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# Flash Generation of $\alpha$ -(Trifluoromethyl)vinyl lithium and an Application to Continuous Flow Three-Component Synthesis of $\alpha$ -Trifluoromethylamides†

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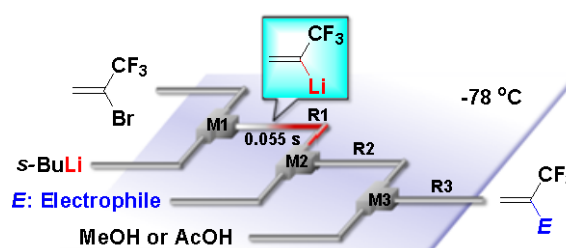
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$\alpha$ -(Trifluoromethyl)vinyl lithium was generated and used for the reaction with electrophiles at  $-78\text{ }^{\circ}\text{C}$  in a flow microreactor although the batch reaction should be carried out at ca.  $-100\text{ }^{\circ}\text{C}$ , and the method was applied to continuous flow three-component synthesis of  $\alpha$ -trifluoromethylamides.

Trifluoromethyl-substituted vinylmetals<sup>1</sup> such as  $\alpha$ -(trifluoromethyl)vinyl lithium serve as powerful building blocks<sup>2</sup> for constructing  $\text{CF}_3$ -containing molecules.<sup>3</sup> However, because  $\alpha$ -(trifluoromethyl)vinyl lithium is very unstable,<sup>4</sup> it should be generated and reacted at extremely low temperatures if we use batch macro reactors. In fact, Tarrant<sup>4a</sup> and Ichikawa<sup>2c</sup> reported independently that the generation of  $\alpha$ -(trifluoromethyl)vinyl lithium followed by the reaction with an electrophile should be carried out at ca.  $-100\text{ }^{\circ}\text{C}$  because of rapid elimination of LiF to give 1,1-difluoroallene. Notably, batch reactions are often carried out using an excess amount of  $\alpha$ -(trifluoromethyl)vinyl lithium, and the yields are usually reported based on the amounts of electrophiles. Here, we show that flash chemistry<sup>5,6</sup> using flow microreactor systems<sup>7,8,9</sup> enables the generation and reactions of  $\alpha$ -(trifluoromethyl)vinyl lithium at more easily accessible temperatures to give the desired products in good yields without using an excess amount of the lithium reagent. We also report here that the method enables continuous flow three-component synthesis<sup>10,11,12</sup> of  $\alpha$ -trifluoromethylamides,<sup>13</sup> which serve as fascinating motifs in peptidomimetics.

A flow microreactor system consisting of three T-shaped micromixers (**M1**, **M2** and **M3**) and three microtube reactors (**R1**, **R2** and **R3**) shown in Figure 1 was used for Br/Li exchange of 2-bromo-3,3,3-trifluoropropene with *s*-BuLi to generate  $\alpha$ -(trifluoromethyl)vinyl lithium followed by reactions with electrophiles.

First, we examined the reaction using benzaldehyde as an electrophile, and the desired product was obtained in a good yield (79%) based on 2-bromo-3,3,3-trifluoropropene at  $-78\text{ }^{\circ}\text{C}$  (Table 1). The reactions with other aldehydes also gave the corresponding products in good yields as shown in Table 1. Thus, the flash method enables efficient generation and use of  $\alpha$ -(trifluoromethyl)vinyl lithium at easily accessible conditions.



**Fig. 1** A flow microreactor system for generation of  $\alpha$ -(trifluoromethyl)vinyl lithium followed by reactions with electrophiles and the subsequent quenching with methanol or acetic acid. T-shaped micromixers: **M1**, **M2** and **M3**, microtube reactors: **R1**, **R2** and **R3**.

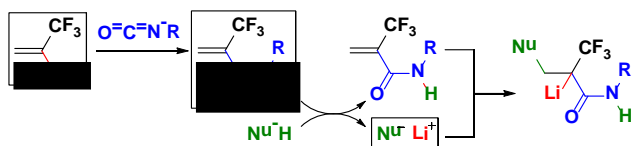
**Table 1** Reactions of  $\alpha$ -(trifluoromethyl)vinyl lithium with various electrophiles.

electrophile	quenching agent	product	yield (%)
PhCHO	MeOH		79
( <i>p</i> -CF <sub>3</sub> )PhCHO	MeOH		72
	MeOH		90
O=C=N-Bn	MeOH		80
	AcOH		62
O=C=N-Ph	MeOH		65
	AcOH		63
O=C=N-Bu	MeOH		83

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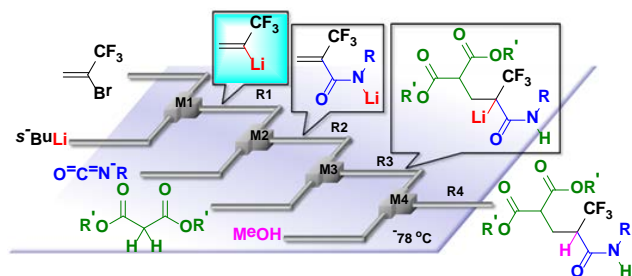
The reactions with isocyanates are interesting. Quenching with methanol gave the compounds having a methoxy group, although the use of acetic acid as a quenching agent gave the desired alkenes having CF<sub>3</sub> and amide groups in good yields (Table 1).

The formation of the compounds having a methoxy group can be explained by deprotonation of methanol by the initially formed lithium amide followed by the addition of the methoxide ion to the carbon-carbon double bond activated by the electron withdrawing CF<sub>3</sub> and amide groups. This explanation leads to the idea of using carbon nucleophiles having an acidic proton instead of methanol (Figure 2). The lithium amide deprotonates a subsequently added carbon nucleophile (Nu-H), and the resulting carbanion (Nu<sup>-</sup> Li<sup>+</sup>) adds to the electron-deficient carbon-carbon double bond. Protonation gives the corresponding three-component coupling products.



**Fig. 2** The reaction of  $\alpha$ -(trifluoromethyl)vinyl lithium with an isocyanate followed by the reaction with a subsequently added nucleophile.

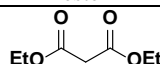
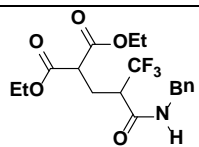
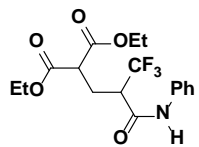
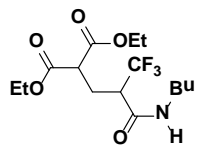
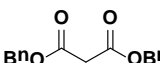
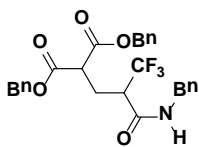
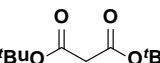
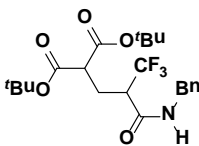
We chose to use malonate esters as carbon nucleophiles. Thus, the Br/Li exchange of 2-bromo-3,3,3-trifluoropropene, the reaction of the resulting  $\alpha$ -(trifluoromethyl)vinyl lithium with an isocyanate, and the subsequent reaction with a malonate ester were integrated<sup>14</sup> using a flow microreactor system consisting of four T-shaped micromixers (M1, M2, M3 and M4) and four microtube reactors (R1, R2, R3 and R4) shown in Figure 3.



**Fig. 3** An integrated flow microreactor system for generation of  $\alpha$ -(trifluoromethyl)vinyl lithium followed by the reactions with isocyanates and subsequently added malonate esters. T-shaped micromixers: M1, M2, M3 and M4, microtube reactors: R1, R2, R3 and R4.

As shown in Table 2, the integration of the reactions was successfully achieved with diethyl malonate, dibenzyl malonate, and di-*tert*-butyl malonate to obtain the corresponding addition products in good yields, although the use of 1,3-diketones such as 2,4-pentanedione did not give the desired products.

**Table 2** Three-component coupling of  $\alpha$ -(trifluoromethyl)vinyl lithium, isocyanate, and malonate esters.

malonate ester	isocyanate	product	yield (%)
	O=C=N-Bn		80
	O=C=N-Ph		65
	O=C=N-Bu		73
	O=C=N-Bn		51
	O=C=N-Bn		66

In conclusion, flash chemistry enables efficient generation of  $\alpha$ -(trifluoromethyl)vinyl lithium and its reactions with electrophiles at  $-78$  °C. Space integration of reactions enabled three-component synthesis of  $\alpha$ -trifluoromethylamides by successive reactions of  $\alpha$ -(trifluoromethyl)vinyl lithium with isocyanates and malonate esters. The key to the success of the three-component coupling is deprotonation of malonate esters by the lithium amide intermediates followed by the nucleophilic attack of the resulting carbanions on the carbon-carbon double bond activated by the CF<sub>3</sub> and the amide groups. This mode of reaction integration adds a new dimension to continuous flow multicomponent coupling.<sup>15</sup> Further applications of the present method to the continuous-flow synthesis of fluorine-containing organic compounds<sup>16</sup> are currently in progress in our laboratory.

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