Microreactors

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Nitro-Substituted Aryl Lithium Compounds in Microreactor Synthesis: Switch between Kinetic and Thermodynamic Control**

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The nitro group is one of the strongest electron-withdrawing groups. It has great potential in the activation of organic molecules to drive and direct reactions that are otherwise difficult to perform. However, the use of nitro compounds in organic synthesis[1] has been very limited, presumably because of their incompatibility with various nucleophilic and electrophilic reagents.[2] For example, a nitro group reacts with organometallic compounds, such as organolithium and Grignard reagents, very rapidly.[3] Therefore, the generation of aryl lithium and aryl magnesium compounds with a nitro group in the *ortho* position is possible only at very low temperatures.[4,5] Moreover, the generation of *m*- or *p*-nitro-substituted aryl lithium and aryl magnesium compounds in a conventional manner has been reported to be very difficult.[6] We envisioned that the concept of flash chemistry could provide a solution to this problem.[7]

Herein we report that a microflow system[8,9] enables the generation and transformation of *o*-, *m*-, and *p*-nitro-substituted aryl lithium compounds in a controlled manner.[10] Furthermore, either the kinetically preferred or the thermodynamically preferred aryl lithium reagent can be used selectively through control of the residence time.

In preliminary studies, we found that PhLi was an effective reagent for the halogen–lithium exchange of halonitrobenzenes, whereas MeLi, *n*BuLi, and *s*BuLi gave the products in low yields (see the Supporting Information for details). Therefore, we decided to use PhLi in the following studies.

The microflow system used consisted of two T-shaped micromixers (M1 and M2) and two microtube reactors (R1 and R2; Figure 1). Aryl lithium reagents were generated from *o*-iodonitrobenzene (**1a**), *m*-iodonitrobenzene (**1b**), and *p*-iodonitrobenzene (**1c**) by varying the temperature (*T*) of the cooling bath and the residence time (t^R) in R1, and were trapped with methanol in R2.

Figure 2 summarizes the results obtained by varying the temperature and residence time. Irrespective of the substitution pattern, the products were formed in high yields (> 80%)

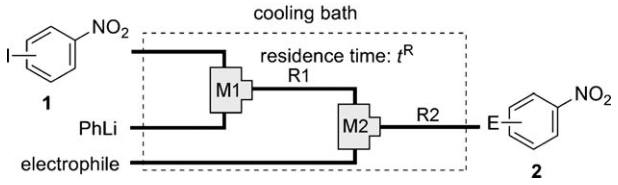

Figure 1. A microflow system for the I–Li exchange reaction of **1** followed by the reaction of the lithiated species with electrophiles. Flow rate of the solution of **1** (0.10 M) in THF: 6.00 mL min^{-1}; flow rate of the solution of PhLi (0.42 M) in Et_2O and cyclohexane (72:28 v/v): 1.50 mL min^{-1}; flow rate of the solution of an electrophile (0.60 M) in THF: 3.00 mL min^{-1}.

at 0 °C when an appropriate residence time was chosen. The possibility of carrying the reactions out at this temperature is a significant advantage of a microflow system over a conventional macrobatch system, which requires much lower temperatures (yield of **2** (E = H): 70% from **1a**, 43% from **1b**, 39% from **1c** at −78 °C). The yields of the reactions in the microflow system decreased with an increase in t^R, presumably because of decomposition of the nitrophenyllithium compounds. The *o*-nitrophenyllithium reagent generated from **1a** was more stable than the *m*- and *p*-nitrophenyllithium species generated from **1b** and **1c**, respectively, presumably because of a chelation effect. Slightly better yields were observed when the reactions were carried out at −28 °C.

Under the optimized conditions, lithium reagents derived from **1a–c** reacted with various electrophiles to give the desired products in good yields (Table 1).

The reaction of **3** demonstrates the potential of the microflow method (Figure 3). Treatment with PhLi (t^R = 0.06 s at −48 °C) followed by an aldehyde gave the product **4** in 84% yield. Belardi and Micalizio recently used **3** in the synthesis of macbecin I.[11] In their synthesis, **3** was reduced to the amine and protected. An aryl lithium reagent containing a protected amino group was then generated and treated with an aldehyde.[12] After methylation, the amino group was deprotected. The present transformation via a nitro-substituted aryl lithium reagent would serve as an alternative straightforward route. After the treatment of lithiated **3** with an aldehyde, O-methylation of the product and simple reduction of the nitro group should give the desired compound without protection–deprotection processes.[13]

In the reaction of **3**, an increase in t^R led to the formation of a significant amount of the isomeric product **5**, which resulted from isomerization of the aryl lithium reagent.[14] With a residence time of 63 seconds, **5** was obtained exclusively; thus, complete isomerization occurred during this period of time. This experiment demonstrates that the

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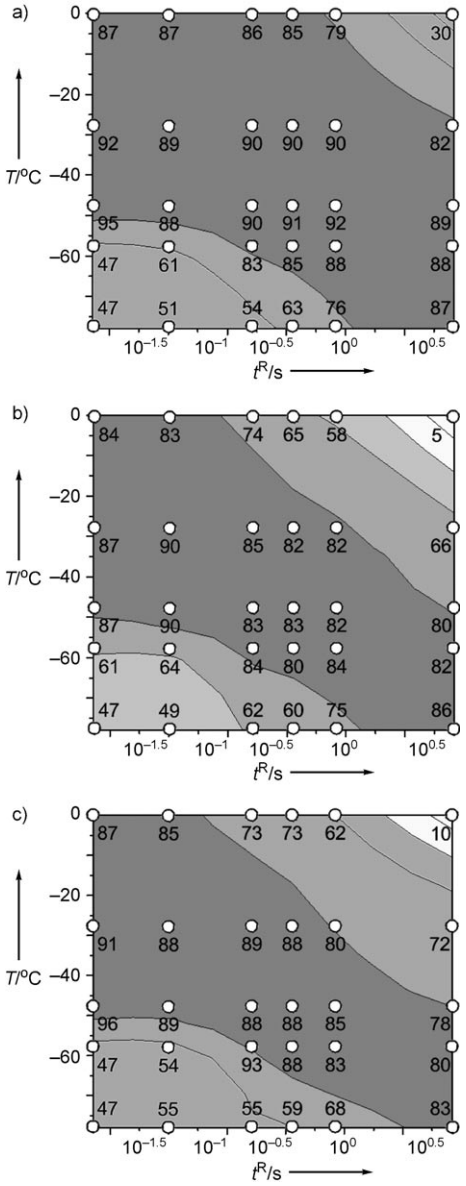
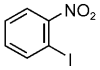
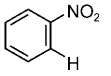
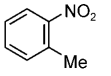
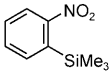
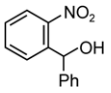
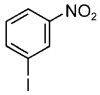
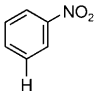
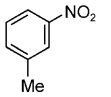
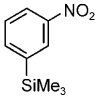
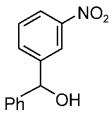
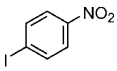
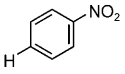
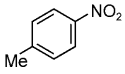
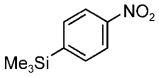
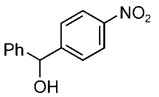


Figure 2. Effects of the reaction temperature and residence time on the yield of nitrobenzene in the I–Li exchange reaction of a) *o*-iodonitrobenzene (**1a**), b) *m*-iodonitrobenzene (**1b**), and c) *p*-iodonitrobenzene (**1c**) with PhLi in the microflow system.

microflow method is very effective for the selective use of either the kinetically formed or the thermodynamically preferred organolithium reagent, whereby the desired reactivity can be selected by controlling the residence time.

In conclusion, we have developed a microflow method for the generation and transformation of *o*-, *m*-, and *p*-nitrophenyllithium reagents. Such reactions are very difficult or impossible with a conventional macrobatch system. Furthermore, the selective use of either kinetically formed or thermodynamically preferred organolithium reagents by changing the residence time demonstrates the power of the microflow method in organic synthesis.

Table 1: The I–Li exchange reaction of iodonitrobenzenes **1**, followed by reaction with an electrophile.[a]

1		Electrophile	Product	Yield [%][b]
	**1a**	MeOH		87
		MeI		36
		MeOTf		82
		Me_3SiCl		62
		Me_3SiOTf		88
		PhCHO		93
	**1b**	MeOH		87
		MeI		44
		MeOTf		86
		Me_3SiCl		85
		PhCHO		93
	**1c**	MeOH		91
		MeI		46
		MeOTf		82
		Me_3SiCl		70
		Me_3SiOTf		80
		PhCHO		86

[a] For substrate **1a**, $T = 0\,°C$ ($t^R = 0.01$ s); for **1b** and **1c**, $T = -28\,°C$ ($t^R = 0.01$ s). [b] The yield was determined by GC. Tf = trifluoromethanesulfonyl.

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 precooling units (P1 (inner diameter $\phi = 1000$ μm, length $L = 100$ cm), P2 ($\phi = 1000$ μm, $L = 50$ cm), and P3 ($\phi = 1000$ μm, $L = 100$ cm)) was used. A solution of iodonitrobenzene (**1**; 0.10 M) in THF (flow rate: 6.0 mL min^{-1}) and a solution of PhLi (0.42 M) in Et_2O and cyclohexane (72:28 v/v; flow rate: 1.5 mL min^{-1}) were introduced into M1 ($\phi = 250$ μm) by syringe pumps. The resulting solution was passed through R1 and was mixed with a solution of an electrophile (0.60 M) in THF (flow rate: 3.0 mL min^{-1}) in M2 ($\phi = 250$ μm). The resulting solution was passed through R2 ($\phi = 1000$ μm, $L = 50$ cm). After a steady state was reached, the product solution was collected for 30 s and quenched with H_2O. The reaction mixture was analyzed by GC.

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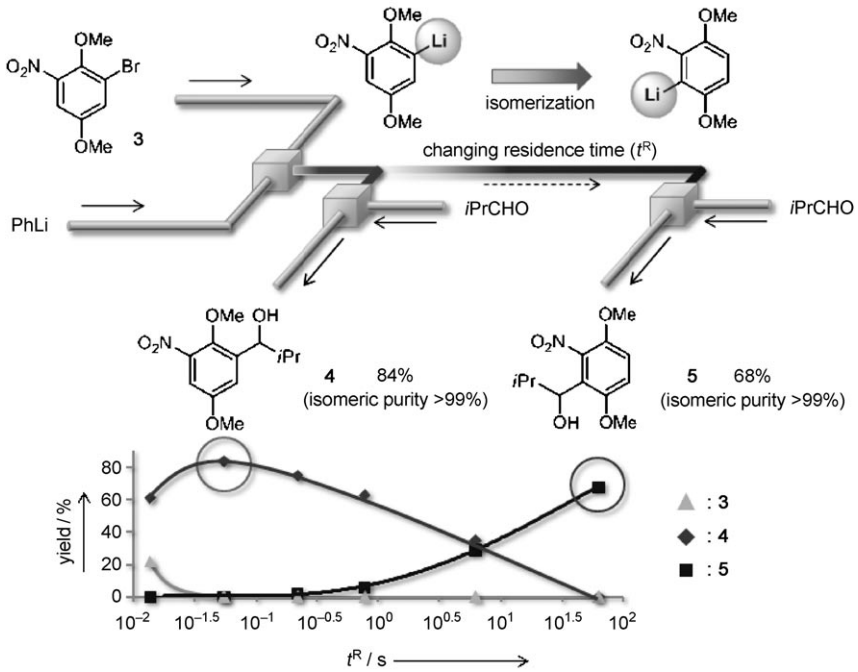

Figure 3. Switch between kinetic and thermodynamic control by changing the residence time.

Keywords: arenes · kinetic control · lithiation · microreactors · thermodynamic control

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