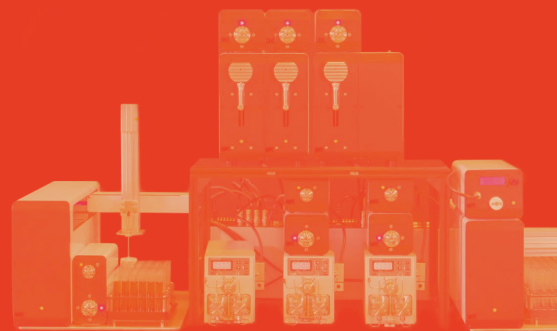
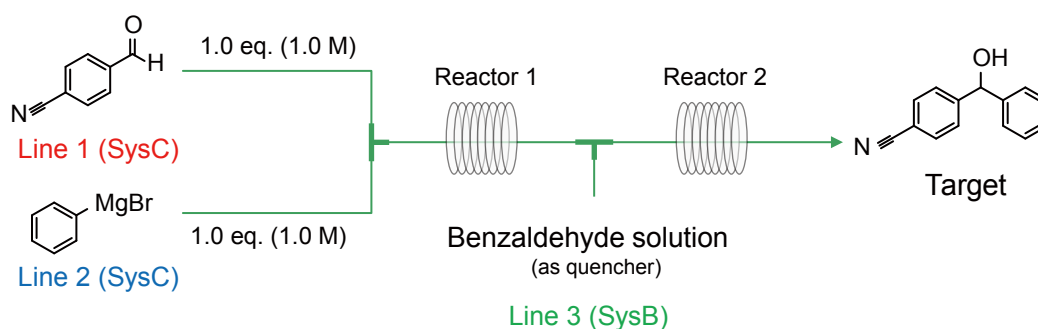


# Grignard reaction: 2 + 1 mixture reaction



## Overview

The 2 + 1 line system performs the Grignard reaction in this application example. Using a 1-bottle dry box, the **OptimFlow** allows reactions in a nitrogen atmosphere for safe use of water-prohibited and pyrophoric reagents. Below is an example of condition optimization using Grignard reagents.

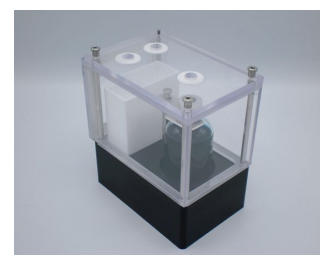


## Preparation of Reagents

**Reagent A:** 4-Cyanobenzaldehyde (1.31 g, 10.0 mmol) was dissolved in 10 mL of THF to obtain a 1.0 mol/L solution.

**Reagent B:** 1M Phenyl magnesium bromide in THF solution (Kanto Chemical Co., Inc.) was placed in a dedicated 1-bottle dry box (right photo).

**Reagent C:** Benzaldehyde (1.06 g, 10.0 mmol) was dissolved in 10 mL of THF to obtain a 1.0 mol/L solution.



## Device Setup

Line 1, System C ver. 3.1; Line 2, System C ver. 3.2; Line3, System B

From Loop to Reactor: A PTFE tube with a length of 500 mm and an I.D. of 0.50 mm

BPR = 0–0.2 MPa (see the Experimental section), the 2 + 1-reagent mode with two T-shaped mixers

The experiment started when the flow velocity stabilized.

## Reactors

Reactor 1: A PTFE tube (I.D. 0.5 mm, volume 2000  $\mu\text{L}$ ) was connected to the **OptimFlow** as a reactor.

Reactor 2: A PTFE tube (I.D. 0.5 mm, volume 295  $\mu\text{L}$ ) was connected to Line 3 as a quench reactor to stop the reaction.

A PTFE tube with a length of 500 mm and an I.D. of 0.50 mm was used for connection to ABPR.

## Fraction Collector

The reaction solutions were collected in five test tubes, with the Pre Stream set to 1000  $\mu\text{L}$ , the Post Stream to 1000  $\mu\text{L}$ , and the Fraction Volume to 1000  $\mu\text{L}$  (entries 1 and 2), and the Pre Stream set to 500  $\mu\text{L}$ , the Post Stream to 500  $\mu\text{L}$ , and the Fraction Volume to 500  $\mu\text{L}$  (entries 3 to 6).

Experiment

The amount of Reagent A used, Residence Time, and BPR were set as shown in the figure below. For all experiments, the reagent ratio of A:B:C was set to 1:1:1. 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 the **OptimFlow**.

Experimental Parameter										
Experimental parameter	Calculated value						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	1A1	1A1				
Reagent2	2A1	2A1	2A1	2A1	2A1	2A1				
Reagent3	3A1	3A1	3A1	3A1	3A1	3A1				
Residence Time [min]	12.5000	12.5000	12.5000	12.5000	4.1700	1.2500				
Volume Of Reagent1 [uL]	1000	1000	500	500	500	500				
Conc.of Reagent1 [M]	1.00	1.00	1.00	1.00	1.00	1.00				
Conc.of Reagent2 [M]	1.00	1.00	1.00	1.00	1.00	1.00				
Conc.of Reagent3 [M]	1.00	1.00	1.00	1.00	1.00	1.00				
Mol Ratio of Reagent1	1.000	1.000	1.000	1.000	1.000	1.000				
Mol Ratio of Reagent2	1.000	1.000	1.000	1.000	1.000	1.000				
Mol Ratio of Reagent3	1.000	1.000	1.000	1.000	1.000	1.000				
Pre Stream [uL]	1000	1000	500	500	500	500				
Post Stream [uL]	1000	1000	500	500	500	500				
Fraction Volume [uL]	1000	1000	500	500	500	500				
Set BPR [MPa]	0.0	0.2	0.0	0.2	0.0	0.0	0.0	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

Expt.1	
RT	Reactor1: 12.5000 [min] Reactor2: 1.2292 [min]
Flow rate	PP-1: 0.080 [mL/min] PP-2: 0.080 [mL/min] PP-3: 0.080 [mL/min] reactor1: 0.160 [mL/min] reactor2: 0.240 [mL/min]
Volume	Reagent1: 1000 [uL] Reagent2: 1000 [uL] Reagent3: 1000 [uL] Total: 3000 [uL]
Fraction	Main: 3000 [uL] Pre: 1000 [uL] Post: 1000 [uL] Total: 5000 [uL] Use of tubes: 5 Use of total tubes: 30

All resulting fractions were combined. After saturated ammonium chloride aqueous solution was added, the fractions were extracted twice with dichloromethane. The combined organic layer was dried with sodium sulfate and filtered, and the solvent was removed. Crude products were purified by column chromatography (NH-SiO<sub>2</sub>, normal heptane/ethyl acetate = 10/1 to 5/1) and calculated as an isolated yield for each entry.

Entry	BPR (MPa)	Sample 1 Injection Volume (mL)	Residence Time (min)	Flow rate (mL/min)	Isolated Yield (%)
1	0.0	1	12.5	0.08	54
2	0.2	1	12.5	0.08	60
3	0.0	0.5	12.5	0.08	56
4	0.2	0.5	12.5	0.08	51
5	0.0	0.5	4.17	0.24	56
6	0.0	0.5	1.25	0.80	57