Organic & Biomolecular Chemistry

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2015, **13**, 7140

Received 12th May 2015,
Accepted 21st May 2015

DOI: 10.1039/c5ob00958h

www.rsc.org/obc

Benzyllithiums bearing aldehyde carbonyl groups. A flash chemistry approach†

Aiichiro Nagaki, Yuta Tsuchihashi, Suguru Haraki and Jun-ichi Yoshida*

Reductive lithiation of benzyl halides bearing aldehyde carbonyl groups followed by reaction with subsequently added electrophiles was successfully accomplished without affecting the carbonyl groups by taking advantage of short residence times in flow microreactors.

Chemoselectivity is one of the central issues in chemistry and chemical synthesis.[1] One of the goals in synthetic chemistry is the development of chemoselective transformations without affecting the highly reactive functional groups that are not involved in the desired transformation. We have been interested in organolithium reactions without affecting the aldehyde carbonyl groups as an extreme case of chemoselective transformations.[2] According to the textbooks of organic chemistry, organolithiums react with aldehydes very quickly and they are not compatible with each other. On the other hand, aldehyde carbonyl groups are very common functional groups and organolithium reactions are frequently used in organic synthesis.[3] Therefore, if we could perform organolithium reactions without affecting the aldehyde carbonyl groups, such reactions would serve as powerful synthetic methods. We took an approach to this challenge based on flash chemistry,[4] in which highly unstable reactive species are generated and transferred to another location to be used in the next reaction[5] before they decompose by high-resolution residence time control using flow microreactor systems.[6–8] In fact, recently, we had already reported the generation and reactions of aryllithiums bearing ketone carbonyl groups.[5e] However, in general, aldehyde carbonyl groups are more reactive than ketone carbonyl groups. Therefore, faster generation is necessary to solve the more challenging problem of aldehyde cases. Here, we show that flash chemistry enables the generation of benzyllithiums[9–12] bearing aldehyde carbonyl groups and their use in the reactions with subsequently added electrophiles without affecting the aldehyde carbonyl groups.

We first examined the generation of simple benzyllithiums by reductive lithiation[13] of benzyl halides (Fig. 1). This reaction is problematic because of Wurtz-type coupling, *i.e.* the coupling of benzyllithiums with starting benzyl halides. It was reported that benzyllithium can be generated from benzyl chloride by using lithium naphthalenide (LiNp) in a mixed solvent (Et_2O/THF/light petroleum = 4 : 3 : 1) at −95 °C in a conventional batch reactor.[9a] However, the reaction in THF and/or at higher temperatures such as −78 °C leads to a dramatic decrease in the yield because of Wurtz-type coupling. We envisioned that extremely fast micromixing is effective to avoid undesired Wurtz-type coupling because it is known that the product selectivity of fast consecutive competitive reactions[14] can be dramatically improved by extremely fast micromixing.[15] Thus, we examined the reactions of benzyl halides with LiNp in a flow microreactor system, which consists of two T-shaped micromixers M1 (ϕ = 250 μm) and M2 (ϕ = 250 μm) and two microtube reactors R1 (ϕ = 1000 μm, length = 3.5 cm and R2 (ϕ = 1000 μm, length = 50 cm) (see the ESI† for details). For the reactions with very short residence times such as 1.3 ms, a built-in type system as shown in Fig. 2a (R1: ϕ = 250 μm,

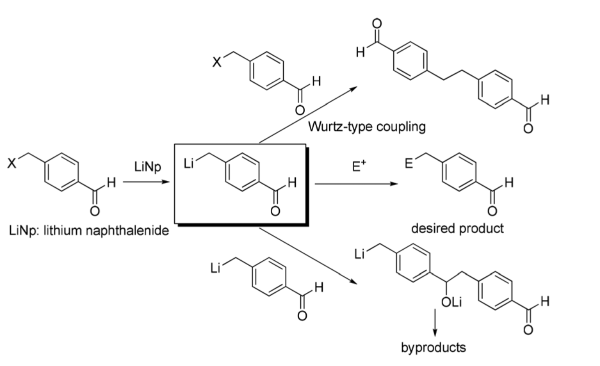


Fig. 1 Generation and reactions of benzyllithiums bearing aldehyde carbonyl groups.

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/c5ob00958h

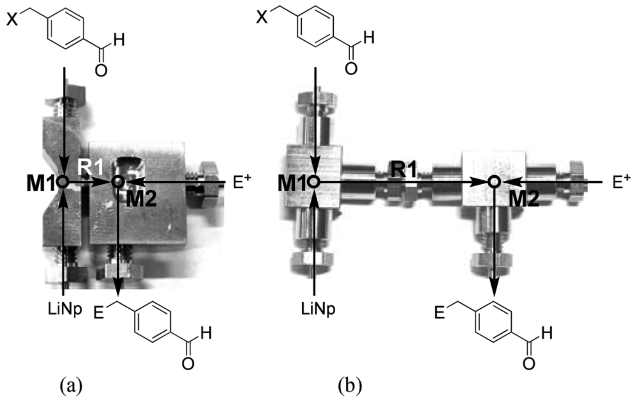


Fig. 2 Flow microreactor systems. (a) Built-in type system, (b) modular type system.

length = 1.0 cm) was used, whereas a conventional modular type system was used for the reactions with longer residence times (Fig. 2b).

Because it is well known that the mixing speed in a micromixer depends on the inner diameter and the flow rate,[16] we examined the reactions by varying the inner diameter of M1 and the flow rates of the solution of benzyl halide and LiNp. The 1 : 1 molar ratio of benzyl halide and LiNp was maintained in all experiments. Methanol was used as an electrophile and the reactions were carried out at 20 °C using a conventional modular type system (Fig. 2b). As summarized in Table 1, the yield of the desired protonated product, toluene, increased with a decrease in the inner diameter. The yield also increased with an increase in the flow rate. Satisfactory yields were obtained with M1 of 250 μm inner diameter and the total flow rate of 9.0 mL min^{-1} in the case of benzyl chloride. In the case of benzyl bromide, a higher flow rate was necessary to obtain satisfactory yields, presumably benzyl bromide is more reactive toward benzyllithium than benzyl chloride. Anyway, it is noteworthy that the flow microreactor system enables the generation of benzyllithium at 20 °C, although the reactions should be carried out at −95 °C in a conventional batch macro reactor. It is also advantageous that THF can be used instead of the mixed solvent. Furthermore, benzyl bromide can be used as a starting material, although such transformation is impossible in a conventional batch macro reactor. These remarkable features seem to be ascribed to the extremely fast micromixing of benzyl halide and LiNp at 1 : 1 molar ratio.

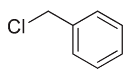
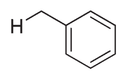
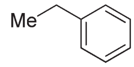
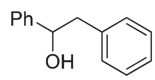
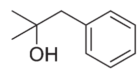
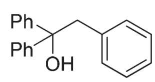
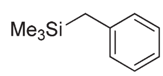
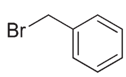
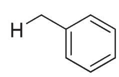
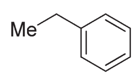
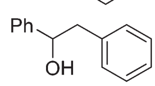
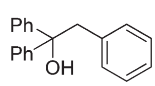
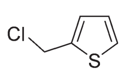
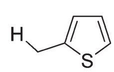
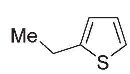
Under the optimized conditions, the reactions of benzyllithium with other electrophiles, such as methyl iodide, aldehydes, ketones, trimethylsilyl chloride, and isocyanates, were examined. As shown in Table 2, the corresponding products were obtained in good yields. Notably, the lithiation of 2-(chloromethyl)thiophene followed by the reaction with an

Table 1 Effect of the flow rate and the inner diameter of M1 on the lithiation of benzyl halides using the flow microreactor system[a]

	Flow rate (mL min^{-1})			Inner diameter of M1 (μm)	Yield[b] (%)	
X	Benzyl halide	LiNp	Total		Toluene	Bibenzyl
Cl	6.0	3.0	9.0	500	70	13
	6.0	3.0	9.0	250	89	4
	3.0	1.5	4.5	250	81	4
Br	6.0	3.0	9.0	800	15	29
	6.0	3.0	9.0	500	38	30
	6.0	3.0	9.0	250	77	10
	12	6.0	18	250	80	8
	3.0	1.5	4.5	250	49	24
	1.5	0.75	2.25	250	39	30

[a] R1: ϕ = 250 μm, L = 3.5 cm, 20 °C. [b] Determined by GC using an internal standard.

Table 2 The generation of benzyllithiums followed by reaction with an electrophile[a]

Benzyl halides	Electrophile	Product	Yield[b] (%)
	MeOH		89[c]
	MeI		82[c]
	PhCHO		80
	$(CH_3)_2CO$		42[c]
	Ph_2CO		93
	Me_3SiCl		80[c]
	MeOH		80[c]
	MeI		82[c]
	PhCHO		75
	Ph_2CO		71
	MeOH		97[c]
	MeI		72[c]

[a] R1: ϕ = 250 μm, L = 3.5 cm, 20 °C. Benzyl chloride: total flow rate = 9 ml min^{-1}. Benzyl bromide, 2-(chloromethyl)thiophene: flow rate of benzyl halide = 18 ml min^{-1}. [b] Isolated yield. [c] Determined by GC using an internal standard.

electrophile was successfully carried out without ring-opening, although conventional batch reactions often suffer from this side reaction.[17] The productivity of the present method is high enough for laboratory synthesis. In the case of the reaction of benzyllithium with benzophenone, a 15 min operation gave 1.09 g of the desired product (see the ESI† for details).

With the successful generation of benzyllithiums by virtue of extremely fast micromixing in hand, we next examined the generation and reactions of benzyllithiums bearing carbonyl groups. In this case the high-resolution residence time control is critical because such benzyllithiums should be transferred extremely quickly to another location to be used in the reaction with electrophiles before they decompose. Temperature–residence time mapping serves as a powerful tool for optimizing the residence time. Fig. 3a shows the contour plots with scattered overlay of the yields of the protonated product for the lithiation of *p*-propanoylbenzyl chloride, which has a ketone

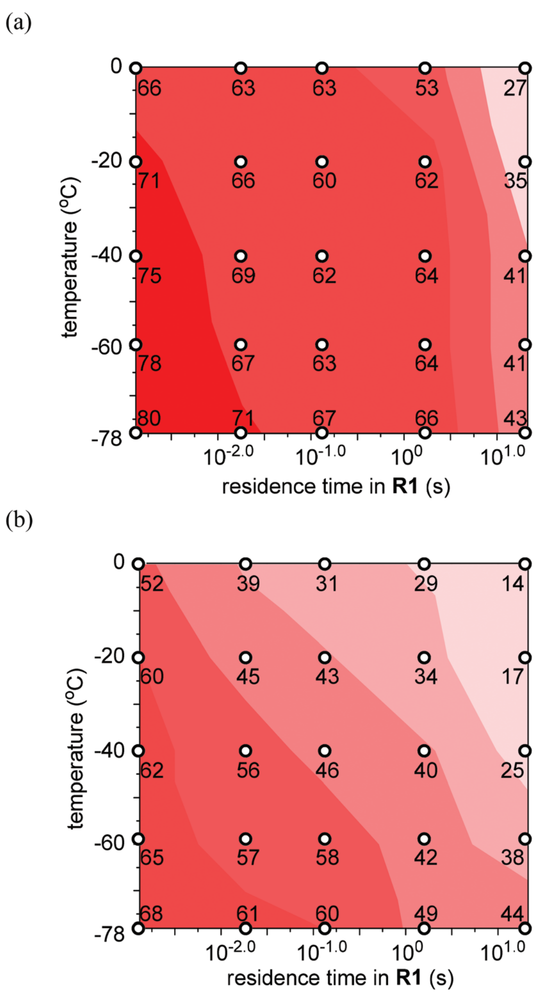


Fig. 3 Effects of the temperature and the residence time in R1 on the yield of the protonated product for the lithiation of (a) *p*-propanoylbenzyl chloride and (b) *p*-formylbenzyl chloride with LiNp followed by trapping with methanol using the flow microreactor system. Contour plots with scattered overlay of the yields of the protonated products, which are indicated by numbered circles.

Table 3 The generation of benzyllithiums bearing ketone and aldehyde carbonyl groups followed by reaction with an electrophile[a]

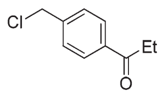
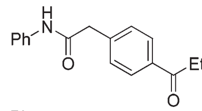
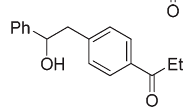
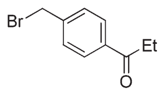
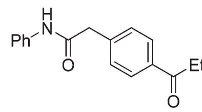
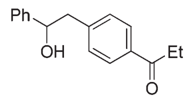
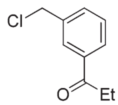
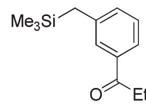
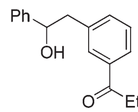
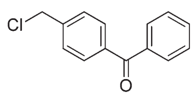
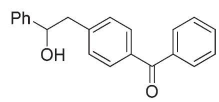
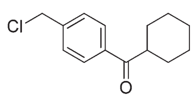
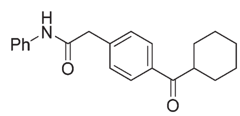
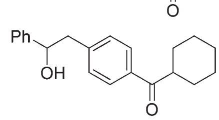
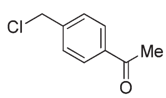
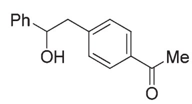
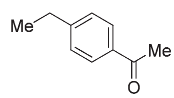
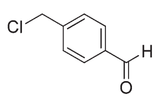
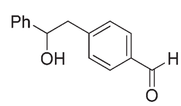
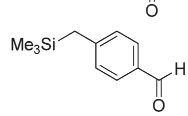
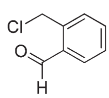
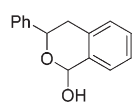
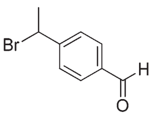
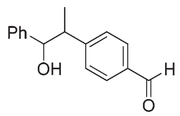
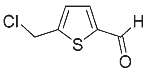
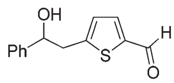
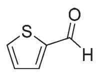
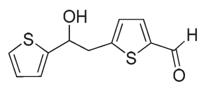
Benzyl halides	Electrophile	Product	Yield[b] (%)
	PhNCO		78
	PhCHO		88
	PhNCO		60
	PhCHO		64
	Me_3SiOTf		68
	PhCHO		67
	PhCHO		89
	PhNCO		77
	PhCHO		83
	PhCHO		85
	MeOTf		41[c]
	PhCHO		55
	Me_3SiOTf		58
	PhCHO		59[d]

Table 3 *(Contd.)*

Benzyl halides	Electrophile	Product	Yield[b] (%)
	PhCHO		76[e]
	PhCHO		77
			72

[a] R1: ϕ = 250 μm, L = 1.0 cm, −78 °C. [b] Isolated yield. [c] Determined by GC. [d] Diastereomeric ratio = 88 : 12 (determined by ^{1}H NMR spectra). [e] Diastereomeric ratio = 60 : 40 (determined by ^{1}H NMR spectra).

carbonyl group, followed by trapping with methanol. The yield decreases with an increase in the residence time in R1. The yield also decreases with an increase in the temperature although the effect of the temperature is not large. The optimal yield (80%) was obtained with the residence time of 1.3 ms at −78 °C.

The effects of the residence time and the temperature are more significant in the lithiation of *p*-formylbenzyl chloride, which has an aldehyde carbonyl group (Fig. 3b). As can be seen obviously by comparing Fig. 3a and b, *p*-formylbenzyllithium is significantly less stable than *p*-propanoylbenzyllithium. With the residence time of 1.3 ms at −78 °C, however, *p*-formylbenzyllithium can be generated and used in the subsequent reaction with methanol to give the protonated product in a reasonable yield (68%). This means that the aldehyde carbonyl group can survive in the organolithium reaction.

Under the optimized conditions several benzyllithiums bearing ketone and aldehyde carbonyl groups were generated and reacted with several electrophiles including phenylisocyanate, benzaldehyde, TMSOTf, and MeOTf. The results are summarized in Table 3. Such transformations are very difficult or practically impossible by using conventional batch macro reactors.

As an application of the present method, we accomplished the synthesis of a π-conjugated system as shown in Fig. 4. The reaction of benzaldehyde with (5-formylthiophen-2-yl)methyllithium followed by elimination with bis[α,α-bis(trifluoromethyl)benzenemethanolato]diphenylsulfur (Martin sulfurane) gave aldehyde **1** in 61% isolated yield. The aldehyde carbonyl group in **1** was used for subsequent reaction with benzyllithium. The subsequent dehydration gave compound **2** (78% isolated yield), in which one thiophene ring and two benzene rings are connected by carbon–carbon double bonds.[18]

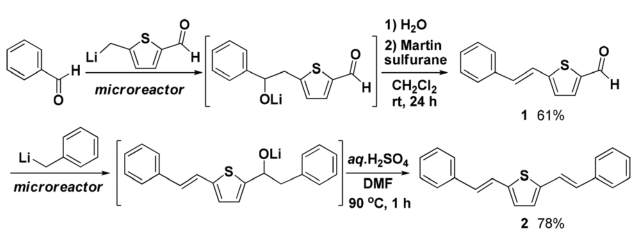


Fig. 4 Synthesis of π-conjugated systems using (5-formylthiophen-2-yl)methyllithium.

In conclusion, flash chemistry using flow microreactor systems enables the generation and reactions of benzyllithiums bearing aldehyde carbonyl groups. Extremely fast micromixing is responsible for the generation of benzyllithiums avoiding Wurtz-type coupling, and high-resolution residence time control is responsible for survival of aldehyde carbonyl groups. The present findings open a new aspect of protecting-group-free[19] organolithium chemistry.

Acknowledgements

This work was partially supported by the Grant-in-Aid for Scientific Research (S) (no. 26220804) and Scientific Research (B) (no. 26288049). We also thank Taiyo Nippon Sanso for providing a low temperature cooling device and partial financial support.

References

1 (*a*) R. W. Hoffmann, *Synthesis*, 2006, 3531; (*b*) N. A. Afagh and A. K. Yudin, *Angew. Chem., Int. Ed.*, 2010, **49**, 262.
2 (*a*) J. A. Bajgrowicz, A. El Hallaoui, R. Jacquier, Ch. Pigiere and Ph. Viallefont, *Tetrahedron*, 1985, **41**, 1833; (*b*) T. Mandai, S. Matsumoto, M. Kohama, M. Kawada and J. Tsuji, *J. Org. Chem.*, 1990, **55**, 5671; (*c*) T. Mandai, T. Murakami, M. Kawada and J. Tsuji, *Tetrahedron Lett.*, 1991, **32**, 3399; (*d*) J. F. Gil, D. J. Ramón and M. Yus, *Tetrahedron*, 1993, **49**, 4923.
3 (*a*) J. E. Baldwin and R. M. Williams, *Organolithiums: Selectivity for Synthesis*, Pergamon, Amsterdam, 2002; (*b*) P. Knochel, *Handbook of Functionalized Organometallics*, Wiley-VCH, Weinheim, 2005; (*c*) R. Luisi and V. Capriati, *Lithium Compounds in Organic Synthesis - From Fundamentals to Applications*, Wiley-VCH, Weinheim, 2014.
4 Flash chemistry is defined as a field of chemical synthesis where extremely fast reactions are conducted in a highly controlled manner to produce the desired compounds with high selectivity: (*a*) J. Yoshida, *Chem. Commun.*, 2005, 4509; (*b*) J. Yoshida, A. Nagaki and T. Yamada, *Chem. – Eur. J.*, 2008, **14**, 7450; (*c*) P. J. Nieuwland, K. Koch, N. van Harskamp, R. Wehrens, J. C. M. van Hest and F. P. J. T. Rutjes, *Chem. – Asian J.*, 2010, **5**, 799; (*d*) J. Yoshida, *Chem. Rec.*, 2010, **10**, 332; (*e*) J. Yoshida, Y. Takahashi and A. Nagaki, *Chem. Commun.*, 2013, **49**, 9896.
5 Some examples of generation and reactions of short-lived organolithiums in flow: (*a*) H. Usutani, Y. Tomida,

A. Nagaki, H. Okamoto, T. Nokami and J. Yoshida, *J. Am. Chem. Soc.*, 2007, **129**, 3046; (*b*) A. Nagaki, E. Takizawa and J. Yoshida, *J. Am. Chem. Soc.*, 2009, **131**, 1654; (*c*) A. Nagaki, A. Kenmoku, Y. Moriwaki, A. Hayashi and J. Yoshida, *Angew. Chem., Int. Ed.*, 2010, **49**, 7543; (*d*) Y. Tomida, A. Nagaki and J. Yoshida, *J. Am. Chem. Soc.*, 2011, **133**, 3744; (*e*) H. Kim, A. Nagaki and J. Yoshida, *Nat. Commun.*, 2011, **2**, 264; (*f*) A. Nagaki, C. Matsuo, S. Kim, K. Saito, A. Miyazaki and J. Yoshida, *Angew. Chem., Int. Ed.*, 2012, **51**, 3245.

6 Books on flow microreactor synthesis: (*a*) W. Ehrfeld, V. Hessel and H. Löwe, *Microreactors*, Wiley-VCH, Weinheim, 2000; (*b*) V. Hessel, S. Hardt and H. Löwe, *Chemical Micro Process Engineering*, Wiely-VCH Verlag, Weinheim, 2004; (*c*) J. Yoshida, *Flash Chemistry. Fast Organic Synthesis in Microsystems*, Wiley-Blackwell, 2008; (*d*) *Micro Precess Engineering*, ed. V. Hessel, A. Renken, J. C. Schouten and J. Yoshida, Wiley-VCH Verlag, Weinheim, 2009; (*e*) *Microreactors in Organic Chemistry and Catalysis*, ed. T. Wirth, Wiley-VCH Verlag, Weinheim, 2nd edn, 2013.

7 Reviews on flow microreactor synthesis: (*a*) K. Jähnisch, V. Hessel, H. Löwe and M. Baerns, *Angew. Chem., Int. Ed.*, 2004, **43**, 406; (*b*) J. Kobayashi, Y. Mori and S. Kobayashi, *Chem. – Asian. J.*, 2006, **1**, 22; (*c*) B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan and D. T. McQuade, *Chem. Rev.*, 2007, **107**, 2300; (*d*) B. Ahmed-Omer, J. C. Brandt and T. Wirth, *Org. Biomol. Chem.*, 2007, **5**, 733; (*e*) T. Fukuyama, M. T. Rahman, M. Sato and I. Ryu, *Synlett*, 2008, 151; (*f*) R. L. Hartman and K. F. Jensen, *Lab Chip*, 2009, **9**, 2495; (*g*) J. Yoshida, H. Kim and A. Nagaki, *ChemSusChem*, 2011, **4**, 331; (*h*) C. Wiles and P. Watts, *Green Chem.*, 2012, **14**, 38; (*i*) A. Kirschining, L. Kupracz and J. Hartwig, *Chem. Lett.*, 2012, **41**, 562; (*j*) D. T. McQuade and P. H. Seeberger, *J. Org. Chem.*, 2013, **78**, 6384; (*k*) J. C. Pastre, D. L. Browne and S. V. Ley, *Chem. Soc. Rev.*, 2013, **42**, 8849; (*l*) I. R. Baxendale, *J. Chem. Technol. Biotechnol.*, 2013, **88**, 519.

8 Some selected recent examples: (*a*) D. Cantillo, M. Baghbanzadeh and C. O. Kappe, *Angew. Chem., Int. Ed.*, 2012, **51**, 10190; (*b*) W. Shu and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2012, **51**, 5355; (*c*) A. Nagaki, Y. Moriwaki and J. Yoshida, *Chem. Commun.*, 2012, **48**, 11211; (*d*) F. Lévesque and P. H. Seeberger, *Angew. Chem., Int. Ed.*, 2012, **51**, 1706; (*e*) K. C. Basavaraju, S. Sharma, R. A. Maurya and D. P. Kim, *Angew. Chem., Int. Ed.*, 2013, **52**, 6735; (*f*) C. Brancour, T. Fukuyama, Y. Mukai, T. Skrydstrup and I. Ryu, *Org. Lett.*, 2013, **15**, 2794; (*g*) J. D. Nguyen, B. Reiß, C. Dai and C. R. J. Stephenson, *Chem. Commun.*, 2013, **49**, 4352; (*h*) C. Battilocchio, J. M. Hawkins and S. V. Ley, *Org. Lett.*, 2013, **15**, 2278; (*i*) A. S. Kleinke and T. F. Jamison, *Org. Lett.*, 2013, **15**, 710; (*j*) L. Guetzoyan, N. Nikbin, I. R. Baxendale and S. V. Ley, *Chem. Sci.*, 2013, **4**, 764; (*k*) S. Fuse, Y. Mifune and T. Takahashi, *Angew. Chem., Int. Ed.*, 2014, **53**, 851; (*l*) Z. He and T. F. Jamison, *Angew. Chem., Int. Ed.*, 2014, **53**, 3353; (*m*) A. Nagaki, Y. Takahashi and J. Yoshida, *Chem. – Eur. J.*, 2014, **20**, 7931; (*n*) A. Nagaki, D. Ichinari and J. Yoshida, *J. Am. Chem. Soc.*, 2014, **136**, 12245; (*o*) S. Sharma, K. Basavaraju, A. Singh and D. Kim, *Org. Lett.*, 2014, **16**, 3974; (*p*) S. Umezu, Y. Yoshiiwa, M. Tokeshi and M. Shindo, *Tetrahedron Lett.*, 2014, **55**, 1822.

9 Generation of benzyllithiums by reductive lithiation: (*a*) K. Smith and D. Hou, *J. Chem. Soc., Perkin Trans. 1*, 1995, 185; (*b*) C. Gómez, F. F. Huerta and M. Yus, *Tetrahedron*, 1997, **53**, 13897; (*c*) C. Gómez, F. F. Huerta and M. Yus, *Tetrahedron*, 1998, **54**, 1853; (*d*) C. Gómez, S. Ruiz and M. Yus, *Tetrahedron*, 1999, **55**, 7017; (*e*) D. Guijarro and M. Yus, *J. Organomet. Chem.*, 2001, **624**, 53.

10 Generation of benzyllithiums by halogen–lithium exchange: (*a*) W. E. Parham, L. D. Jones and Y. A. Sayed, *Org. Chem.*, 1976, **41**, 1184; (*b*) S. Warren, P. Wyatt, M. McPartlin and T. Woodroffe, *Tetrahedron Lett.*, 1996, **37**, 5609; (*c*) L. Kupracz and A. Kischning, *Adv. Synth. Catal.*, 2013, **355**, 3375.

11 Generation of benzyllithiums by other methods: (*a*) H. Gilman and H. McNinch, *J. Org. Chem.*, 1961, **26**, 3723; (*b*) D. F. Hoeg and D. I. Lusk, *J. Organomet. Chem.*, 1966, **5**, 1; (*c*) C. G. Screttas and M. Micha-Screttas, *J. Org. Chem.*, 1979, **44**, 713; (*d*) M. Schlosser and S. Sven, *Tetrahedron Lett.*, 1984, **25**, 741; (*e*) M. Clarembeau and A. Krief, *Tetrahedron Lett.*, 1985, **26**, 1093; (*f*) T. Hiiro, N. Kambe, A. Ogawa, N. Miyoshi, S. Murai and N. Sonoda, *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 1187; (*g*) D. Guijarro, B. Mancheño and M. Yus, *Tetrahedron*, 1992, **48**, 4593; (*h*) C. Strohmann, K. Lehmen, K. Wild and D. Schildbach, *Organometallics*, 2002, **21**, 3079; (*i*) M. Casimiro, P. Oña-Burgos, J. Meyer, S. Styra, I. Kuzu, F. Breher and I. Fernández, *Chem. – Eur. J.*, 2013, **19**, 691.

12 Generation of other benzylmetallics: (*a*) A. H. Stoll, A. Krasovskiy and P. Knochel, *Angew. Chem., Int. Ed.*, 2006, **45**, 606; (*b*) A. Metzger, F. M. Piller and P. Knochel, *Chem. Commun.*, 2008, 5824; (*c*) Y.-H. Chen, M. Sun and P. Knochel, *Angew. Chem., Int. Ed.*, 2009, **48**, 2236; (*d*) C. Duplais, A. Krasovskiy, A. Wattenberg and B. H. Lipshutz, *Chem. Commun.*, 2010, **46**, 562; (*e*) T. D. Bluemke, K. Groll, K. Karaghiosoff and P. Knochel, *Org. Lett.*, 2011, **13**, 6440; (*f*) D.-G. Yu, X. Wang, R.-Y. Zhu, S. Luo, X.-B. Zhang, B.-Q. Wang, L. Wang and Z.-J. Shi, *J. Am. Chem. Soc.*, 2012, **134**, 14638; (*g*) Y. Fu, Y. Liu, Y. Chen, H. M. Hügel, M. Wang, D. Huanga and Y. Hua, *Org. Biomol. Chem.*, 2012, **10**, 7669; (*h*) G. Dagousset, C. Francois, T. Leon, R. Blanc, E. Sansiaume-Dagousset and P. Knochel, *Synthesis*, 2014, 3133.

13 N. Chinkov, H. Chechik, S. Majumdar, A. Liard and I. Marek, *Synthesis*, 2002, 2473.

14 (*a*) P. Rys, *Acc. Chem. Res.*, 1976, **10**, 345; (*b*) P. Rys, *Angew. Chem., Int. Ed. Engl.*, 1977, **12**, 807.

15 (*a*) A. Nagaki, M. Togai, S. Suga, N. Aoki, K. Mae and J. Yoshida, *J. Am. Chem. Soc.*, 2005, **127**, 11666; (*b*) J. Yoshida, A. Nagaki, T. Iwasaki and S. Suga, *Chem. Eng. Technol.*, 2005, **28**, 259; (*c*) A. Nagaki, N. Takabayashi, Y. Tomida and J. Yoshida, *Org. Lett.*, 2008, **18**, 3937;

(*d*) A. Nagaki, D. Ichinari and J. Yoshida, *Chem. Commun.*, 2013, **49**, 3242.

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

17 T. Jing, T. Ting, C. Chia, L. Hsing, Z. Jia and T. Sheng, *Synthesis*, 2010, 4242.

18 (*a*) Y. He, W. Wu, G. Zhao, Y. Liu and Y. Li, *Macromolecules*, 2008, **41**, 9760; (*b*) A. H. Younes, L. Zhang, M. W. Davidson and L. Zhu, *Org. Biomol. Chem.*, 2010, **8**, 5431; (*c*) C. Zhang, J. Sun, R. Li, S. Sun, E. Lafalce and X. Jiang, *Macromolecules*, 2011, **44**, 6389.

19 I. S. Young and P. S. Baran, *Nat. Chem.*, 2009, **1**, 193.