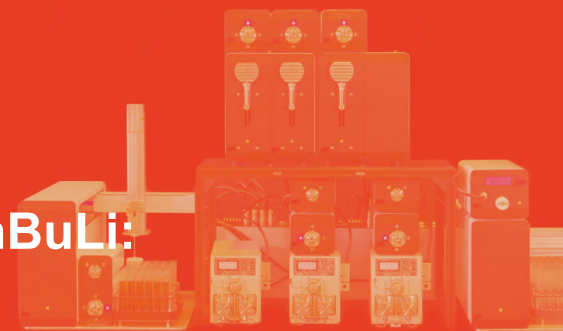
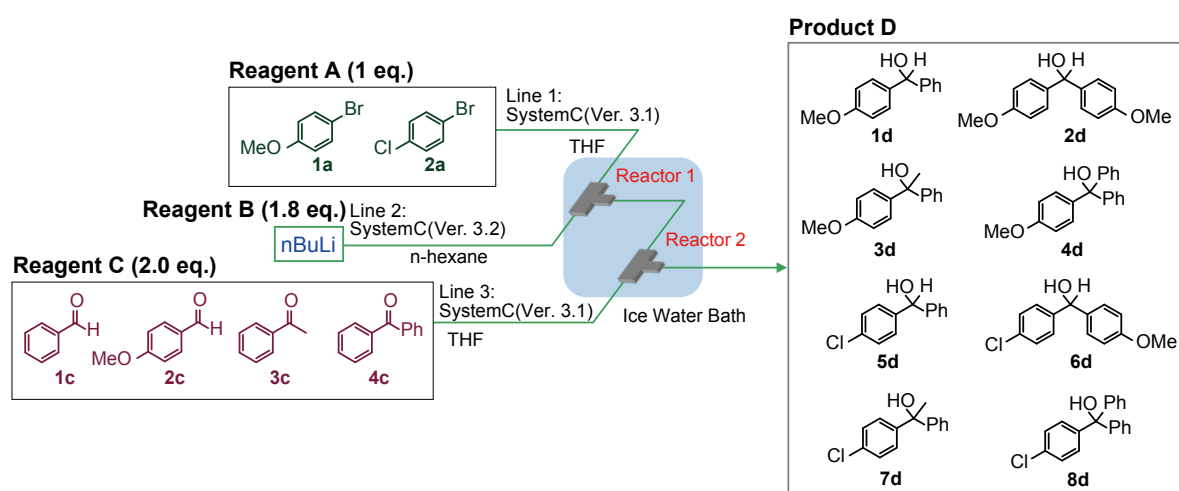


Water-prohibition reaction using nBuLi: 3-liquid mixture reaction



Overview

The 3-line system performs water-prohibition reactions using an aryl halide, n-BuLi, and an aromatic carbonyl compound as an electrophile in this example. Handling n-BuLi in a 1-bottle dry box filled with an inert gas can greatly reduce clogging in the line due to the Li salt precipitation. The lines can be easily cleaned by operating the PC, thus enabling consecutive reactions of different aryl halides and electrophiles and also enabling library synthesis.



Preparation of Reagents

Reagent A: 4-Bromoanisole 1a (1.00 g, 5.35 mmol) was dissolved in 19.8 mL of THF to have a concentration of 0.27 M. 1-Bromo-4-chlorobenzene 2a (1.00 g, 5.22 mmol) was dissolved in 19.3 mL of THF to have a concentration of 0.27 M.

Reagent B: Commercially available n-BuLi (1.58 mol/L of n-hexane solution in a 25 mL brown container) was used.

Reagent C: Benzaldehyde 1c (1.13 g, 10.7 mmol) was dissolved in 11.7 mL of THF to have a concentration of 0.92 M. [4-Methoxybenzaldehyde 2c (1.46 g, 10.7 mmol), Acetophenone 3c (1.29 g, 10.7 mmol), and Benzophenone 4c (1.95 g, 10.7 mmol) were each dissolved in 11.7 mL of THF to have a concentration of 0.92 M]

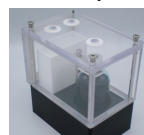
Device Setup

Line 1 (**Reagent A**): System C ver. 3.1 with a 12-well dry box

Line 2 (**Reagent B**): System C ver. 3.2 with a 1-bottle dry box

Line 3 (**Reagent C**): System C ver. 3.1 with a 12-well dry box

1 Bottle dry box



12 well dry box



From Loop (Line 1) to Reactor 1: A SUS tube with a length of 1000 mm and an I.D. of 0.50 mm

From Loop (Line 2) to Reactor 1: A SUS tube with a length of 500 mm and an I.D. of 0.50 mm

From Reactor 1 to Reactor 2: A SUS tube with a length of 120 mm and an I.D. of 1.0 mm

From Loop (Line 3) to Reactor 2: A SUS tube with a length of 500 mm and an I.D. of 1.0 mm

From Reactor 2 to BPR: A SUS tube with a length 800 mm and an I.D. of 1.0 mm

For mixing in Reactor 1, a T-shaped mixer (I.D. 0.25 mm) was used. For mixing in Reactor 2, a T-shaped mixer (I.D. 0.50 mm) was used.

BPR = 0.2 MPa, the 3-reagent mode

Reactors

Reactor 1: SUS tubes (I.D. 1.0 mm, volume 94 μ L each), a T-shaped mixer, and the SUS tubes (500 mm each) in Lines 1 and 2 immediately before the T-shaped mixer were immersed in an ice water bath and connected to the **OptimFlow** as **Reactor 1**.

Reactor 2: A SUS tube (I.D. 1.0 mm, volume 393 μ L), a T-shaped mixer, and the SUS tube (500 mm) in Line 3 immediately before the T-shaped mixer were immersed in the ice water bath and connected to the **OptimFlow** as **Reactor 2**.

Fraction Collector

The reaction solutions were collected in a total of three test tubes (Fr. 1, 2, and 3) with the Pre Stream set to 0 μ L, the Post Stream to 250 μ L, and the Fraction Volume to 600 μ L.

Experiment

The parameters for each experiment were set as shown in the software input example (Experimental parameter).

Experimental Parameter										
Experimental parameter	Calculated value			Procedure & details				Common parameter		
	Expt.1	Expt.2	Expt.3	Expt.4	Expt.5	Expt.6	Expt.7	Expt.8	Expt.9	Expt.10
Reagent1	1A1	1A1	1A1	1A1	1A2	1A2	1A2	1A2	1A9	1A10
Reagent2	2A1	2A1	2A1	2A1	2A1	2A1	2A1	2A1	2A9	2A10
Reagent3	3A1	3A2	3A3	3A4	3A1	3A2	3A3	3A4	3A9	3A10
Residence Time [min]	0.0127	0.0127	0.0127	0.0127	0.0127	0.0127	0.0127	0.0127	0.0127	0.0127
Volume Of Reagent1 [μ L]	800	800	800	800	800	800	800	800	800	800
Conc.of Reagent1 [M]	0.27	0.27	0.27	0.27	0.27	0.27	0.27	0.27	0.27	0.27
Conc.of Reagent2 [M]	1.58	1.58	1.58	1.58	1.58	1.58	1.58	1.58	1.58	1.58
Conc.of Reagent3 [M]	0.92	0.92	0.92	0.92	0.92	0.92	0.92	0.92	0.92	0.92
Mol Ratio of Reagent1	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
Mol Ratio of Reagent2	1.800	1.800	1.800	1.800	1.800	1.800	1.800	1.800	1.800	1.800
Mol Ratio of Reagent3	2.000	2.000	2.000	2.000	2.000	2.000	2.000	2.000	2.000	2.000
Pre Stream [μ L]	0	0	0	0	0	0	0	0	0	0
Post Stream [μ L]	250	250	250	250	250	250	250	250	250	250
Fraction Volume [μ L]	600	600	600	600	600	600	600	600	600	600
Set BPR [MPa]	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
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

The reference amount of Reagent A (Volume of Reagent 1) was 800 μ L, and the RT in Reactor 1 was set to 0.0127 min (0.8 s). 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, in which the RT in Reactor 2 is 0.0366 min (2.2 s).

After the reactions, 600 μ L of each resulting reaction solution in Fr. 2 was collected in a test tube with 200 μ L of methanol pre-added. The solution underwent liquid separation using dichloromethane and water and then GC analysis.

Entry	Reagent A	Reagent C	Product D	D (%) [*]	A (%) [*]	C (%) [*]
1	1a	1c	1d	59	5	36
2	1a	2c	2d	58	4	37
3	1a	3c	3d	36	10	46
4	1a	4c	4d	52	3	45
5	2a	1c	5d	34	17	49
6	2a	2c	6d	49	10	39
7	2a	3c	7d	53	6	38
8	2a	4c	8d	48	4	48

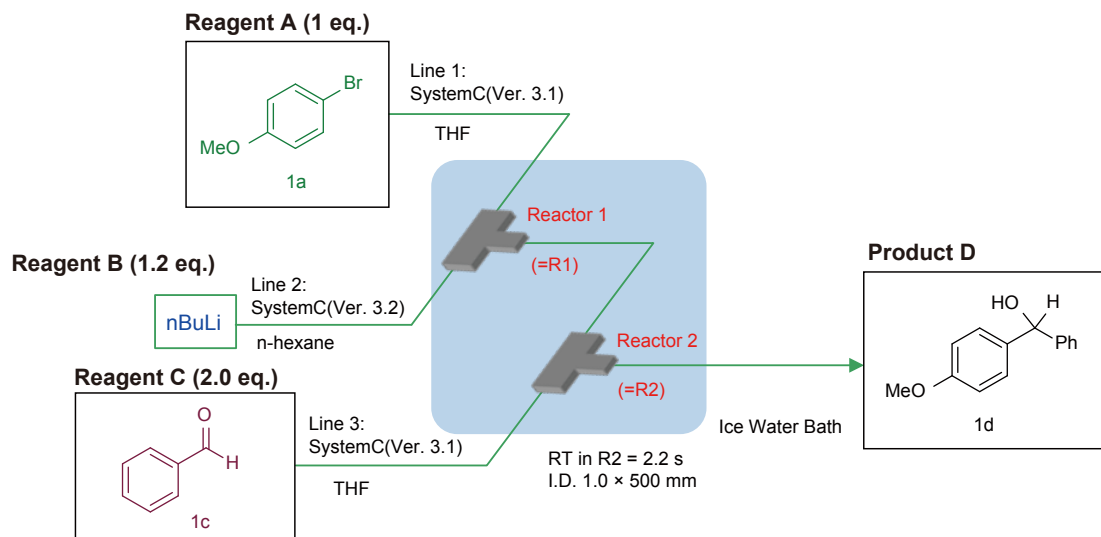
^{*}GC area normalization

Analysis conditions

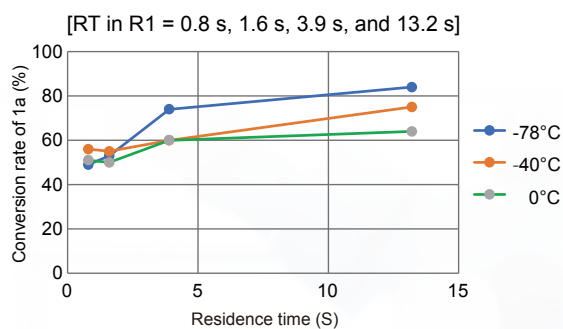
Column: DB-1 (I.D. 0.25 mm \times 30 m, film thickness 0.25 μ m)
50 $^{\circ}$ C (3 min) \rightarrow 25 $^{\circ}$ C/min \rightarrow 300 $^{\circ}$ C (9 min), 22 min in total
Vaporizing chamber temperature: 300 $^{\circ}$ C
Detector temperature: 300 $^{\circ}$ C
Carrier gas (He) pressure: 60 kPa
Split ratio: 10

Example Condition Determination (optimization of conditions for library synthesis)

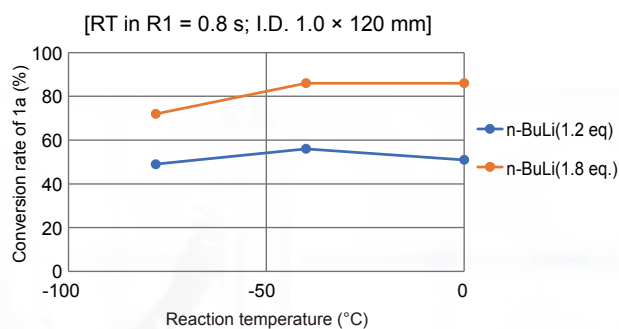
The tables below show the results of example condition determination for **Reagent A: 4-Bromoanisole (1a)**, **Reagent C: Benzaldehyde (1c)**, and **Product D (1d)**. The library synthesis was conducted based on the results.



(1) Relationship between reaction temperature and the residence time in R1



(3) Equivalents of n-BuLi



(2) Effects of the SUS-tube inner diameter and flow velocity at R1

