Copper-catalyzed 1,4-Addition Reaction of Grignard Reagent to Enones Using Microflow System

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The copper-catalyzed conjugate addition of a Grignard reagent to an α , β -unsaturated ketone was performed in a microflow system. In the reaction using the microflow system, a chemoselective 1,4-addition reaction to an enone in the presence of a saturated ketone group proceeded successfully.

Organocopper reagents are one of the most prevalent synthetic tools for performing conjugate addition to enones.¹ Various types of organocopper species have been developed and used in practical syntheses. Among them, the copper-catalyzed reaction of a Grignard reagent is favored owing to its simple procedure and the complete consumption of the Grignard reagent as a nucleophile.^{1,2} Enantioselective addition by using a catalytic amount of an optically active ligand is also beneficial.³ The stoichiometric magnesiocuprates, however, are still the frequent choice in natural-product synthesis, as they can be guaranteed to be unreactive toward the coexisting saturated ketone moiety. For extreme control of the stoichiometry of a reagent in organic synthesis, the microflow system (space integration)⁴ has shown several promising results.⁵ Application of the microflow system to the copper-catalyzed 1,4-addition reaction of a Grignard reagent may result in a chemoselective reaction, that is, the 1,4addition to an enone in the presence of a simple ketone, because the microflow system can realize the accurate control of a stoichiometric ratio between substrates and reagents. It will also lead to an efficient method for the realization of a tandem reaction (time and space integration), that is, an enone-derived enolate trap with an intramolecular carbonyl group.⁶

As shown in Scheme 1, we constructed a microflow system consisting of two T-shaped SUS micromixers (M1 and M2; $\Phi = 0.5$ mm) and two SUS microtube reactors (R1 and R2;



Scheme 1. Copper-catalyzed 1,4-addition of BuMgBr (1a) with a microflow system.

 $\Phi = 1.0 \text{ mm}$) for the copper-catalyzed 1,4-addition of a Grignard reagent. Optimization of the copper-catalyzed 1,4addition reaction was performed as shown in Table 1. A THF solution of BuMgBr (1a, 1.0 M, 1.0 mL min⁻¹) and a THF solution of CuCN•2LiCl (0.26 mL min⁻¹) were introduced via a syringe pump into the micromixer M1. The amount of copper catalyst was controlled by the concentration of the solution (x M). For maintenance of the reaction temperature, M1, M2, R1, and R2 were immersed in a water bath with a temperature controller. After 15s at 25°C in R1, a THF solution of cyclohexenone (0.8 M, 1.26 mL min^{-1}) was introduced via M2. The amount of cyclohexenone (2a) introduced was equimolar with BuMgBr (1a). In some cases, 1.5 molar equivalents of chlorotrimethylsilane were also introduced simultaneously.7 The resulting mixture was passed through R2 at 25 °C. The residential period (ts) was varied by its length (ym). The results are summarized in Table 1. As shown in Entry 6, the product 3a was obtained in 94% yield even in the absence of chlorotrimethylsilane.

As shown in Table 2, a tandem reaction, that is, the trap of an enolate with an aldehyde, was performed through connection of the third micromixer **M3**. When cyclohexenone (**2a**) was used as the starting enone, it was treated in **M2** with a mixture of an equimolar amount of Grignard reagent **1** and 1.0 mol% CuCN•2LiCl, premixed in **M1**. Continuous introduction of an aldehyde to this system via **M3** gave the corresponding aldol adduct in good yield (Entries 1–5). In the reaction using cyclopentenone as the enone, 3.0 mol% copper salt was necessary to obtain the corresponding product in good yield (Entries 6 and 7). In all cases, the products were obtained as a mixture of two major diastereomers.

 Table 1. Optimization of copper-catalyzed 1,4-addition of BuMgBr (1a) with a microflow system^a

Entry	x/M	$\mathrm{mol}\%^{\mathrm{b}}$	TMSCl/equiv	y/m	t/s^{c}	3a/%
1	0.038	1.0	1.5	0.8	15	>99
2	0.12	3.0	1.5	0.8	15	>99
3	0.19	5.0	1.5	0.8	15	92
4	0.38	10	1.5	0.8	15	93
5	0.12	3.0	0	0.25	5.0	58
6	0.12	3.0	0	0.8	15	94
7	0.12	3.0	0	2.0	22	91

^aThe reaction was performed with the microflow system in Scheme 1: T-shaped SUS micromixer: **M1** (inner diameter: 0.5 mm) and **M2** (inner diameter: 0.5 mm); SUS microtube reactor: **R1** ($\Phi = 1.0$ mm, length = 1.0 m), **R2** ($\Phi = 1.0$ mm, length = 0.25–2.0 m). ^bCalculated from the concentration of CuCN•2LiCl (*x* M). ^cResidential period: Calculated from the length of **R2** (*y* m).



Table 2. Sequential 1,4-addition and aldol reaction with a microflow system a,b,c

472

^aThe reaction was performed with the microflow system in Scheme 1: T-shaped SUS micromixer: **M1** (inner diameter: 0.5 mm) and **M2** (inner diameter: 0.5 mm); SUS microtube reactor: **R1** ($\phi = 1.0$ mm, length = 1 m), **R2** ($\phi = 1.0$ mm, length = 0.8 m), and **R3** ($\phi = 1.0$ mm, length = 2.2 m). ^bThe amount of copper catalyst was calculated from the concentration of CuCN-2LiCl. 1.0 mol % of copper salt was used in Entries 1–5. 3.0 mol % of copper salt was used in Entries 6 and 7. ^cResidential period was calculated from the flow rate and the length of **R**. ^dThe product was obtained as a diastereomer mixture. In all cases, two major diastereomers were observed.



Scheme 2. Chemoselective sequential 1,4-addition and aldol reaction with a microflow system.

The copper-catalyzed 1,4-addition reaction of a Grignard reagent in a microflow system can show a chemoselective reaction. As shown in Scheme 2, the tandem reaction to give the aldol adduct **5a** (Entry 1, Table 2) can be performed in the presence of an equimolar amount of cyclohexanone. The adduct **5a** was obtained in 78% yield, while cyclohexanone was recovered quantitatively.

The performance in Scheme 2 encouraged us to examine an intramolecular tandem reaction. As shown in Scheme 3, an enone carrying ketone 6 was treated with a copper-catalyzed Grignard reagent. As reported previously, the copper-catalyzed reaction in a normal batch reactor did not give the corresponding cyclized product reasonably. Although the yield was not very



Scheme 3. Intramolecular tandem reaction with a microflow system.

high, the adduct 7 was isolated in 38% yield with the microflow system.^{8,9}

Thus, we have demonstrated the efficient use of the microflow system for the copper-catalyzed 1,4-addition of Grignard reagents. Accurate control of the stoichiometry by means of the microflow system enables the tandem reaction of the copper-catalyzed 1,4-addition of a Grignard reagent.

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