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Selective Mono Addition of Aryllithiums to Dialdehydes by Micromixing

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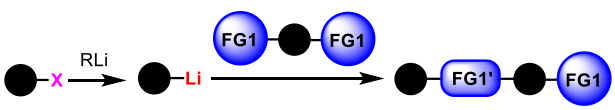
Micromixing enables highly selective mono addition of aryllithiums to dialdehydes. Because the unchanged formyl group in the products can be used for further transformations, the present approach serves as a powerful method for protecting-group-free synthesis.

Chemoselectivity,[1] *i.e.* the differentiation of one of two or more different functional groups, is one of the central issues in organic synthesis, and extensive studies on chemoselective reactions have been reported so far.[2] On the other hand, the selective reactions of one of two identical functional groups remains rather unexplored. Because the remaining functional group in the initial product has similar reactivity to that of the starting material, it is difficult to avoid the subsequent reaction. Eventually, the two functional groups in the starting material react to give the final product. Therefore, controlling such reactions is still a big challenge in current synthetic chemistry.[3]

Recent investigations have revealed that the product selectivity of fast competitive parallel and serial reactions can be significantly improved by using extremely fast micromixing.[4] Based on these reports, we have come up with the following working hypothesis. Extremely fast micromixing in flow microreactors[5-7] enables the selective reaction with one among several identical functional groups. The method would serve as a powerful and straightforward technique of synthesizing molecules bearing unreacted functional groups without protecting them. However, to the best of our knowledge, such an approach has not yet been reported so far. We report herein the results of this proof-of-principle study.

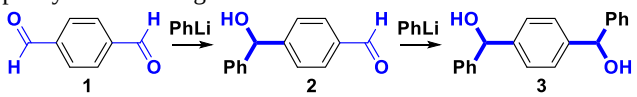


Scheme 1. Selective reaction with one among several identical functional groups

Selective mono addition of highly reactive nucleophiles to dialdehydes are not easy even when one equivalent of a nucleophile is used, because the second reaction is too fast. For example, when one equivalent of phenyllithium was added to a stirred solution of 4-formylbenzaldehyde (**1**) for 3.0 min at –78 ºC in a 50 mL round bottom glass flask equipped with a magnetic stirrer, the mono addition product **2** was obtained in only 33% yield. A significant amount of the di-addition product **3** was obtained in 23% yield while some **1** remained unreacted (Table 1). Reactions at higher temperatures led to a decrease in the yield of desired product **2**. In addition, when a solution of 4-formylbenzaldehyde (1) was added to a stirred solution of one equivalent of phenyllithium, less **2** was generated. In contrast, the use of phenylmagunesium bromide improved the yield of **2** (52%) (See the Supporting information for details).

Despite it is well known that the selectivity generally depends on the stirring method, the size and shape of the reactor, as well as the speed of the addition, the results revealed that controlling the selectivity of such fast reactions is extremely difficult, if not impossible, with batch reactors.

Table 1. Reactions of 4-formylbenzaldehyde (**1**) and phenyllithium using a conventional macro batch reactor



temperature/ºC	method of addition	**1**/%	yield/%	
			2	**3**
-78	addition of PhLi to **1**	39	33	23
-40	addition of PhLi to **1**	37	26	26
-20	addition of PhLi to **1**	40	16	18
0	addition of PhLi to **1**	44	5	12
-78	addition of **1** to PhLi	38	18	30
-40	addition of **1** to PhLi	41	13	29
-20	addition of **1** to PhLi	40	8	26
0	addition of **1** to PhLi	38	5	30

In the next step, we examined the reactions using a flow microreactor system consisting of V-shaped micromixer (ϕ = 250 μm) (**M**) and a microtube reactor (**R**) shown in Figure 1.

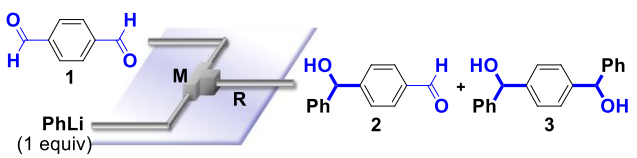


Figure 1. A flow microreactor system for the reaction of **1** with one equiv of PhLi.

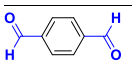
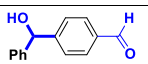
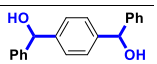
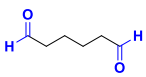
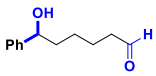
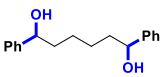
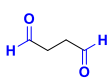
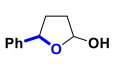
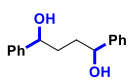
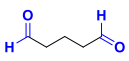
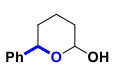
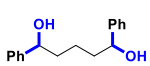
Notably, at high flow rates (total flow rate: 30 mL/min, **2**: 71%, **3**: 7%), the selectivity was remarkably high, and the desired compound **2** was obtained in good yield at -78 °C. Generally, the mixing speed in a micromixer increases with an increase in the flow speed.[8] In fact, an increase in the total flow rate led to the increase in the yield of **2** and the decrease in the yield of **3** as shown in Table 2. The results indicate that extremely fast mixing accounts for high selectivity.

Table 2. Reactions of 4-formylbenzaldehyde (**1**) and phenyllithium using flow microreactors

temperature /°C	total flow rate /ml min^{-1}	**1**/%	yield/%	
			2	**3**
-78	2.5	61	17	18
	5.0	43	18	12
	10	42	31	26
	20	20	64	6
	30	21	71	7
-40	30	24	54	21
-20	30	48	29	13
0	30	39	33	31

Based on the great influence of mixing greatly on the reaction selectivity, we next examined the reactions of other compounds having two formyl groups with phenyllithium. As shown in Table 3, high selectivity was achieved with flow microreactor system, whereas the use of a batch reactor led to much poorer selectivity. Moreover, the other unaffected formyl group will be able to use for further transformations in order to generate more complex compounds.

Table 3. The reaction of dialdehydes with PhLi using the flow microreactor system.

difunctional electrophiles	reaction method	temperature (°C)	yield (%) mono-addition product	yield (%) di-addition product
				
	batch macro	-78	33	23
	flow micro	-78	71	7
				
	batch macro	-70	57	10
		-40	54	14
		-20	52	21
		0	45	26
	flow micro	-70	70	15
		-40	68	15
		-20	70	16
		0	67	18
				
	batch macro	-40	68	6
		-20	79	10
		0	75	12
	flow micro	-40	88	7
		-20	81	3
		0	89	3
				
	batch macro	-20	47	6
	flow micro	-20	74	6

We have already reported that aryllithiums bearing electrophilic functional groups can be rapidly generated and used in a subsequent reaction before they decompose by virtue of high-resolution reaction time control in flow microreactor systems.[9] The present finding prompted us to integrate[10] the generation of functional aryllithiums and their selective reactions with dialdehydes using an integrated flow microreactor system (Figure 2). The residence time (t^{R1}) was optimized individually for the halogen-lithium exchange reactions of each functionalized aryl halides (See Supporting Information for the details). In this case we have to worry about the competition between the formyl groups on the electrophile (**FG1**)[11] and a functional group on the nucleophile (**FG2**)[12] as well. The reactions of various aryllithiums bearing electrophilic functional groups were examined. As shown in Table 4, selective mono addition to dialdehydes occurred without affecting nitro[13], and cyano groups in the aryllitiums to give desired products in good yields.

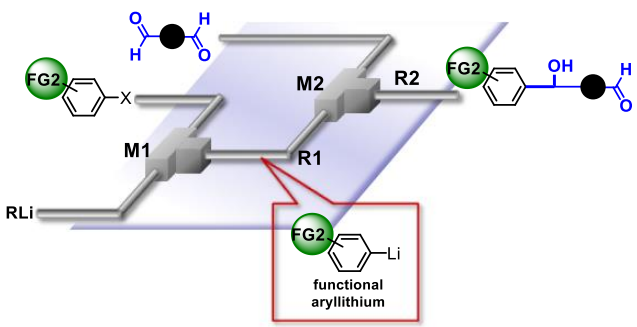
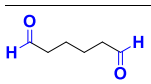
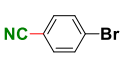
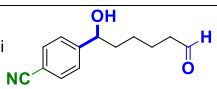
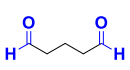
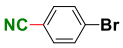
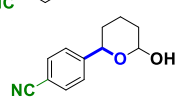
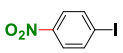
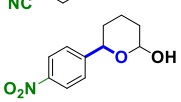
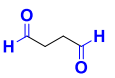
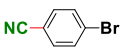
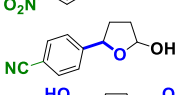
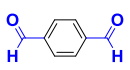
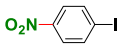
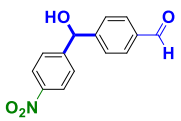


Figure 2. An integrated flow microreactor system for selective reactions of dialdehydes with functional organolithiums generated by halogen-lithium exchange.

Table 4. Reactions of dialdehydes with functional aryllithiums.

	functional aryl halide	lithiating agent	product	yield/%
		*n*-BuLi		91
		*n*-BuLi		79
		PhLi		62
		*n*-BuLi		71
		PhLi		57

In conclusion, we have developed a flash method for highly selective mono addition of aryllithiums to aromatic and aliphatic compounds having two formyl groups using an

integrated flow microreactor system. Notably, aryllithiums bearing electrophilic functional groups can be used without affecting their functionality. The present approach serves as a powerful method for protecting-group-free synthesis using organolithium compounds and opens a new possibility in the synthesis of polyfunctional organic molecules.

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