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Flow Update for the Carbonylation of 1-Silyl-Substituted Organolithiums under CO Pressure

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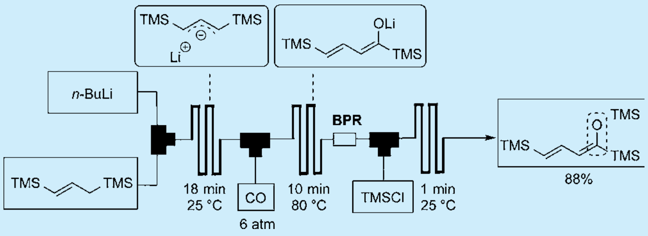
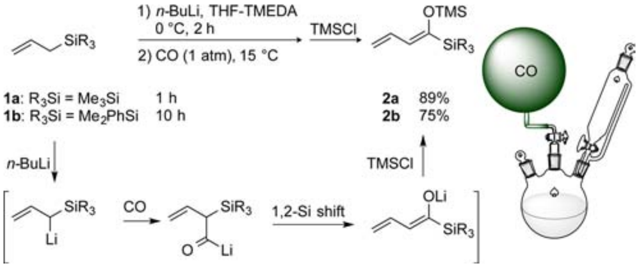
S *Supporting Information*

ABSTRACT: The generation of, and subsequent reactions with, 1-silyl-substituted organolithiums with CO was carried out using serially connected flow microreactors. The flow system proved to be quite useful for the carbonylation of silyl-substituted organolithiums under slightly pressurized conditions of CO, which was created conveniently by the use of a back-pressure regulator. This flow system, coupled with heating, accelerated the carbonylation reaction of 1-silyl-substituted organolithiums and allowed the stable silyl-substituted alkyllithium, 1,3-disilylallyllithium, which was not effective in a batch-flask reaction under a CO atmosphere, to participate in an efficient carbonylation reaction.



The reactions of organolithiums with CO are thought to give acyllithiums as the first intermediates.[1,2] Since a carbonyl functionality of acyllithiums can be the target of the nucleophilic addition of organolithiums and acyllithiums themselves, the trapping reaction of acyllithiums by electrophiles must be done under carefully controlled low-temperature conditions.[3] On the other hand, the intramolecular conversion of kinetically unstable acyllithiums to stable lithium enolates can be carried out at elevated temperatures, since lithium enolates cannot be a target of nucleophilic reactions.[4,5] For example, 1-silyl-substituted alkyllithiums react with the atmospheric pressure of CO at ambient temperatures to give lithium enolates of acylsilanes via a 1,2-anionic silicon shift from initially formed 1-silyl-substituted acyllithiums.[4a] The reaction time for the carbonylation depended on the structure of the 1-silyl-substituted organolithiums. For example, the reaction of (1-trimethylsilyl)allyllithium with atmospheric CO was complete within 1 h, whereas a reaction with the more stable (1-dimethylphenylsilyl)allyllithium with CO required 10 h to complete (Scheme 1).[4c] The long reaction time of organolithiums at ambient temperatures causes a premature quenching of key organolithiums from moisture or from proton abstraction from solvent such as THF and results in a decrease in the yields of the desired reaction products.

Scheme 1. Generation and Carbonylation of 1-Silyl-Substituted Allyllithiums with Atmospheric CO in a Batch System[4c]



To accelerate the reaction of 1-silyl-substituted organolithiums with CO, an increase in the concentration of CO by the use of pressurized conditions was expected to be effective. However, the employment of a stainless-steel batch autoclave, which is standard equipment for the reaction of pressurized CO, for a reaction of organolithiums presented several experimental hurdles. Executing such a high-pressure batch process dealing with organolithium compounds includes a careful syringe technique for the transfer of the organolithiums generated in a separate batch flask, along with the complete substitution of an inert gas, such as Ar or nitrogen, that has been dissolved in a solvent by CO. The CO then must be charged to the envisaged pressure, while shielding the autoclave, and a quenching process must follow the reaction. A series of these operations involves procedures with pressurized CO that presents a risk of exposure for moisture- and air-sensitive organolithium compounds.

We believed that flow microreaction technology[6,7] might circumvent the issues surrounding the pressurized carbonylation reactions of organolithiums: (i) that organolithium reagents would be generated effectively by mixing silyl-containing precursors and *n*-BuLi through a micromixer;[8] (ii) that a subsequent reaction with a pressurized CO could be attained simply by adjusting the back-pressure regulator (BPR); (iii) that the quenching reaction by electrophiles would be simple to carry out in a consecutive-flow manner. In particular, in the second step, a gas/liquid plug flow would be created in a

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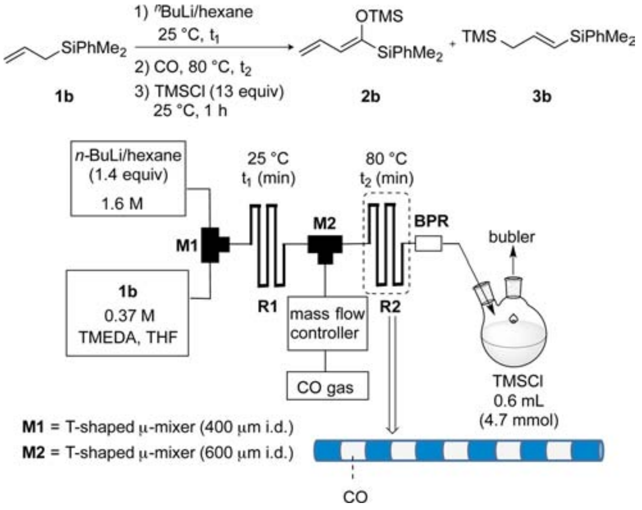
tiny reaction space, in which the high surface area to volume ratios would ensure an effective carbonylation reaction.[9,10] Herein, we report that a consecutive microflow system allowed for a sequence for the generation of 1-silyl-substituted organolithiums, a subsequent reaction with pressurized CO, and a quenching of the resultant lithium enolates with a smooth generation of electrophiles and carbonylation. This system should expand the utility of the anionic carbonylation reaction in organic synthesis.

Scheme 2. Generation and Carbonylation of (1-Dimethylphenylsilyl)allyllithium with Pressurized CO in a Microflow System



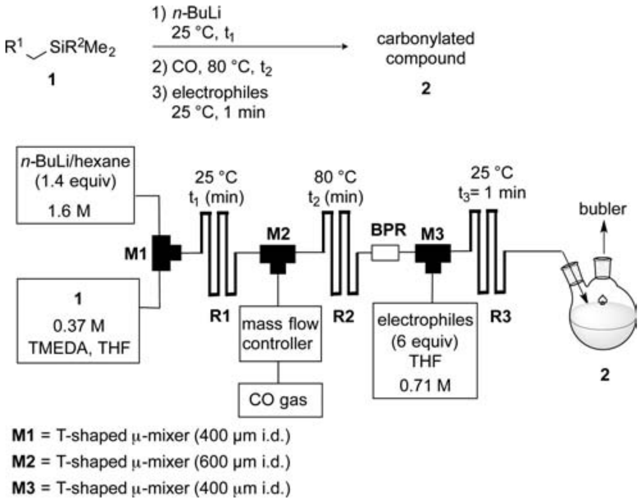
The serially connected microflow system illustrated in Scheme 2 was applied to accelerate the lithiation and carbonylation of allyl(phenyl)dimethylsilane (**1b**) as a model for a batch reaction with an atmospheric CO that was known to be very sluggish.[4c] A THF/TMEDA solution of **1b** (0.15 mL min^{-1}) and a hexane solution of *n*-BuLi (0.048 mL min^{-1}) were mixed using a T-shaped micromixer (**M1**, stainless-steel made, 400 μm channel diameter) at 25 °C, and the resultant mixture was guided to the residence time unit (**R1**, 25 °C, 1000 μm channel diameter × 6 m length) to ensure complete deprotonation to form (1-dimethylphenylsilyl)allyllithium (residence time, 23 min) and was then mixed with pressurized carbon monoxide (4 atm, 5.55 mL min^{-1} (in terms of 1 atm)) using a T-shaped micromixer (**M2**, stainless-steel made, 600 μm channel size), with a flow rate that could be adjusted by a mass flow controller. The reaction mixture was passed through a second residence time unit (**R2**, 80 °C, 1000 μm channel diameter × 10 m length) (80 °C, residence time, 4 min). The exiting reaction mixture was then quenched by TMSCl in a batch flask (25 °C, 1 h). After being quenched with TMSCl, the desired dienol silyl ether **2b** was obtained in a 51% NMR yield together with a 44% yield of noncarbonylated product **3b** (Table 1, entry 1), which meant that the residence time (4 min) of the flow carbonylation step was insufficient under these conditions. An extension of the reaction time for carbonylation of from 4 to 7 min increased the yield of **2b** to 91% (by NMR) together with 5% of **3b** (Table 1, entry 2). Using a slightly higher CO pressure of 6 atm resulted in the sole formation of the carbonylated product **2b** in a 91% yield after isolation by silica gel chromatography (Table 1, entry 3).

Table 1. Optimization of Reaction Conditions Using Allyldimethyl(phenyl)silane (1b)[a]

entry	residence time[b] t_1 (min)	residence time[b] t_2 (min)	CO (atm)	yield[c] (%)	
				2b	**3b**
1	23	4	4	51	44
2	31	7	4	91	5
3	18	10	6	91[d]	0

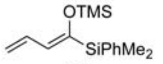
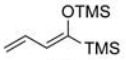
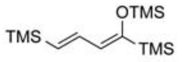
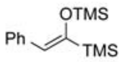
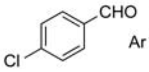
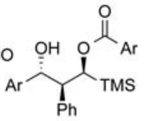
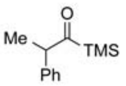
[a] Conditions: **1b** (4 mmol, 0.37 M in THF and TMEDA (3 equiv)), *n*-BuLi (1.6 M in hexane, 1.4 equiv). For further detailed conditions, see the Supporting Information. [b] Calculated time. [c] NMR yield using anisole as an internal standard. [d] Isolated yield by column chromatography on SiO$_2$.

Scheme 3. Continuous Flow Generation, Carbonylation, and Quenching with Electrophiles of 1-Silyl-Substituted Organolithiums



Encouraged by the result of two consecutive flow reactions, we then built a three-consecutive-flow reaction system comprising the generation of organolithiums, carbonylation, and a quenching of the resultant lithium enolates by electrophiles (Scheme 3). Thus, the flow-TMS quenching step was sequenced after the carbonylation reaction step, which gave silyl enol ether **2b** in a 93% yield (Table 2, entry 1). In a similar manner, the consecutive flow reaction of allyltrimethylsilane (**1a**) gave the desired dienol silyl ether **2a** in an 88% yield (Table 2, entry 2). The batch reaction of 1,3-bis(trimethylsilyl)propene (**1c**) at 1 atm of CO was quite sluggish. For example, the reaction of 1,3-bis(trimethylsilyl)-allyllithium with 1 atm of CO following 13.5 h gave a mixture of 27% of the desired product **2c** and 59% of noncarbonylated 1,3,3-tris(trimethylsilyl)propene after silylation by TMSCl. We were pleased to find that continuous-flow reaction conditions following 10 min residence time for the carbonylation step gave an 88% yield of **2c** (Table 2, entry 3). When using a similar procedure at 4 min of residence time for the carbonylation step, benzyltrimethylsilane (**1d**) was converted to one-carbon homologated enol silyl ether **2d** in an 88% yield (Table 2, entry 4). Some electrophiles other than TMSCl were also examined for use in the flow quenching system for lithium enolates. Thus, an Aldol-Tishchenko type reaction[11] comprising-benzyltrimethylsilane (**1d**), CO, and 4-chlorobenzaldehyde took place to give the stereodefined product **4** in an 81% yield

Table 2. Microflow Generation, Carbonylation, and Reaction with Electrophiles of 1-Silyl-Substituted Organolithiums

entry	1	time (min)[b] t_1	t_2	electrophiles	products	yield(%)[c] (*E*/*Z*)[d]
1	**1b**	18	10	TMSCl	 **2b**	93 (93/7)
2	**1a**	18	4	TMSCl	 **2a**	88 (91/9)
3	 **1c**	18	10	TMSCl	 **2c**	88[e]
4	 **1d**	31	4	TMSCl	 **2d**	88 (97/3)
5	**1d**	31	4		 **4** Ar = *p*-Cl-C_6H_4	81[f]
6	**1d**	31	4	MeI[g]	 **5**	77

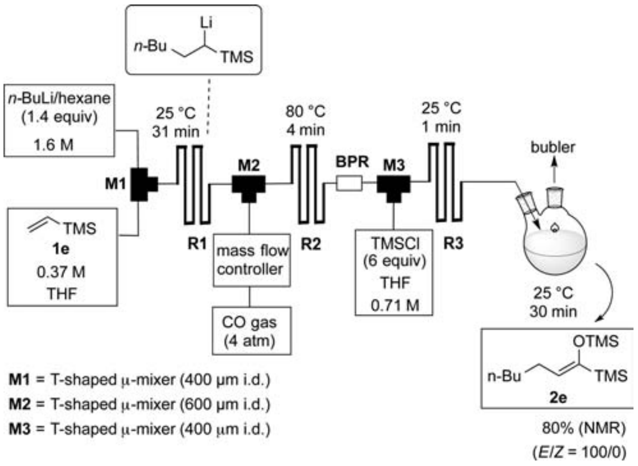
[a] Conditions: **1** (4 mmol, 0.37 M in THF and TMEDA (3 equiv), *n*-BuLi (1.6 M in hexane, 1.4 equiv), CO 4 atm (6 atm for entries 1 and 3), electrophiles (0.71 M in THF, 6 equiv). For further detailed conditions, see the Supporting Information. [b] Calculated residence time. [c] Isolated yield after column chromatography on SiO_2. [d] Determined by GC and/or NMR. [e] Three isomers (1*E*,3*E*/1*Z*, 3*E*/1*E*,3*Z* = 87/9/4). [f] One diastereomer. [g] After collection in a flask, the reaction mixture was stirred at 25 °C for 1 h.

(Table 2, entry 5). Alkylation of lithium enolate by MeI gave a 77% yield of acylsilane **5** (Table 2, entry 6).

Since 1-silyl-substituted alkyllithiums can be generated by the addition of organolithiums to vinylsilanes, we then examined a consecutive-flow-microreaction system comprising carbolithiation, carbonylation, and TMSCl quenching (Scheme 4). This also worked well, and the desired **2e** was formed in an 80% NMR yield.

In summary, we demonstrated that the generation of, and reaction with, 1-silyl-substituted organolithiums with a slightly pressurized CO could be conveniently carried out by using a flow microreactor equipped with BPR. This flow-carbonylation system uses slightly pressurized CO to override a tedious batch procedure via the use of a pressurized CO reaction and, coupled with heating to 80 °C, accelerates the CO trapping reaction (typically, from 1−10 h to 4−10 min). The quenching of the resultant dienolates with electrophiles was also successful with a sequentially connected microreactor system. The overall reaction time for the three-step reactions was considerably minimized. This work demonstrates the first example of the carbonylation of organolithiums carried out by the use of a microflow system.

Scheme 4. Generation and Carbonylation of 1-Silyl-Substituted Alkyllithium, Derived by Carbolithiation, Using a Microreactor



■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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