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Reactions of Difunctional Electrophiles with Functionalized Aryllithium Compounds: Remarkable Chemoselectivity by Flash Chemistry**

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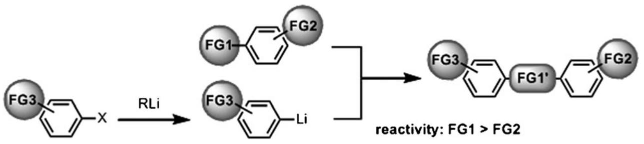
Abstract: *Flash chemistry using flow microreactors enables highly chemoselective reactions of difunctional electrophiles with functionalized aryllithium compounds by virtue of extremely fast micromixing. The approach serves as a powerful method for protecting-group-free synthesis using organolithium compounds and opens a new possibility in the synthesis of polyfunctional organic molecules.*

Flow chemistry[1–3] has attracted significant attention by researchers from both academia and industries. Various benefits over conventional batch processes include increased controllability, safety, and selectivity because of improved heat and mass transfer and shorter residence times. In particular, flash chemistry[4,5] using flow microreactors enables synthetic transformations that are very difficult or impossible to achieve by conventional batch reactions. Herein we report a proof-of-principle study that shows how remarkable chemoselectivity that is difficult to attain by conventional batch processes, can be achieved by flash chemistry.

Chemoselectivity is defined as “the preferential reaction of a chemical reagent or reactive species with one of two or more different functional groups”, and is one of the central issues in organic synthesis. The development of new methods or principles for controlling chemoselectivity is still a big challenge in current synthetic chemistry.[6] Chemoselectivity is particularly important for reactions of highly reactive species, such as organolithium compounds.[7] Herein we focused on the following transformation, that is, the reactions with difunctional electrophiles, such as the reactions of aromatic compounds bearing two different electrophilic functional groups (**FG1** and **FG2**) with aryllithium compounds also bearing an electrophilic functional group (**FG3**; Scheme 1). The transformation should serve as a useful method for protecting-group-free synthesis[8] of a variety of polyfunctional organic molecules.



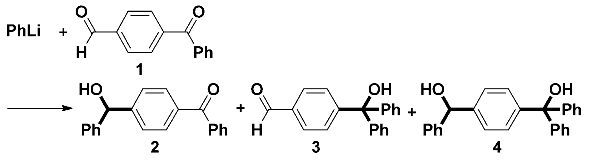
Scheme 1. Reactions of functionalized aryllithium compounds with aromatic compounds bearing two electrophilic functional groups.

To achieve the transformation, we must solve the following three problems:

1. A lithiating agent (RLi) should undergo halogen–lithium exchange to generate a functionalized aryllithium without affecting **FG3**.[9]
2. The functionalized aryllithium should react selectively with difunctional electrophiles at **FG1** without affecting **FG2**.[10,11]
3. The functionalized aryllithium should not attack **FG3**.

We have already solved the first problem by high-resolution control of the reaction time by space in flow microreactors, but the second problem seems to be more challenging because controlling the reaction time is not effective. We envisaged extremely fast micromixing[12] to be effective in solving the second problem, because mixing is crucial for the product selectivity of fast competitive parallel and serial reactions.[13]

One may think that chemoselective nucleophilic reactions of difunctional electrophiles are easy if the reactivity of **FG1** is higher than that of **FG2**. However, this is not true if the reaction is very fast. In fact, the reaction of 4-benzoylbenzaldehyde (**1**) with one equivalent of phenyllithium (Scheme 2) in a batch reactor (50 mL round-bottom glass flask with a magnetic stirrer) leads to the formation of a mixture of three products, that is, **2**, **3**, and **4**, although aldehyde carbonyl groups are generally more reactive than ketone carbonyl groups.



Scheme 2. Reaction of 4-benzoylbenzaldehyde (**1**) with one equivalent of PhLi in a batch macro reactor.

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Table 1: Reactions of **1** with PhLi using a conventional macro batch reaction.

T [°C]	Method of addition	**1** [%][a,b]	Yield [%][b]		
			2	**3**	**4**
−78	PhLi to **1**	35	28	7	25
−40	PhLi to **1**	36	23	7	26
−20	PhLi to **1**	36	20	7	30
0	PhLi to **1**	36	12	6	30
20	PhLi to **1**	39	12	5	33
−78	**1** to PhLi	67	6	2	26
−40	**1** to PhLi	63	5	1	27
−20	**1** to PhLi	54	4	1	35
0	**1** to PhLi	49	2	1	37
20	**1** to PhLi	45	1	1	40
−78	simultaneous addition of **1** and PhLi	49	16	9	26

[a] Recovered starting material. [b] Determined by GC analysis using an internal standard (pentadecane).

The addition of one equivalent of phenyllithium to a stirred solution of **1** for 1.0 min gave **2** at −78°C in only 28% yield, and a significant amount of **4** (25%) was produced together with unchanged **1** (Table 1). Interestingly, compound **3**, which is formed by the reaction of PhLi with the ketone carbonyl group without affecting the more reactive aldehyde carbonyl group, was also obtained in 7% yield. The increase in the temperature caused a decrease in the yield of desired **2**. The reverse addition resulted in lower yields of **2**, and the simultaneous addition did not give better results. Although the selectivity should generally also depend on the size and shape of the reactor, the stirring method, and the speed of the addition, the present data demonstrate the limitations of the batch method for achieving this type of chemoselectivity of fast reactions.

In the next step, we examined the reactions using a flow microreactor system composed of a V-shaped micromixer ($\varphi = 250\ \mu$m; **M**) and a microtube reactor (**R**) shown in Figure 1. Remarkable chemoselectivity was achieved and the desired compound **2** was obtained in high selectivity at high flow rates (total flow rate: 30 mL min^{-1}, **2**: 73%, **3**: 1%, **4**: 7%). It is known that the mixing speed in a micromixer decreases with a decrease in the flow speed.[14] In fact, the decrease in the total flow rate resulted in a decrease in the yield of **2** and increases in the yields of **3** and **4** (Figure 2). Interestingly, the yield of **3** also decreases with an increase in the flow rate, although the reason is not clear at present. The present observations indicate that extremely fast mixing is responsible for the high selectivity.

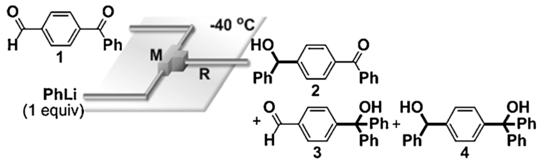


Figure 1. A flow microreactor system for the reaction of **1** with one equivalent of PhLi.

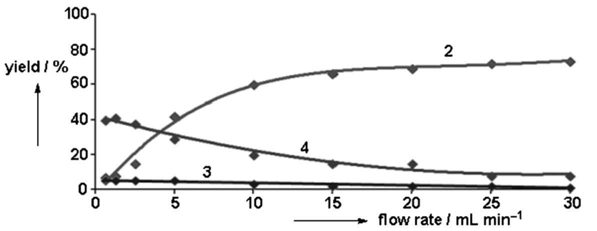
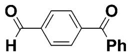
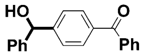
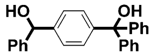
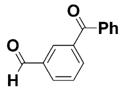
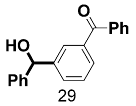
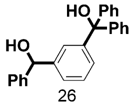
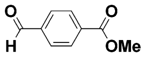
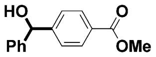
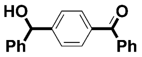


Figure 2. Plots of the yields of **2**, **3**, and **4** against the total flow rate for the reaction of **1** with one equivalent of PhLi.

With the remarkable effect of micromixing on the selectivity established, we next examined the reactions of various benzaldehydes having an electrophilic functional group, such as ketone carbonyl, ester carbonyl, nitro,[15] and cyano groups with phenyllithium (Table 2). High chemoselectivity was obtained by using the flow microreactor system, whereas the use of a batch reactor resulted in much lower selectivity. Furthermore, the reactions of phenylisocyanates having a cyano or an alkoxycarbonyl group with PhLi were also accomplished with high chemoselectivity, although the reactions in a batch reactor gave complex mixtures.

Table 2: Reaction of aromatic compounds having two different electrophilic functional groups with PhLi using the flow microreactor system.

Difunctional electrophile	Reaction method	Yield [%][a]	
		Mono-addition product	Di-addition product
			
	batch macro	28	25
	flow micro	73	7
			
	batch macro	29	26
	flow micro	71	7
			
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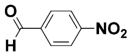
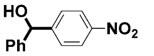
	flow micro	76	0
			
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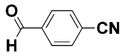
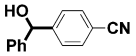
	flow micro	76	
			
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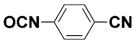
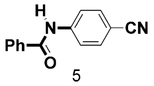
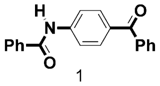
	flow micro	89	
			
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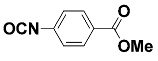
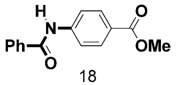
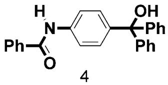
			
	batch macro	18	4
	flow micro	91	trace

[a] Yields of products were determined by GC analysis using an internal standard.

Recently, we have reported that aryllithium compounds bearing cyano, nitro, alkoxycarbonyl, and ketone carbonyl groups can be rapidly generated and used in a subsequent reaction before they decompose by virtue of high-resolution control of the reaction time in flow microreactor systems.[5] The present finding prompted us to integrate[16] the generation of functionalized aryllithium compounds and their chemoselective reactions with difunctional electrophiles using an integrated flow microreactor system (Figure 3). The residence time (t^{R1}) was optimized individually for the halogen–lithium exchange reactions of each of the functionalized aryl halides (see the Supporting Information for details). In this case we have to worry about the competition between two electrophilic functional groups on the electrophile (**FG1** and **FG2**), and also about the competition between functional groups on the electrophile (**FG1** and **FG2**) and a functional group on the nucleophile (**FG3**).

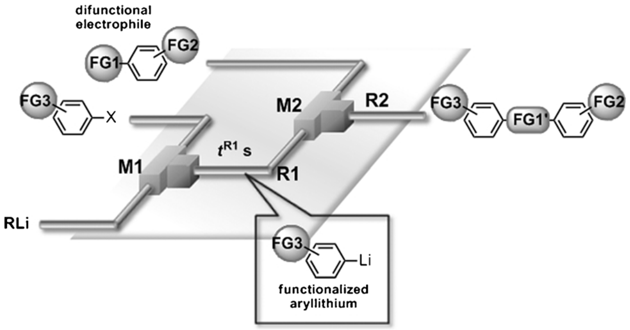


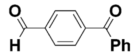
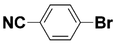
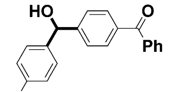
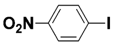
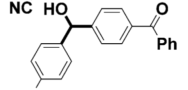
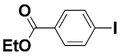
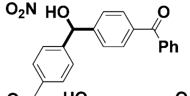
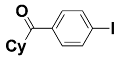
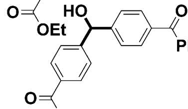
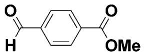
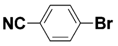
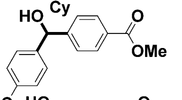
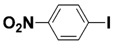
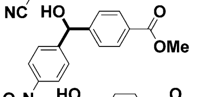
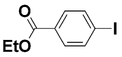
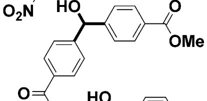
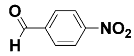
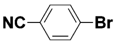
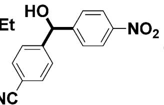
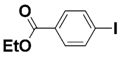
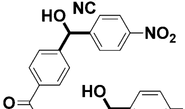
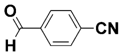
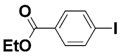
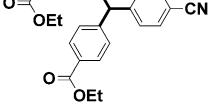
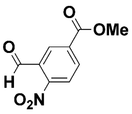
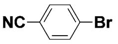
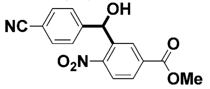
Figure 3. An integrated flow microreactor system for the chemoselective reactions of aromatic compounds having two different electrophilic functional groups with functionalized organolithium compounds generated by halogen–lithium exchange.

The reactions of various aryllithium compounds bearing electrophilic functional groups were examined (Table 3). When one equivalent of functionalized aryllithium was used, the aldehyde carbonyl group reacted selectively without affecting other electrophilic functional groups, such as ketone carbonyl, ester carbonyl, nitro, and cyano groups, to give the desired products in good yields. Furthermore, the functional groups on the nucleophile were not affected. It is also noteworthy that a benzaldehyde that bears two other electrophilic functional groups, such as an ester carbonyl group and a nitro group (a trifunctional electrophile), also reacted chemoselectively.

The competition between an isocyanate group and other electrophilic functional groups present on the aryllithium compound is also interesting (Table 4). The nucleophilic addition took place selectively on the isocyanate group without affecting other functional groups on both the electrophile and the nucleophile. The reactions seem to be useful because amides having two functional groups can be easily synthesized.

To demonstrate the utility of the present flash method, we examined a chemoselective three-component coupling using benzaldehyde with a ketone carbonyl group (**1**) in an integrated flow microreactor system (Figure 4). The reaction with *p*-cyanophenyllithium at the aldehyde carbonyl group followed by the reaction with *p*-nitrophenyllithium at the ketone carbonyl group was successfully achieved to obtain the desired product in 61% yield. High productivity (156 mg min^{-1}) of the present method as a result of high flow rates and short residence times is also noteworthy.

Table 3: Reactions of benzaldehydes having electrophilic functional groups with functionalized aryllithium compounds.

Difunctional electrophile	Functionalized aryl halide	Lithiating agent	Product	Yield [%] [a]
		BuLi		78
		PhLi		79[b]
		PhLi		67
		MesLi		65
		BuLi		86
		PhLi		90
		PhLi		78
		BuLi		86
		PhLi		69
		PhLi		74
		BuLi		75

[a] Yield of products were determined by GC analysis using an internal standard, unless otherwise stated. [b] Yield of isolated product.

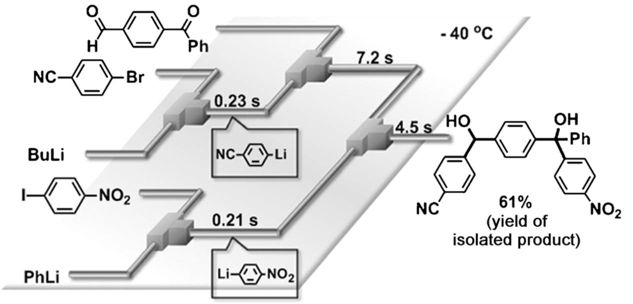
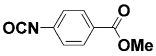
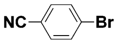
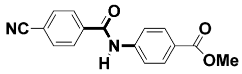
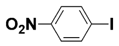
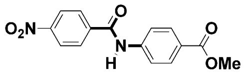
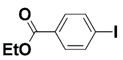
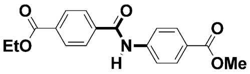
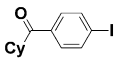
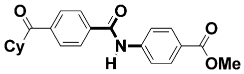
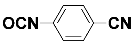
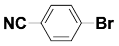
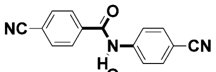
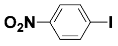
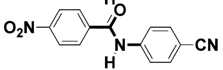
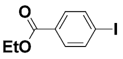
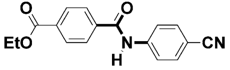
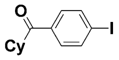
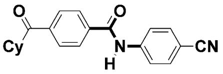


Figure 4. Chemoselective three-component coupling using an integrated flow microreactor system.

In conclusion, we have developed a flash method for highly chemoselective reactions of aromatic compounds

Table 4: Reactions of phenylisocyanates having electrophilic functional groups with functionalized aryllithium compounds.

Difunctional electrophile	Functionalized aryl halide	Lithiating agent	Product	Yield [%][a]
		BuLi		79
		PhLi		90
		PhLi		72
		MesLi		73
		BuLi		74
		PhLi		74
		PhLi		71
		MesLi		52[b]

[a] Yields of products were determined by GC analysis using an internal standard, unless otherwise stated. [b] Yields of isolated products.

having two electrophilic functional groups with unstable aryllithium compounds bearing an electrophilic functional group using integrated flow microreactor systems. 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.

Experimental Section

Typical procedure for the generation of functionalized aryllithium compounds followed by the selective reaction with difunctional electrophiles in a flow microreactor system (Figure 3): A flow microreactor system consisting of a T-shaped micromixer ($\varphi = 250$ μm; M1), a V-shaped micromixer ($\varphi = 250$ μm; M2), two microtube reactors (R1 and R2), and three pre-cooling units (P1 (inner diameter $\varphi = 1000$ μm, length $L = 100$ cm), P2 ($\varphi = 1000$ μm, $L = 50$ cm) and P3 ($\varphi = 1000$ μm, $L = 200$ cm)) was used. The system was dipped in a cooling bath of −40 °C. A solution of a halobenzene (0.10 M in THF; flow rate: 6.8 mL min^{-1}) and a solution of a lithiating agent (0.42 M in hexane; flow rate: 1.4 mL min^{-1}) were introduced to M1 by syringe pumps. The resulting solution was passed through R1 (residence time t^{R1} (s)) and was mixed with a solution of a difunctional electrophile (0.040 M in THF; flow rate: 14 mL min^{-1}) in M2. The resulting solution was passed through R2 ($\varphi = 1000$ μm, $L = 200$ cm). After a steady state was reached, an aliquot of the product solution was collected in a flask containing the saturated aqueous NH_4Cl solution for 30 s. The reaction mixture was analyzed by GC, and the product was isolated by column chromatography on silica gel.

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Keywords: chemoselectivity · flash chemistry · flow chemistry · microreactors · organolithium compounds

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[1] Books on flow chemistry and flow microreactor synthesis: a) W. Ehrfeld, V. Hessel, H. Löwe, *Microreactors*, Wiley-VCH, Weinheim, **2000**; b) V. Hessel, S. Hardt, H. Löwe, *Chemical Micro Process Engineering*, Wiely-VCH, Weinheim, **2004**; c) *Micro Precess Engineering* (Eds.: V. Hessel, A. Renken, J. C. Schouten, J. Yoshida), Wiley-Blackwell, Chichester, **2009**; d) T. Wirth, Ed, *Microreactors in Organic Chemistry and Catalysis, 2nd ed.*, Wiley, New York, **2013**.

[2] Reviews on flow chemistry and flow microreactor synthesis: a) K. Jähnisch, V. Hessel, H. Löwe, M. Baerns, *Angew. Chem. Int. Ed.* **2004**, *43*, 406; *Angew. Chem.* **2004**, *116*, 410; b) G. N. Doku, W. Verboom, D. N. Reinhoudt, A. van den Berg, *Tetrahedron* **2005**, *61*, 2733; c) J. Yoshida, A. Nagaki, T. Iwasaki, S. Suga, *Chem. Eng. Technol.* **2005**, *28*, 259; d) P. Watts, S. J. Haswell, *Chem. Soc. Rev.* **2005**, *34*, 235; e) K. Geyer, J. D. C. Codée, P. H. Seeberger, *Chem. Eur. J.* **2006**, *12*, 8434; f) A. J. deMello, *Nature* **2006**, *442*, 394; g) H. Song, D. L. Chen, R. F. Ismagilov, *Angew. Chem. Int. Ed.* **2006**, *45*, 7336; *Angew. Chem.* **2006**, *118*, 7494; h) J. Kobayashi, Y. Mori, S. Kobayashi, *Chem. Asian J.* **2006**, *1*, 22; i) M. Brivio, W. Verboom, D. N. Reinhoudt, *Lab Chip* **2006**, *6*, 329; j) B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. McQuade, *Chem. Rev.* **2007**, *107*, 2300; k) B. Ahmed-Omer, J. C. Brandt, T. Wirth, *Org. Biomol. Chem.* **2007**, *5*, 733; l) P. Watts, C. Wiles, *Chem. Commun.* **2007**, 443; m) T. Fukuyama, M. T. Rahman, M. Sato, I. Ryu, *Synlett* **2008**, 151; n) R. L. Hartman, K. F. Jensen, *Lab Chip* **2009**, *9*, 2495; o) J. P. McMullen, K. F. Jensen, *Annu. Rev. Anal. Chem.* **2010**, *3*, 19; p) J. Yoshida, H. Kim, A. Nagaki, *ChemSusChem* **2011**, *4*, 331; q) C. Wiles, P. Watts, *Green Chem.* **2012**, *14*, 38; r) A. Kirschning, L. Kupracz, J. Hartwig, *Chem. Lett.* **2012**, *41*, 562; s) D. T. McQuade, P. H. Seeberger, *J. Org. Chem.* **2013**, *78*, 6384; t) K. S. Elvira, X. C. Solvas, R. C. R. Wootton, A. J. deMello, *Nat. Chem.* **2013**, *5*, 905; u) J. C. Pastre, D. L. Browne, S. V. Ley, *Chem. Soc. Rev.* **2013**, *42*, 8849; v) I. R. Baxendale, *J. Chem. Technol. Biotechnol.* **2013**, *88*, 519; w) J. Yoshida, A. Nagaki, D. Yamada, *Drug Discovery Today Technol.* **2013**, *10*, e53; x) T. Fukuyama, T. Totoki, I. Ryu, *Green Chem.* **2014**, *16*, 2042.

[3] Some selected recent examples: a) D. Cantillo, M. Baghbanzadeh, C. O. Kappe, *Angew. Chem. Int. Ed.* **2012**, *51*, 10190; *Angew. Chem.* **2012**, *124*, 10337; b) W. Shu, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2012**, *51*, 5355; *Angew. Chem.* **2012**, *124*, 5451; c) A. Nagaki, Y. Moriwaki, J. Yoshida, *Chem. Commun.* **2012**, *48*, 11211; d) F. Lévesque, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2012**, *51*, 1706; *Angew. Chem.* **2012**, *124*, 1738; e) K. C. Basavaraju, S. Sharma, R. A. Maurya, D. P. Kim, *Angew. Chem. Int. Ed.* **2013**, *52*, 6735; *Angew. Chem.* **2013**, *125*, 6867; f) C. Brancour, T. Fukuyama, Y. Mukai, T. Skrydstrup, I. Ryu, *Org. Lett.* **2013**, *15*, 2794; g) J. D. Nguyen, B. Reiß, C. Dai, C. R. J. Stephenson, *Chem. Commun.* **2013**, *49*, 4352; h) C. Battilocchio, J. M. Hawkins, S. V. Ley, *Org. Lett.* **2013**, *15*, 2278; i) A. S. Kleinke, T. F. Jamison, *Org. Lett.* **2013**, *15*, 710; j) K. Asano, Y. Uesugi, J. Yoshida, *Org. Lett.* **2013**, *15*, 2398; k) L. Guetzoyan, N. Nikbin, I. R. Baxendale, S. V. Ley, *Chem. Sci.* **2013**, *4*, 764; l) S. Fuse, Y. Mifune, T. Takahashi, *Angew. Chem. Int. Ed.* **2014**, *53*, 851; *Angew. Chem.* **2014**, *126*, 870; m) Z, He, T. F. Jamison, *Angew. Chem. Int. Ed.* **2014**, *53*, 3353; *Angew. Chem.* **2014**, *126*, 3421; n) A. Nagaki, Y. Takahashi, J. Yoshida, *Chem. Eur. J.* **2014**, *20*, 7931.

[4] Flash chemistry is defined as a field of chemical synthesis in which extremely fast reactions are conducted in a highly controlled manner to produce the desired compounds with high selectivity: a) J. Yoshida, *Flash Chemistry, Fast Organic*

Synthesis in Microsystems, Wiley-Blackwell, Chichester, **2008**; b) J. Yoshida, A. Nagaki, T. Yamada, *Chem. Eur. J.* **2008**, *14*, 7450; c) J. Yoshida, Y. Takahashi, A. Nagaki, *Chem. Commun.* **2013**, *49*, 9896.

[5] a) A. Nagaki, H. Kim, J. Yoshida, *Angew. Chem. Int. Ed.* **2008**, *47*, 7833; *Angew. Chem.* **2008**, *120*, 7951; b) A. Nagaki, H. Kim, J. Yoshida, *Angew. Chem. Int. Ed.* **2009**, *48*, 8063; *Angew. Chem.* **2009**, *121*, 8207; c) A. Nagaki, H. Kim, Y. Moriwaki, C. Matsuo, J. Yoshida, *Chem. Eur. J.* **2010**, *16*, 11167; d) A. Nagaki, H. Kim, C. Matsuo, H. Usutani, J. Yoshida, *Org. Biomol. Chem.* **2010**, *8*, 1212; e) H. Kim, A. Nagaki, J. Yoshida, *Nat. Commun.* **2011**, *2*, 264; f) Y. Tomida, A. Nagaki, J. Yoshida, *J. Am. Chem. Soc.* **2011**, *133*, 3744; g) A. Nagaki, C. Matsuo, S. Kim, K. Saito, A. Miyazaki, J. Yoshida, *Angew. Chem. Int. Ed.* **2012**, *51*, 3245; *Angew. Chem.* **2012**, *124*, 3299.

[6] a) R. W. Hoffmann, *Synthesis* **2006**, 3531; b) N. A. Afagh, A. K. Yudin, *Angew. Chem. Int. Ed.* **2010**, *49*, 262; *Angew. Chem.* **2010**, *122*, 270.

[7] a) J. E. Baldwin, R. M. Williams, *Organolithiums*: *Selectivity for Synthesis*, Pregamon, Amsterdam, **2002**; b) N. Chinkov, H. Chechik, S. Majumdar, A. Liard, I. Marek, *Synthesis* **2002**, *17*, 2473.

[8] I. S. Young, P. S. Baran, *Nat. Chem.* **2009**, *1*, 193.

[9] a) P. Knochel, *Handbook of Functionalized Organometallics*, Wiley-VCH, Weinheim, **2005**; b) A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem. Int. Ed.* **2000**, *39*, 4414; *Angew. Chem.* **2000**, *112*, 4584; c) W. E. Parham, C. K. Bradsher, *Acc. Chem. Res.* **1982**, *15*, 300.

[10] a) V. Péron, E. Porhiel, V. Ferrand, H. Le Bozec, *J. Organomet. Chem.* **1997**, *539*, 201; b) A. L. K. S. Shun, E. T. Chernick, S. Eisler, R. R. Tykwinski, *J. Org. Chem.* **2003**, *68*, 1339; c) C. W. Chen, T. Y. Luh, *J. Org. Chem.* **2008**, *73*, 8357; d) K. D. Safa, J. V. Mardipour, Y. M. Oskoei, *J. Organomet. Chem.* **2011**, *696*, 802; e) K. D. Safa, T. Shokri, H. Abbasi, R. T. Mofrad, *J. Heterocycl. Chem.* **2014**, *51*, 80.

[11] a) V. H. Rawal, J. A. Rao, M. P. Cava, *Tetrahedron Lett.* **1985**, *26*, 4275; b) V. B. Schmidt, D. Seebach, *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1321; *Angew. Chem.* **1991**, *103*, 1383; c) K. Soai, H. Hori, M. J. Kawahata, *J. Chem. Soc. Chem. Commun.* **1992**, 106; d) D. Seebach, A. K. Beck, B. Schmidt, Y. M. Wang, *Tetrahedron* **1994**, *50*, 4363; e) M. Yasuda, T. Fujibayashi, I. Shibata, A. Baba, H. Matsuda, M. Sonoda, *Chem. Lett.* **1995**, *24*, 167; f) K. Soai, Y. Inoue, T. Takahashi, T. Shibata, *Tetrahedron* **1996**, *52*, 13355; g) T. C. Chan, C. P. Lau, T. H. Chan, *Tetrahedron Lett.* **2004**, *45*, 4189; h) A. M. Piggott, P. Karuso, *Tetrahedron Lett.* **2005**, *46*, 8241; i) J. X. Wang, K. Wang, L. Zhao, H. Li, Y. Fu, *Adv. Synth. Catal.* **2006**, *348*, 1262; j) S. Chassaing, M. K. Stotz, G. Isorez, R. Brouillard, *Eur. J. Org. Chem.* **2007**, 2438; k) K. Yoshida, H. Takahashi, T. Imamoto, *Chem. Eur. J.* **2008**, *14*, 8246; l) H. Zheng, Q. Zhang, J. Chen, M. Liu, S. Chen, J. Ding, H. Wu, W. Su, *J. Org. Chem.* **2009**, *74*, 943; m) N. Ahlsten, A. Bartoszewicz, S. Agrawal, B. M. Matute, *Synthesis* **2011**, 2600; n) M. Mineno, Y. Sawai, K. Kanno, N. Sawada, H. Mizufune, *J. Org. Chem.* **2013**, *78*, 5843; o) W. Zeng, M. Ishida, S. Lee, Y. M. Sung, Z. Zeng, Y. Ni, C. Chi, D. Kim, J. Wu, *Chem. Eur. J.* **2013**, *19*, 16814; p) Z. Sun, S. Lee, K. H. Park, X. Zhu, W. Zhang, B. Zheng, P. Hu, Z. Zeng, S. Das, Y. Li, C. Chi, R. W. Li, K. W. Huang, J. Ding, D. Kim, J. Wu, *J. Am. Chem. Soc.* **2013**, *135*, 18229.

[12] a) A. Nagaki, M. Togai, S. Suga, N. Aoki, K. Mae, J. Yoshida, *J. Am. Chem. Soc.* **2005**, *127*, 11666; b) A. Nagaki, N. Takabayashi, Y. Tomida, J. Yoshida, *Org. Lett.* **2008**, *10*, 3937; c) J. Yoshida, A. Nagaki, T. Iwasaki, S. Suga, *Chem. Eng. Technol.* **2005**, *28*, 259; d) A. Nagaki, D. Ichinari, J. Yoshida, *Chem. Commun.* **2013**, *49*, 3242.

[13] a) P. Rys, *Acc. Chem. Res.* **1976**, *9*, 345; b) P. Rys, *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 807; *Angew. Chem.* **1977**, *89*, 847.

[14] W. Ehrfeld, K. Golbig, V. Hessel, H. Löwe, T. Richter, *Ind. Eng. Chem. Res.* **1999**, *38*, 1075.

[15] It has been reported that aryllithium compounds react with nitroarenes to give diarylamines. T. Yang, B. P. Cho, *Tetrahedron Lett.* **2003**, *44*, 7549.

[16] a) S. Suga, D. Yamada, J. Yoshida, *Chem. Lett.* **2010**, *39*, 404; b) A. Nagaki, A. Kenmoku, Y. Moriwaki, A. Hayashi, J. Yoshida, *Angew. Chem. Int. Ed.* **2010**, *49*, 7543; *Angew. Chem.* **2010**, *122*, 7705; c) J. Yoshida, K. Saito, T. Nokami, A. Nagaki, *Synlett* **2011**, 1189.

Communications

Microreactors

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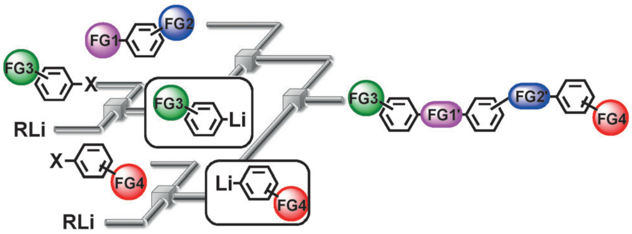
J.-i. Yoshida* ________ ▮▮▮▮–▮▮▮▮

Reactions of Difunctional Electrophiles with Functionalized Aryllithium Compounds: Remarkable Chemoselectivity by Flash Chemistry



Microreactors: Flash chemistry using flow microreactors enables highly chemoselective reactions of difunctional electrophiles with functionalized aryllithium compounds by virtue of extremely fast micromixing. The approach serves as a powerful method for protecting-group-free synthesis using organolithium compounds.