Aryllithium Compounds Bearing Alkoxycarbonyl Groups: Generation and Reactions Using a Microflow System**

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Control of reactive intermediates[1] to selectively obtain desired products is a central issue in organic synthesis. In macrobatch processes, generation of a reactive intermediate usually takes minutes or hours. If the lifetime of the intermediate is shorter than the generation or accumulation time, it is difficult to obtain a solution of that intermediate because it undergoes decomposition during the accumulation. In such a case, a subsequent reaction using the intermediate cannot be performed. Therefore, the generation of reactive intermediates is usually carried out at very low temperatures to avoid undesired decomposition. In flash chemistry[2,3] using a microflow system,[4,5] a reactive intermediate can be rapidly generated and transferred for use in a subsequent reaction before decomposition, because the residence time can be significantly reduced.[6] Therefore, chemical conversions that are impossible in conventional macroreactors can become possible using microflow reactors. Herein, we report that aryllithium compounds having a highly reactive alkoxycarbonyl group, such as ethoxycarbonyl and methoxycarbonyl, can be easily generated and used for reactions with electrophiles by exploiting the features of microflow systems.[7]

Organolithium compounds, such as aryllithiums, have been widely used in organic synthesis because of their high reactivity.[8,9] However, organolithium compounds suffer from a problem of functional group compatibility.[10] In fact, it is difficult to prepare organolithium compounds incorporating many functional groups, for example alkoxycarbonyl groups, because such functional groups react with organolithium species. To overcome this problem, generation reactions, such as Br/Li exchange reactions of organic bromides, are often conducted at very low temperatures. It is, however, still difficult to prepare organolithium compounds having highly reactive functional groups, such as methoxycarbonyl and ethoxycarbonyl groups.[11] The second approach is the use of less-reactive, hence more-stable, organometallic compounds,[12] such as organomagnesium[13] and organozinc compounds.[14] However, preparation of such organometallic compounds by a metal-exchange reaction from organolithium

compounds suffers from the same problem of undesirable reaction of organolithium species with such functional groups. Such organometallic compounds can also be prepared directly without using organolithium reagents. However, direct preparation requires the use of highly reactive precursors such as organic iodides, which are usually more difficult to prepare.[15] We envisaged that the concept of flash chemistry using a microflow system would solve this problem.

We focused on the Br/Li exchange reaction of alkyl *o*-bromobenzoates.[7] The Br/Li exchange reaction of alkyl bromobenzoates, followed by reaction with an electrophile, can be performed in a conventional macrobatch reactor only with *tert*-butyl bromobenzoates at very low temperatures (e.g. −100°C). The use of esters of secondary and primary alcohols dramatically decreases the yields. To confirm this assumption, we reexamined the Br/Li exchange reactions of *tert*-butyl *o*-bromobenzoate (**1a**), isopropyl *o*-bromobenzoate (**1b**), ethyl *o*-bromobenzoate (**1c**), and methyl *o*-bromobenzoate (**1d**) in a conventional macrobatch reactor (Table 1).

Table 1: The Br/Li exchange reaction of alkyl *o*-bromobenzoates (BrC₆H₄CO₂R) followed by reaction with ROH in a conventional macrobatch reactor.

o-Bromobenzoates	Yield of **3** [%][a]
R = *tert*-butyl: **1a**	61
R = isopropyl: **1b**	12
R = ethyl: **1c**	0
R = methyl: **1d**	0

[a] A solution of sBuLi in hexane/cyclohexane was added dropwise to a solution of *o*-bromobenzoates **1** in THF at −78°C. After stirring for 10 min at −78°C, an alcohol was added as an electrophile (3.0 equiv). After stirring for 10 min at −78°C, the yield of the product **3** was determined by GC.

The exchange reaction of **1a** at −78°C, followed by quenching with an alcohol, gave *tert*-butyl benzoate (**3a**) in 61% yield. This yield can be attributed to partial decomposition of **2a** at this temperature. At lower temperatures (−100°C), this reaction affords higher yields.[11] The use of **1b** as the starting material caused a further decrease in the yield of **3**. Moreover, in reactions of **1c** and **1d**, the desired products were not obtained at all (Table 1).

We then examined the reactions using a microflow system consisting of two T-shaped micromixers (M1 and M2) and two

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microtube reactors (R1 and R2; Figure 1). The reactions were carried out with varying temperatures (T) and residence times (t^R) in R1. The results are summarized in Figure 2,[16,17] in which the yield of **3** is plotted against T and t^R in R1 as a contour map with a scattered overlay.
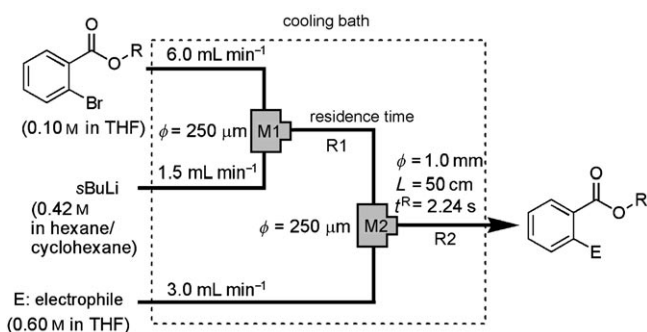

Figure 1. A microflow system for the Br/Li exchange reaction of alkyl *o*-bromobenzoates followed by reaction with electrophiles (see text for details).

In reactions of *tert*-butyl *o*-bromobenzoate (**1a**), **3a** was obtained in high yields (> 80%, brown region) for a wide range of temperatures and residence times. At low temperatures and short residence times the yield of **3a** was low presumably because of an incomplete Br/Li exchange reaction. Low yields also occurred in the high-temperature/long-residence-time region, probably as a result of the decomposition of **2a**.

In the case of isopropyl *o*-bromobenzoate (**1b**), the reaction profile was similar, although the high-yield region became smaller. The reaction of ethyl *o*-bromobenzoate (**1c**) also exhibited a similar profile. The high-yield region shifted to a lower temperature and shorter residence-time, probably because of faster decomposition of the organolithium compound **2c**. However, it is noteworthy that the reaction can be effectively carried out to give **3c** in 90% yield by using an appropriate temperature (−48°C) and residence time (0.06 s).

Of even greater significance is the fact that **3d** can be obtained in relatively good yields (> 70%, not shown) from methyl *o*-bromobenzoate (**1d**), although the high-yield region (> 80%) disappeared, presumably because of the small steric demand of the methoxycarbonyl group for the reaction with organolithium species, leading to the formation of side-products.

These results clearly show that the stability of the organolithium compounds decreases in the order **2a** > **2b** > **2c** > **2d**. However, it is important to note that the Br/Li exchange reaction followed by reaction with an electrophile can be successfully carried out without significant decomposition of the organollithium intermediate (**2**) by optimizing temperature and residence time, even in the case of the methyl ester.

Under the optimized conditions obtained for the Br/Li exchange reaction followed by reaction with an alcohol, the reactions of **2a–2d** with other electrophiles, such as methyl
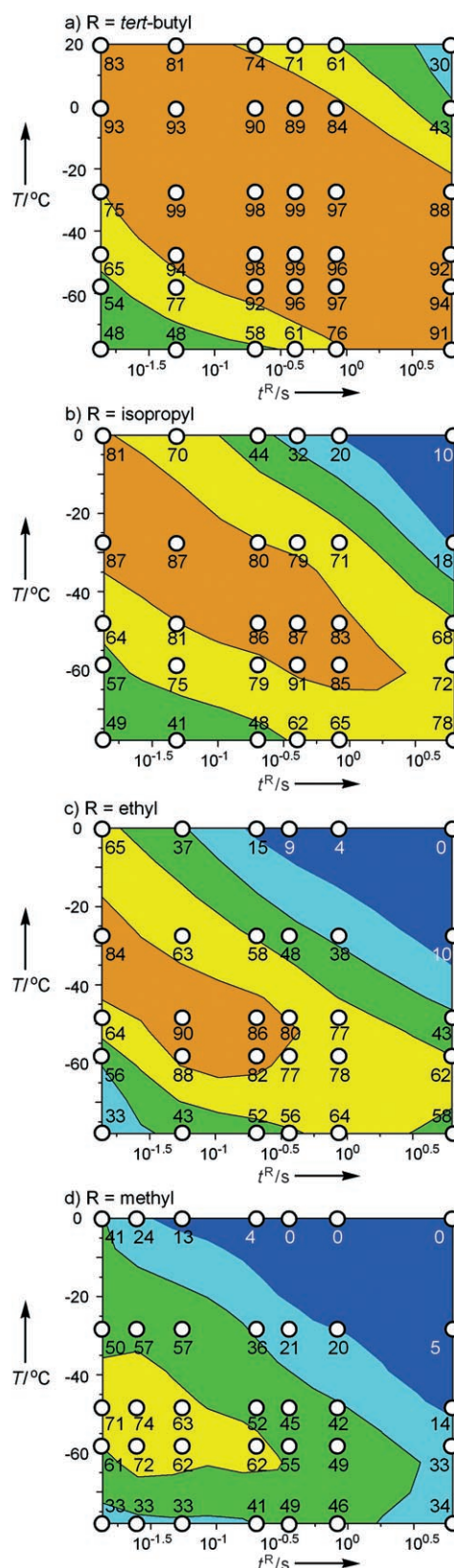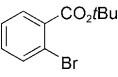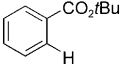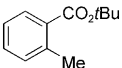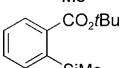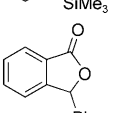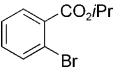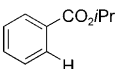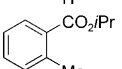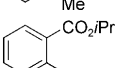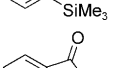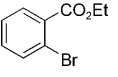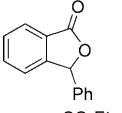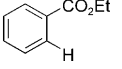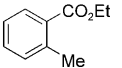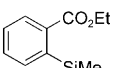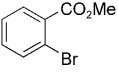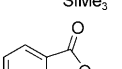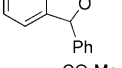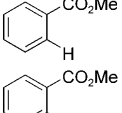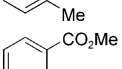

Figure 2. Effects of temperature and residence time of R1 on the yield of **3** in the Br/Li exchange reaction of **1** with *s*BuLi followed by reaction with ROH in the microflow system (■: < 20%, ■: 20–40%, ■: 40–60%, ■: 60–80%, ■: > 80%). T = temperature, t^R = residence time in R1.

iodide, methyl triflate, trimethylsilyl chloride, trimethylsilyl triflate, and benzaldehyde were examined. The reactions were successful and the corresponding products were obtained in good yields (Table 2). Interestingly, methyl iodide can be used as an electrophile for the reactions of **1a** and **1b** whereas, for

the reactions of **1c** and **1d**, methyl triflate should be used instead. The reaction of the aryllithium with methyl iodide is slow, and therefore only the more sterically demanding *tert*-butoxycarbonyl and isopropoxycarbonyl groups can survive until the reaction is complete. However, the reaction of the aryllithium with methyl triflate is much faster. Therefore, the reaction can be conducted at much lower temperatures with shorter residence times. Consequently, even the less sterically demanding ethoxycarbonyl and methoxycarbonyl groups can survive until the reaction is complete.

In summary, we have developed an effective method for the generation and reaction of aryllithium compounds having an alkoxycarbonyl group. The key features of the method are a very short residence time, together with fast mixing[18] and efficient temperature control in microflow systems. A wide ran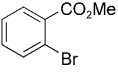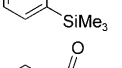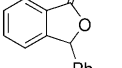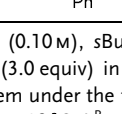ge of alkoxycarbonyl groups including ethoxycarbonyl and methoxycarbonyl groups can tolerate the microflow conditions. These results bode well for the utility of flash chemistry and the reported method adds a new dimension in the chemistry of functionalized organolithium compounds and their applications in organic synthesis.

Table 2: The optimized Br/Li exchange reaction of alkyl *o*-bromobenzoates **1** followed by reaction with an electrophile (E).[a]

Ester	E	Product		Yield [%]
	*t*BuOH	CO₂*t*Bu, H	**3a**	93
	MeI	CO₂*t*Bu, Me	**4a**	88
1a	Me₃SiCl	CO₂*t*Bu, SiMe₃	**5a**	96
	PhCHO	lactone, Ph	**6**	82
	*i*PrOH	CO₂*i*Pr, H	**3b**	87
	MeI / MeOTf	CO₂*i*Pr, Me	**4b**	62 / 82
1b	Me₃SiCl	CO₂*i*Pr, SiMe₃	**5b**	93
	PhCHO	lactone, Ph	**6**	66
	EtOH	CO₂Et, H	**3c**	90
	MeI / MeOTf	CO₂Et, Me	**4c**	12 / 62
1c	Me₃SiCl / Me₃SiOTf	CO₂Et, SiMe₃	**5c**	61 / 79
	PhCHO	lactone, Ph	**6**	70
	MeOH	CO₂Me, H	**3d**	74
	MeOTf	CO₂Me, Me	**4d**	65
1d	Me₃SiOTf	CO₂Me, SiMe₃	**5d**	82
	PhCHO	lactone, Ph	**6**	85

[a] *o*-Bromobenzoates **1a**–**1d** in THF (0.10 M), *s*BuLi in hexane/cyclohexane (0.42 M), and an electrophile (3.0 equiv) in THF (0.60 M) were allowed to react in the microflow system under the following optimized conditions: **1a**: 0°C (t^R = 0.01 s), **1b**: −28°C (t^R = 0.01 s), **1c**: −48°C (t^R = 0.06 s), **1d**: −48°C (t^R = 0.02 s).

Experimental Section

General procedure: A microflow system consisting of two T-shaped micromixers (M1 and M2), two microtube reactors (R1 and R2), and three tube pre-cooling units (P1 (inner diameter ϕ = 1000 μm, length L = 100 cm), P2 (ϕ = 1000 μm, L = 50 cm), and P3 (ϕ = 1000 μm, L = 100 cm)) was used. A solution of an alkyl bromobenzoate (0.10 M) in THF (flow rate: 6.0 mL min⁻¹) and a solution of *s*BuLi (0.42 M) in *n*-hexane/cyclohexane (19:31 v/v, flow rate: 1.5 mL min⁻¹) were introduced to M1 (ϕ = 250 μm) by syringe pumps. The resulting solution was passed through R1 (variable ϕ and L) and was mixed with a solution of an electrophile (0.60 M) in THF (flow rate: 3.0 mL min⁻¹) in M2 (ϕ = 250 μm). The resulting solution was passed through R2 (ϕ = 1000 μm, L = 50 cm). After a steady state was reached, the product solution was collected for 30 s and quenched with 1M aqueous hydrochloric acid. The reaction mixture was analyzed by gas chromatography. After extraction, the crude product was purified by flash chromatography.

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