



Cite this: *Chem. Commun.*, 2018, 54, 547

Received 3rd November 2017,
Accepted 19th December 2017

DOI: 10.1039/c7cc08460a

rsc.li/chemcomm

Tandem chemical changes are often difficult to control at will, because they proceed rapidly through multiple unstable reactive intermediates. It is desirable to develop a novel method for controlling such tandem changes to obtain desired products with high selectivity. Herein, we report a flow microreactor platform for controlling tandem isomerizations of *o*-lithiated aryl benzyl ethers based on precise residence time control.

The control of isomerization of reactive intermediates¹ is an attractive research objective which will enhance product selectivity in chemical synthesis. In cases where an intermediate isomerizes rapidly to give another intermediate, the yield and selectivity of products depend on the controllability of the reaction time and temperature. In general, by using a batch-type reactor such as a flask, an isomerization is often hard to control, because it often occurs intramolecularly and is very fast even at very low temperature. However, by using flow chemistry based on microfluidics,^{2,3} the reaction time can be reduced to milliseconds or less.⁴ Therefore, intermediates can be used selectively at will by choosing the reaction time precisely. Based on this concept, there have been many reports on the control of a rapid isomerization⁵ and rearrangement⁶ of intermediates, as well as decomposition.^{7,8} To the best of our knowledge, however, there has been no attempt on the control of tandem isomerizations involving multiple reactive intermediates using flow microreactors. Moreover, many well-known anionic reactions such as the Favorskii rearrangement and benzilic acid rearrangement proceed through multiple unstable intermediates in organic synthesis. Thus, the study of the control of tandem isomerizations leads to deep understanding of such reactions.

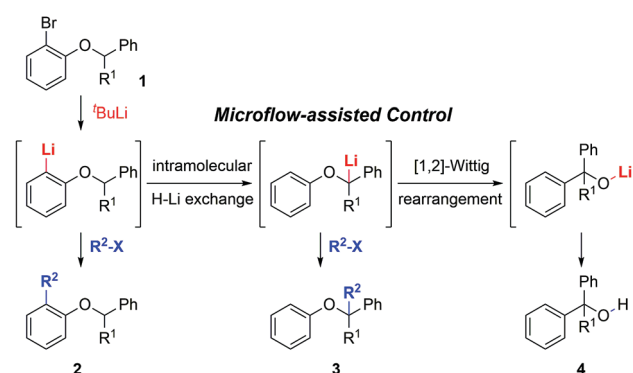
^a Centre for Intelligent Microprocess of Pharmaceutical Synthesis, Department of Chemical Engineering, POSTECH (Pohang University of Science and Technology), Pohang, 790-784, South Korea. E-mail: dpkim@postech.ac.kr

^b Department of Synthetic and Biological Chemistry Graduate School of Engineering, Kyoto University, Nishikyo-ku, Kyoto, 615-8510, Japan. E-mail: yoshida@sbchem.kyoto-u.ac.jp

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c7cc08460a
‡ These authors contributed equally to this work.

Control of tandem isomerizations: flow-assisted reactions of *o*-lithiated aryl benzyl ethers†

Hyune-Jea Lee,^{‡a} Heejin Kim,^{‡b} Jun-ichi Yoshida^{‡*b} and Dong-Pyo Kim^{‡*a}



Scheme 1 Control of tandem isomerization of *o*-lithiated aryl benzyl ethers involving three intermediates.

Herein we report a conceptual study aimed at the complete control of tandem isomerizations involving three chemical intermediates using a flow microreactor system (Scheme 1). The sequential reactions of *o*-lithiated aryl benzyl ethers in the flask were studied by Barluenga and his co-workers.⁹ However, the complete control of these isomerizations was not achieved in conventional flasks, because tandem reactions including an intramolecular H–Li exchange¹⁰ and [1,2]-Wittig rearrangement¹¹ were so fast. In this study, we prove that tandem isomerizations of *o*-lithiated aryl benzyl ethers can be effectively controlled by varying the residence time in a flow-assisted manner. Furthermore, the dual functionalization of aryl benzyl ether was successfully accomplished *via* sequential halogen–lithium exchange and deprotonation reactions.

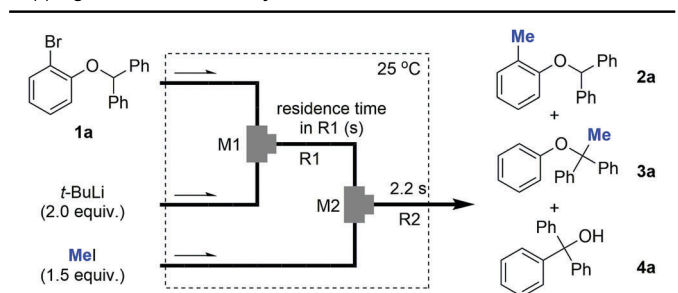
In preliminary studies using a flask, we carried out the sequential reaction of compound **1a** as a starting material. Compound **1a** was lithiated using 2 equiv. of *t*-BuLi at $-78\text{ }^\circ\text{C}$ for 10 min, and methyl iodide was added. A mixture of compounds **2a** and **3a** was obtained in 48% and 42% respectively (Table S1, ESI†). These results indicate that the control of intramolecular H–Li exchange was not efficient. When the reaction time was increased to 1 h, **3a** was obtained as the sole product, while compound **2a** was not observed at all (Table S1, ESI†). The result

indicated that the Br–Li exchange reaction and intramolecular H–Li exchange reaction were complete within 1 h even at $-78\text{ }^{\circ}\text{C}$.

Next, we conducted the same reactions using flow microreactors including two micromixers (inner diameter of M1: 250 μm , M2: 500 μm) and two microtube reactors (R1 and R2) as illustrated in Table 1. A solution of **1a** and *t*-BuLi was reacted in M1 and R1 and the resulting solution was reacted with methyl iodide in M2 and R2. The reaction temperature was kept at $25\text{ }^{\circ}\text{C}$ and the residence time in R1 was changed from 3 ms to 6.3 s by changing the diameter and length of the microtube reactor (entries 1–6, Table 1). The results clearly show the progress of the H–Li exchange reaction with time. With the residence time of 3 ms, **2a** was obtained in excellent yield (96%) (entry 1, Table 1). An increase in the residence time causes a decrease in the yield of **2a** and an increase of the yield of **3a**. With a residence time of 6.3 s, **3a** was obtained in 96% yield as a sole product (entry 6, Table 1). In addition, the solution obtained by the flow reaction for 6.3 s was further reacted in a flask for 1 h at $50\text{ }^{\circ}\text{C}$ to obtain compound **4a** in 74%, which was derived from [1,2]-Wittig rearrangement (entry 7, Table 1). These results indicate that the optimization of the residence time and temperature using a flow-assisted microreactor guarantees the high controllability of fast tandem isomerizations.

Moreover, in addition to **1a**, we conducted flow reactions of various aryl benzyl ethers (Fig. 1a), including **1b** (Ar = naphthyl, R = phenyl), **1c** (Ar = phenyl, R = hydrogen) and **1d** (Ar = naphthyl, R = hydrogen) at $25\text{ }^{\circ}\text{C}$ (Fig. 1b–d). In the case of the reaction of **1b**, both H–Li exchange and [1,2]-Wittig rearrangement seemed to be faster than those of **1a** (Fig. 1b), presumably because of the enhanced reactivity of naphthyllithium by peri-interaction.¹² Even with a residence time of 3 ms, a mixture of **2b** (77%) and **3b** (22%) was obtained.

Table 1 The Br–Li exchange reaction of compound **1a** and subsequent trapping reaction with methyl iodide in flow



Entry	Residence time in R1 [s]	Yield of 2a ^a [%]	Yield of 3a ^a [%]	Yield of 4a ^a [%]
1	0.003	96	0	0
2	0.016	93	5	0
3	0.25	78	20	0
4	0.63	60	38	0
5	3.1	6	91	0
6	6.3	0	96	0
7 ^b	1 ^b h	0	0	74

^a Determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. ^b The resulting solution from R2 was stirred in a flask for 1 h at $50\text{ }^{\circ}\text{C}$. For details, see the ESI.

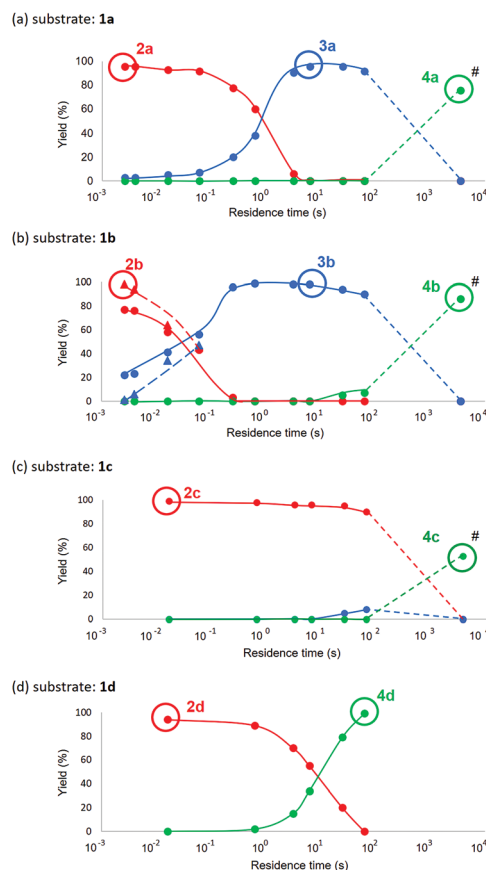
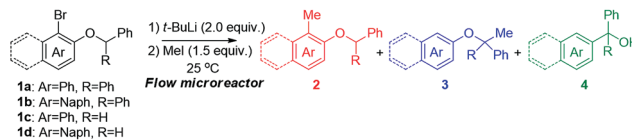


Fig. 1 Tandem isomerizations of various aryl benzyl ethers by changing the residence time in R1 in a flow microreactor system for products **2**, **3** and **4d**, followed by further stirring in a flask at $50\text{ }^{\circ}\text{C}$ for 1 h to obtain products **4a–c** (#). Methyl triflate was used as an electrophile (symbol \blacktriangle with a dashed line), instead of methyl iodide (symbol \bullet with a solid line).

On the other hand, **2b** was obtained in 98% yield when methyl triflate was used as an electrophile (dashed lines, Fig. 1b) instead of methyl iodide. This means that the trapping with methyl iodide competes with the H–Li exchange. However, the trapping with methyl triflate is faster than the H–Li exchange. In the reaction of **1c** (Fig. 1c), the H–Li exchange was slow, probably because the acidity of the benzylic proton is much lower. Even with a residence time of 63 s, only a small amount of **3c** was obtained. When **1d** was used for the reaction (Fig. 1d), the H–Li exchange is somewhat slower than that of **1a**; however, the [1,2]-Wittig rearrangement is much faster than that of **1a**. In this case, the [1,2]-Wittig rearrangement is faster than the H–Li exchange, and therefore **3d** was not obtained with any residence time. With longer residence times, **4d** was obtained in a good yield but at the expense of **2d**.

The rate of the intramolecular H–Li exchange increases in the order $1c < 1d < 1a < 1b$. This tendency is consistent with the acidity of protons (R = Ph or H) and reactivity by peri-interaction. The rate of the [1,2]-Wittig rearrangement increases in the

Table 2 Selective control of tandem isomerizations in various aryl benzyl ethers with different electrophiles in flow-assisted microreactors

Conditions	Product ^a			
condition A ^b	2a, 95% ^c	2aa, 80%	2ab, 82%	2ac, 85%
condition B ^c	2b, 92% ^c	2ba, 81%	2bb, 84%	2bc, 82%
condition C ^d	3a, 96% ^e	3aa, 80%	3ab, 81%	3ac, 74%
	3b, 91% ^e	3ba, 61%	3bb, 81%	3bc, 73%
	4a, 72% ^e	4b, 81% ^e		

^a Yields of isolated products. ^b Residence time for lithiation was 3 ms at 25 °C. ^c Residence time for lithiation was 6.3 s at 25 °C. ^d After the lithiation for 6.3 s at 25 °C in flow, the resulting solution was stirred in a flask at 50 °C for 1 h. For details, see the ESI. ^e Determined by ¹H NMR spectroscopy using 1,3,5-trimethoxy benzene as an internal standard.

order **1a** and **1c** < **1b** < **1d**. The stabilization effect of radicals (Ar = Ph or Naph) seems to be responsible for this tendency. These tendencies are consistent with a reported reaction mechanism.¹³

Under three optimized conditions (conditions A for aryl-functionalization, conditions B for benzyl-functionalization, and conditions C for triaryl alcohols; for details, see the ESI[†]), we conducted selective functionalization with various electrophiles such as methyl iodide (or triflate), ethyl chloroformate, tributyltin chloride, trimethylsilyl chloride, and benzoyl chloride (Table 2). Compounds **2** derived from the non-isomerized intermediate, compounds **3** derived from the deprotonated intermediate and compounds **4** derived from the rearranged intermediate were selectively obtained in good isolated yields.

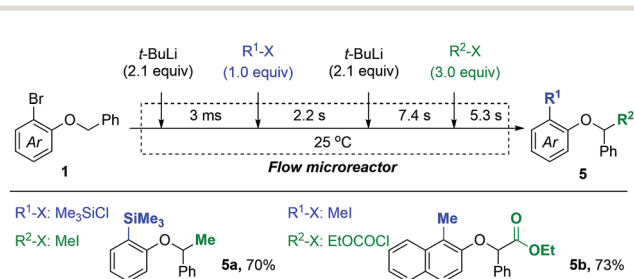


Fig. 2 Dual functionalization of aryl benzyl ethers in a one-flow microreactor via controlled sequential isomerization reactions.

Based on the present method for the control of tandem isomerizations, dual functionalization of aryl benzyl ethers was achieved using a flow microreactor system (Fig. 2). By controlling the residence times precisely for two lithiation-trapping sequences, doubly functionalized products **5a** and **5b** were successfully obtained from substrates **1c** and **1d**, respectively, within 15 s of the total reaction time.

In summary, we have demonstrated the flow-assisted control of tandem isomerizations of H–Li exchange and [1,2]-Wittig rearrangement. Under the optimized conditions based on the kinetic studies, three intermediates can be selectively trapped at will to obtain the desired products. The present study opens a new possibility of chemical synthesis using tandem isomerizations. We hope that the method will be widely applied for the sequential control of various reaction intermediates.

We acknowledge the National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIP) (No. 2017R1A3B1023598). This work was also supported by a Grant-in-Aid for Scientific Research (S) 26220804 and a Grant-in-Aid for Young Scientists (B) 16K17898 funded by the Japan Society for the Promotion of Science (JSPS).

Conflicts of interest

There are no conflicts to declare.

Notes and references

- For example, R. A. Moss, M. S. Platz and M. Jones Jr., *Reactive Intermediate Chemistry*, Wiley, Hoboken, 2004.
- Selected reviews on flow microreactor synthesis: (a) P. Watts and S. J. Haswell, *Chem. Soc. Rev.*, 2005, **34**, 235–246; (b) A. J. deMello, *Nature*, 2006, **442**, 394–402; (c) B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan and D. T. McQuade, *Chem. Rev.*, 2007, **107**, 2300–2318; (d) T. Fukuyama, M. T. Rahman, M. Sato and I. Ryu, *Synlett*, 2008, 151–163; (e) Z. Qian, I. R. Baxendale and S. V. Ley, *Chem. – Eur. J.*, 2010, **16**, 12342–12348; (f) K. S. Elvira, X. C. Solvas, R. C. R. Wootton and A. J. deMello, *Nat. Chem.*, 2013, **5**, 905–915; (g) J. C. Pastre, D. L. Browne and S. V. Ley, *Chem. Soc. Rev.*, 2013, **42**, 8849–8869; (h) S. Mascia, P. L. Heider, H. Zhang, R. Lakerveld, B. Benyahia, P. I. Barton, R. D. Braatz, C. L. Cooney, J. M. B. Evans, T. F. Jamison, K. F. Jensen, A. S. Myerson and B. L. Trout, *Angew. Chem., Int. Ed.*, 2013, **52**, 12359–12363; (i) P. L. Heider, S. C. Born, S. Basak, B. Benyahia, R. Lakerveld, H. Zhang, R. Hogan, L. Buchbinder, A. Wolfe, S. Mascia, J. M. B. Evans, T. F. Jamison and K. F. Jensen, *Org. Process Res. Dev.*, 2014, **18**, 402–409; (j) P. Zhang, M. G. Russell and T. F. Jamison, *Org. Process Res. Dev.*, 2014, **18**, 1567–1570; (k) K. Gilmore, D. Kopetzki, J. W. Lee, Z. Horvath, D. T. McQuade, A. Seidel-Morgenstern and P. H. Seeberger, *Chem. Commun.*, 2014, **50**, 12652–12655; (l) S. Newton, C. F. Carter, C. M. Pearson, L. de C. Alves, H. Lange, P. Thansandote and S. V. Ley, *Angew. Chem., Int. Ed.*, 2014, **53**, 4915–4920; (m) B. Gutmann, D. Cantillo and C. O. Kappe, *Angew. Chem., Int. Ed.*, 2015, **54**, 6688–6728; (n) D. R. Snead and T. F. Jamison, *Angew. Chem., Int. Ed.*, 2015, **54**, 983–987; (o) T. Tsubogo, H. Oyama and S. Kobayashi, *Nature*, 2015, **520**, 329–332; (p) D. Ghislieri, K. Gilmore and P. H. Seeberger, *Angew. Chem., Int. Ed.*, 2015, **54**, 678–682; (q) M. Brzozowski, M. O'Brien, S. V. Ley and A. Polyzos, *Acc. Chem. Res.*, 2015, **48**, 349–362; (r) A. Adamo, R. L. Beingsner, M. Behnam, J. Chen, T. F. Jamison, K. F. Jensen, J.-C. M. Monbaliu, A. S. Myerson, E. M. Revalor, D. R. Snead, T. Stelzer, N. Weeranoppanant, S. Y. Wong and P. Zhang, *Science*, 2016, **352**, 61–67; (s) R. Singh, H.-J. Lee, A. K. Singh and D.-P. Kim, *Korean J. Chem. Eng.*, 2016, **33**, 2253–2267; (t) M. B. Plutschack, B. Pieber, K. Gilmore and P. H. Seeberger, *Chem. Rev.*, 2017, **117**, 11796–11893.

- 3 (a) I. R. Baxendale, S. V. Ley, A. C. Mansfield and C. D. Smith, *Angew. Chem., Int. Ed.*, 2009, **48**, 4017–4021; (b) D. Webb and T. F. Jamison, *Chem. Sci.*, 2010, **1**, 675–680; (c) R. A. Maurya, C. P. Park, J. H. Lee and D.-P. Kim, *Angew. Chem., Int. Ed.*, 2011, **50**, 5952–5955; (d) S. Sharma, R. Maurya, K.-I. Min, G. Jeong and D.-P. Kim, *Angew. Chem., Int. Ed.*, 2013, **52**, 7564–7568; (e) C. Brancour, T. Fukuyama, Y. Mukai, T. Skrydstrup and I. Ryu, *Org. Lett.*, 2013, **15**, 2794–2797; (f) I. R. Baxendale, L. Brocken and C. J. Mallia, *Green Process. Synth.*, 2013, **2**, 211–230; (g) D. T. McQuade and P. H. Seeberger, *J. Org. Chem.*, 2013, **78**, 6384–6389; (h) R. A. Maurya, K.-I. Min and D.-P. Kim, *Green Chem.*, 2014, **16**, 116–120; (i) A. K. Singh, D.-H. Ko, N. K. Vishwakarma, S. Jang, K.-I. Min and D.-P. Kim, *Nat. Commun.*, 2016, **7**, 10714.
- 4 (a) J. Yoshida, A. Nagaki and T. Yamada, *Chem. – Eur. J.*, 2008, **14**, 7450–7459; (b) J. Yoshida, *Flash Chemistry. Fast Organic Synthesis in Microsystems*, Wiley-Blackwell, 2008; (c) J. Yoshida, Y. Takahashi and A. Nagaki, *Chem. Commun.*, 2013, **49**, 9896–9904.
- 5 (a) A. Nagaki, H. Kim and J. Yoshida, *Angew. Chem., Int. Ed.*, 2009, **48**, 8063–8065; (b) A. Nagaki, E. Takizawa and J. Yoshida, *J. Am. Chem. Soc.*, 2009, **131**, 1654–1655 and 3787; (c) A. Nagaki, E. Takizawa and J. Yoshida, *Chem. – Eur. J.*, 2010, **16**, 14149–14158; (d) Y. Tomida, A. Nagaki and J. Yoshida, *J. Am. Chem. Soc.*, 2011, **133**, 3744–3747; (e) A. Nagaki, S. Kim, N. Miuchi, H. Yamashita, K. Hirose and J. Yoshida, *Org. Chem. Front.*, 2016, **3**, 1250–1253.
- 6 H. Kim, K.-I. Min, K. Inoue, D. J. Im, D.-P. Kim and J. Yoshida, *Science*, 2016, **352**, 691–694.
- 7 (a) A. Nagaki, H. Kim and J. Yoshida, *Angew. Chem., Int. Ed.*, 2008, **47**, 7833–7836; (b) A. Nagaki, H. Kim and J. Yoshida, *Angew. Chem., Int. Ed.*, 2009, **48**, 8063–8065; (c) A. Nagaki, H. Kim, H. Usutani, C. Matsuo and J. Yoshida, *Org. Biomol. Chem.*, 2010, **8**, 1212–1217; (d) H. Kim, A. Nagaki and J. Yoshida, *Nat. Commun.*, 2011, **2**, 264; (e) W. Ren, H. Kim, H.-J. Lee, J. Wang, H. Wang and D.-P. Kim, *Lab Chip*, 2014, **14**, 4263–4269; (f) H. Kim, H.-J. Lee and D.-P. Kim, *Angew. Chem., Int. Ed.*, 2015, **54**, 1877–1880; (g) H. Kim, H.-J. Lee and D.-P. Kim, *Angew. Chem., Int. Ed.*, 2016, **55**, 1422–1426.
- 8 (a) L. J. Martin, A. L. Marzinzik, S. V. Ley and I. R. Baxendale, *Org. Lett.*, 2011, **13**, 320–323; (b) D. N. Tran, C. Battilocchio, S. Lou, J. M. Hawkins and S. V. Ley, *Chem. Sci.*, 2015, **6**, 1120–1125; (c) D. N. Tran, C. Battilocchio, R. Labes, R. J. Ingham, J. M. Hawkins and S. V. Ley, *Org. Biomol. Chem.*, 2015, **13**, 2550–2554; (d) J. S. Poh, D. N. Tran, C. Battilocchio, J. M. Hawkins and S. V. Ley, *Angew. Chem., Int. Ed.*, 2015, **54**, 7920–7923; (e) J.-S. Poh, S. Makai, T. V. Keutz, D. N. Tran, C. Battilocchio, P. Pasau and S. V. Ley, *Angew. Chem., Int. Ed.*, 2017, **56**, 1864–1868.
- 9 J. Barluenga, F. J. Fañanás, R. Sanz, C. Marcos and M. Trabada, *Org. Lett.*, 2002, **4**, 1587–1590.
- 10 (a) A. Ahmed, J. Clayden and M. Rowley, *Tetrahedron Lett.*, 1998, **39**, 6103–6106; (b) I. Fleming, S. R. Mack and B. P. Clark, *Chem. Commun.*, 1998, 715–716.
- 11 G. Wittig and H. Doser, *Justus Liebigs Ann. Chem.*, 1942, **550**, 260–268.
- 12 (a) V. Balasubramanian, *Chem. Rev.*, 1966, **66**, 567–641; (b) J.-B. Robert, J. S. SHERfinski, R. E. Marsh and J. D. Roberts, *J. Org. Chem.*, 1974, **39**, 1152–1156; (c) D. Pla, O. Sadek, S. Cadet, B. Mestre-Voegtlé and E. Gras, *Dalton Trans.*, 2015, **44**, 18340–18346.
- 13 (a) P. T. Lansbury, V. A. Pattison, J. D. Sidler and J. B. Bieber, *J. Am. Chem. Soc.*, 1966, **88**, 78–84; (b) J. F. Garst and C. D. Smith, *J. Am. Chem. Soc.*, 1976, **98**, 1526–1537; (c) U. Schöllkopf, *Angew. Chem., Int. Ed.*, 1979, **18**, 563–572.