

## Wittig Like Methylenation of Aldehydes in a Microflow System: Selective Methylenation by Differential of Plural Reactions

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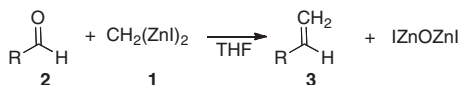
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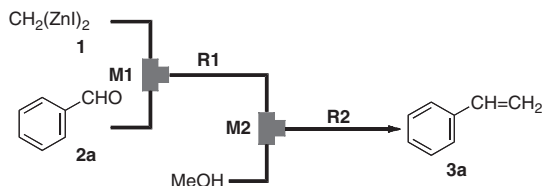
Methylenation of aldehydes with bis(iodozincio)methane was performed using a microflow system. Treatment of a dialdehyde with bis(iodozincio)methane in the system can divide two methylenation reactions and realize selective transformation.

Recently, flow reactions have been intensively studied from the viewpoint of productivity and sustainable chemistry.<sup>1</sup> In addition, space integration of chemical reactions has been also realized by microflow systems.<sup>2</sup> We have focused on the Wittig like methylenation of aldehydes with bis(iodozincio)methane (**1**) as a candidate for flow reaction (Scheme 1).<sup>3</sup> Generally, methylenation of aldehydes is performed with a typical Wittig reagent, methylenetriphenylphosphorane.<sup>4</sup> When this reaction is attempted in a flow reactor,<sup>5</sup> formation of insoluble phosphine oxide may cause difficulty in the flow. As methylenation of an aldehyde with **1** does not form any insoluble salts during the reaction, it may not encounter any obstacle in practical operation. In addition, a flow reaction can divide plural reactions as well as the integration of a single reaction. Along this line, we also expected selective methylenation in substrates carrying plural formyl groups.

When benzaldehyde (**2a**, 1.0 mmol) was treated with bis(iodozincio)methane (1.1 mmol) in THF at 25 °C in a reaction vessel for 0.5 h, styrene (**3a**) was obtained in 83% yield (in 87% at 60 °C).<sup>3</sup> As shown in Figure 1, we examined the reaction in a microflow system consisting of two T-shaped micromixers, **M1** and **M2**, and two microtube reactors, **R1** and **R2**. The yield of **3**



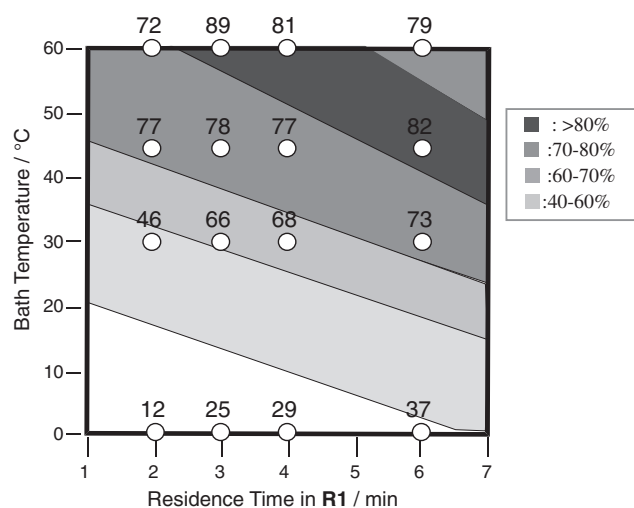
**Scheme 1.** Methylenation of aldehydes with bis(iodozincio)-methane (**1**).



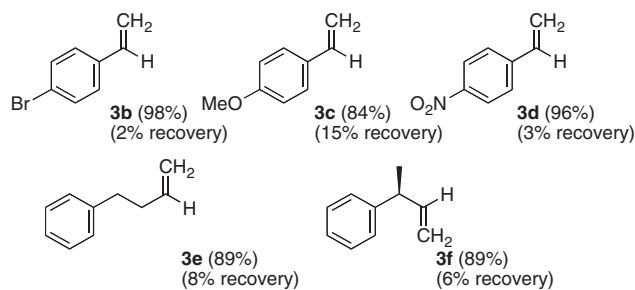
**Figure 1.** Microflow system for methylenation: T-shaped micromixer: **M1** (inner diameter: 250 μm) and **M2** (inner diameter: 250 μm), microtube reactor: **R1** ( $\phi = 1000 \mu\text{m}$ , length = 10 m), **R2** ( $\phi = 1000 \mu\text{m}$ , length = 2 m), a solution of **1**: 0.38 M in THF, a solution of **2**: 0.35 M in THF, methanol ( $3.0 \text{ mL min}^{-1}$ ).

was determined by changing the residence time in **R1** and the temperature of the ethylene glycol bath in the microflow system. The residence time was adjusted by changing the flow rate in 10 m **R1** (Figure 2). In **M2**, quenching reagent MeOH for unreacted **1** was injected.

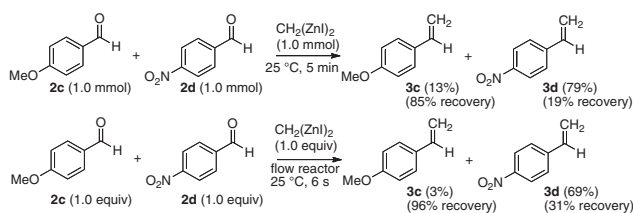
As shown in Figure 2, the highest yield 89% was observed at the intersection of 3 min (residence time in **R1**) and 60 °C (bath temperature). Figure 2 also shows that the methylenation of aldehyde is fast enough to give the alkene in over 70% yield within 1 min residence time. Under these conditions, using the flow reactor, other aldehydes were also converted into the corresponding alkenes as shown in Figure 3. Benzaldehyde derivatives **2b–2d** carrying various substituents were trans-



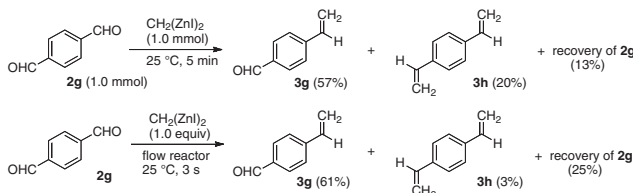
**Figure 2.** Effects of temperature and residence time on the yield of styrene (**3a**): Contour plot with scatter overlay of the yields (%).



**Figure 3.** Yields of the methylenation products **3b–3f** of aldehydes **2b–2f** by the flow reactor (residence time in **R1**: 3 min, 60 °C) in Figure 1. The reaction gave ca. 50.8–60.0 mmol alkene per hour.



**Scheme 2.** Selective methylenation of a mixture of aldehydes with bis(iodozincio)methane.



**Scheme 3.** Selective methylenation of dialdehyde with bis(iodozincio)methane.

formed into the corresponding styrene derivatives **3b–3d** continuously by the flow reaction. An alkanal **2e** was also converted into the corresponding alkene **3e**. A reaction of (*R*)-2-phenylpropanal (**2f**)<sup>6</sup> with bis(iodozincio)methane (**1**) gave the corresponding optically active alkene, (*S*)-3-phenyl-1-butene (**3f**), in 89% yield without loss of optical purity. The flow reaction gives ca. 56.0 mmol optically active alkene **3f** per hour.

Division of two reactions in one pot by a microflow system was examined as shown in Scheme 2. While treatment of an equimolar mixture of *p*-methoxybenzaldehyde (**2c**) and *p*-nitrobenzaldehyde (**2d**) with bis(iodozincio)methane (**1**) in a reaction flask gave a mixture of alkenes, that in a flow reactor resulted in selective methylenation of **2d**.

More practically, transformation of 4-formylbenzaldehyde (**2g**) to 4-formylstyrene by flow reaction was attempted. Treatment of **2g** with bis(iodozincio)methane (**1**) in a flask gave a mixture of monomethylenated product **3g** and dimethylenated product **3h**. In the flow reactor, the monomethylenated product **3g** was produced predominantly as shown in Scheme 3.<sup>7</sup>

It has been shown that a microflow system is efficient for integrating reactions and gives a multistep product at one burst.

Alternatively, it can divide a multistep reaction into each single reaction. Thus, a microflow system may be applied to highly selective reaction.

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## References and Notes

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- Stainless steel (SUS 304) T-shaped micromixers with inner diameter 250  $\mu\text{m}$  were manufactured by Sanko Seiki Co., Inc. Stainless steel (SUS 316) microtube reactors with inner diameter of 1000  $\mu\text{m}$  was purchased from GL Science. The microflow system was dipped in a ethylene glycol bath (25 °C). Solutions were introduced to the microflow system using syring pumps, Harvard Model 11, equipped with gastight syringes purchased from SGE. A solution of bis(iodozincio)methane (0.55 M in THF) and a solution of 4-formylbenzaldehyde (0.55 M in THF) was mixed (flow rate: 3.9 mL min<sup>-1</sup>). After the mixed solution was passed through **R1** (residence time: 3.0 s), the resulting mixture was poured into saturated NH<sub>4</sub>Cl aqueous solution.

