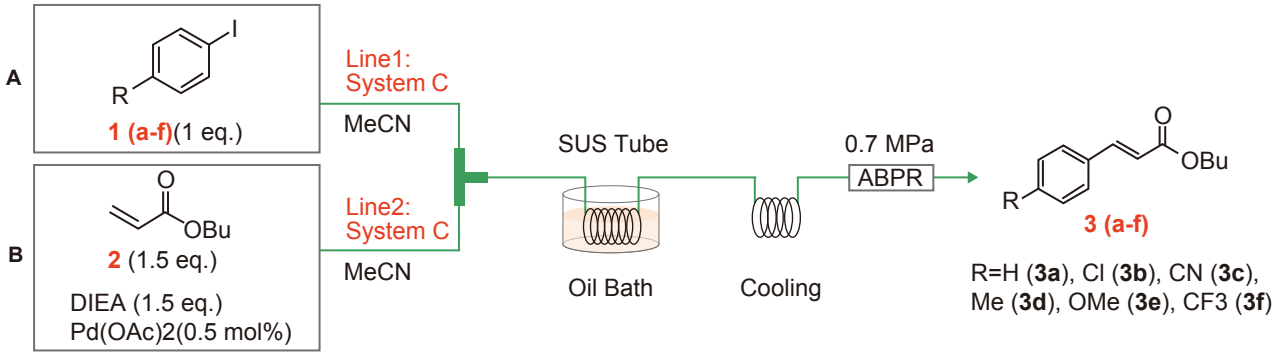
No.3
Application Note

Superheating Mizorogi-Heck reaction: 2-liquid mixture reaction



Overview

The basic 2-line system performs library synthesis under superheating in this application example. The OptimFlow allows safe and easy determination of reaction conditions, such as the concentrations of reaction solutions, equivalents of catalysts, and reaction temperatures.



Preparation of Reagents

Reagent A: Iodobenzene **1a** (50.0 mg, 0.245 mmol) was dissolved in 1 mL of MeCN to have a concentration of 0.24 M.[**1b**: 1-chloro-4-iodobenzene (56.1 mg, 0.245 mmol), **1c**: 4-iodobenzonitrile (58.4 mg, 0.245 mmol), **1d**: 1-iodo-4-methylbenzene (53.4 mg, 0.245 mmol), 1e: 1-iodo-4-methoxybenzene (57.4 mg, 0.245 mmol), and **1f**: 1-iodo-4-(trifluoromethyl)benzene (66.7 mg, 0.245 mmol)]

Reagent B: Butyl acrylate **2** (47.1 mg, 0.368 mmol), N,N-disopropylethylamine (47.5 mg, 0.368 mmol), and palladium(II) acetate (0.275 mg, 1.23 µmol) were dissolved in 1 mL of MeCN.

Device Setup

Line 1, System C ver. 3.1; Line 2, System C ver. 3.1
(Our compact back pressure valve was used for the plunger pump Out to improve the constant flow rate. Discharge pressure: 1.7 MPa)
From Loop to Reactor: A SUS tube with a length of 500 mm and an I.D. of 0.50 mm
BPR = 0.7 MPa, the 2-reagent mode with a T-shaped mixer
The BPR was set to 0.7 MPa. Liquid feeding started at room temperature, which was then raised to 160 °C in an oil bath.
The experiment started when the flow velocity stabilized.

Batch synthesis has an upper limit of 82 °C for heating with reflux.

Reactors

A SUS tube (I.D. 1.0 mm, volume 2 mL) was placed in an oil bath and connected to the OptimFlow as a reactor. A SUS tube (500 mm) was connected immediately after the reactor for air cooling. A PTFE tube (500 mm) was used for the connection to ABPR (From Reactor 1 to BPR: a length of 1000 mm and an I.D. of 0.50 mm).

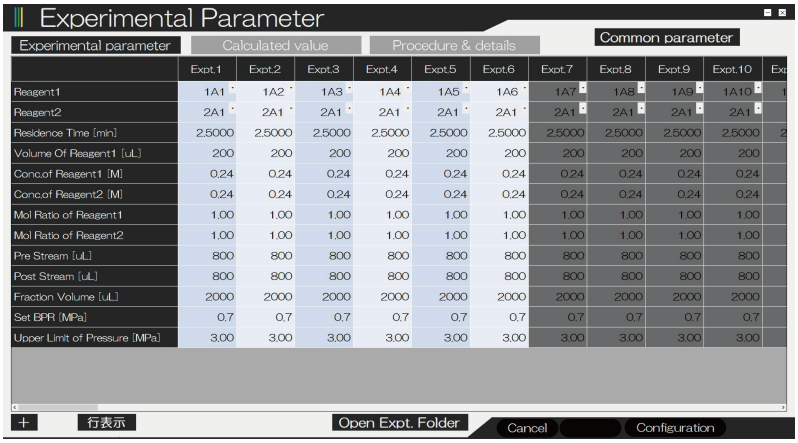
Fraction Collector

In each experiment, the reaction solutions were collected in a test tube, with the Pre Stream Ratio set to 800 µL, the Post Stream Ratio to 800 µL, and the Fraction Volume to 2000 µL.

DFC
Device for Flow Chemistry

Experiment

The parameters for each experiment were set as shown in the software input example (Experimental parameter).The reference amount of Reagent A (Volume of Reagent 1) was 200 µL, and the Residence Time was 2.5 min. 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.



	Expt.1	Expt.2	Expt.3	Expt.4	Expt.5	Expt.6	Expt.7	Expt.8	Expt.9	Expt.10
Reagent1	1A1	1A2	1A3	1A4	1A5	1A6	1A7	1A8	1A9	1A10
Reagent2	2A1	2A1	2A1	2A1	2A1	2A1	2A1	2A1	2A1	2A1
Residence Time [min]	2.5000	2.5000	2.5000	2.5000	2.5000	2.5000	2.5000	2.5000	2.5000	2.5000
Volume Of Reagent1 [uL]	200	200	200	200	200	200	200	200	200	200
Conc.of Reagent1 [M]	0.24	0.24	0.24	0.24	0.24	0.24	0.24	0.24	0.24	0.24
Conc.of Reagent2 [M]	0.24	0.24	0.24	0.24	0.24	0.24	0.24	0.24	0.24	0.24
Mol Ratio of Reagent1	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Mol Ratio of Reagent2	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Pre Stream [uL]	800	800	800	800	800	800	800	800	800	800
Post Stream [uL]	800	800	800	800	800	800	800	800	800	800
Fraction Volume [uL]	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000
Set BPR [MPa]	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7
Upper Limit of Pressure [MPa]	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00

After the reactions, 5 µL of each resulting reaction solution was diluted with 120 µL of MeOH and analyzed with a UPLC-MS. The yields were calculated using area normalization with UV areas of the products, raw materials, and byproducts.

Entry	1	R	3 (%)*	1 (%)*
1	**1a**	H	86	14
2	**1b**	Cl	79	21
3	**1c**	CN	75	11
4	**1d**	Me	74	26
5	**1e**	OMe	55	45
6	**1f**	CF_3	61	34

*The yields were analyzed and calculated for a sample of **1:1** molar ratio mixture of **3** and **1** at wavelengths with equal UV intensity ratios of 3 and 1.

Analysis wavelengths (nm)

R=H: 220, Cl: 225, CN: 262, Me: 225, OMe: 228, CF3: 244

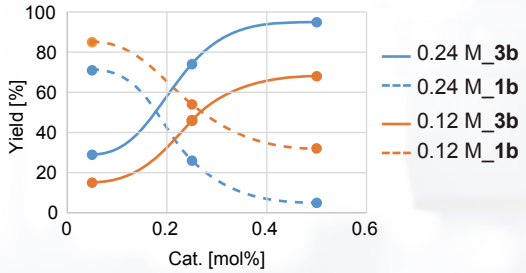
Analysis conditions

Column: ACQUITY UPLC BEH C18(1.7 µm, 2.1× 30mm), 60 °C
Solvent A: 0.05% TFA aq., B: 0.05% TFA/MeCN
Gradient: 30-100% B in 2.2 min Flow Rate: 1.0 mL/min

An example of condition determination for R = Cl is shown below. <Line 1: **1b**, **2**, DIEA, Line 2: $Pd(OAc)_2$>

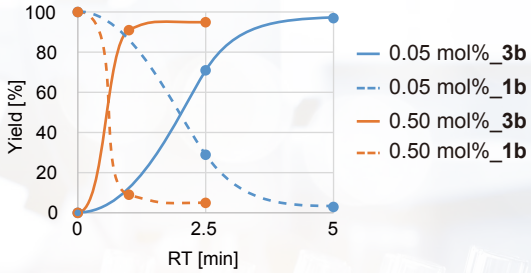
(i) Relationship between reaction concentration and catalyst concentration

[RT2.5 min, 160 °C]



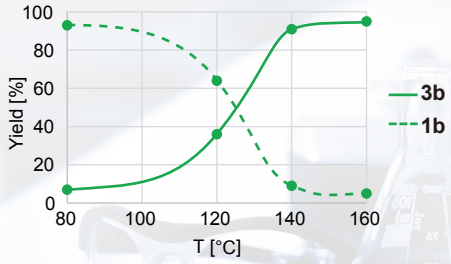
(ii) Relationship between catalyst concentration and residence time

[0.24 M, 160 °C]



(iii) Reaction temperature

[0.24 M, 0.5 mol%, 2.5 min]



- ✔ The **Optim**Flow is designed for multiple samples with liquid handlers and thus requires no repreparation of reaction solutions for determining the reaction concentration and the catalyst concentration.
- ✔ The residence time can be changed only by input on the PC.