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Editor's Choice

Flash Chemistry Using Trichlorovinyllithium: Switching the Reaction Pathways by High-resolution Reaction Time Control

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High-resolution reaction time control in flow microreactors enables the reaction-pathway switching of trichlorovinyllithium generated by the H/Li exchange of trichloroethene. The method was successfully applied to the synthesis of 1,1,2-trichloroalkenes, 1-chloroalkynes, and unsymmetrically disubstituted ethynes.

The development of reactions in which one set of starting materials results in the selective formation of different compounds at will has attracted significant interest in recent organic chemistry.[1] If one set of starting materials gives more than one compound by simply changing the reaction conditions, the method provides a powerful tool in organic synthesis. In particular, the effective use of biomass materials is one of the most prominent examples of such cases.[2] Herein we show that flash chemistry[3] using flow microreactors[4–6] is effective for switching reaction pathways to give different products at will.

Recently, flow microreactors have received significant research interest from both academia and industry, because they are expected to make a revolutionary change in chemical synthesis and production. For example, flow microreactors are advantageous for reactions that involve unstable short-lived reactive intermediates.[7] Unstable intermediates can be transferred to another location to be used in the next reaction before they decompose by virtue of their extremely short residence time in flow microreactors. Therefore, many chemical conversions that are impossible in macro batch reactors have been successfully accomplished using flow microreactors (flash chemistry).

Carbon–carbon triple and double bonds frequently occur in a variety of organic molecules and the development of new, versatile methods for the synthesis of alkenes and alkynes has still received significant research interest. Reactions of 2-halovinylmetals serve as powerful methods for this purpose.[8,9] Especially, 2-halovinyllithiums are attractive intermediates because of their high reactivity compared to other 2-halovinylmetals.[10] Direct reactions with electrophiles give alkenes and the elimination of lithium halides gives alkynes, but the control of β-elimination is often problematic. We have recently, however, found that the elimination of LiCl from *trans*-1,2-dichlorovinyllithium, which is generated by the H/Li exchange of *trans*-1,2-dichloroethene, was successfully controlled by adjusting the residence time in flow microreactors.[11] Either direct reaction with an electrophile, to give substituted 1,2-dichloroethenes, or the β-elimination followed by the reaction with an electrophile, to give substituted ethynes, was performed selectively at will. We envisaged that the use of trichlorovinyllithium should also be useful for similar transformations.[12] Notably, the starting material, trichloroethene, is much cheaper than *trans*-1,2-dichloroethene. However, to the best of our knowledge, such studies have not been reported so far, presumably because of the difficulty in the control of β-elimination of LiCl from trichlorovinyllithium. In this paper we report that the reaction pathways of trichlorovinyllithium generated by the H/Li exchange of trichloroethene can be switched at will based on high-resolution reaction time control in flow microreactors to obtain 1,1,2-trichloroalkenes and 1-chloroalkynes after reaction with electrophiles (Figure 1). The chlorine functionality in the products can be used for further transformation. For example, the Cl/Li exchange of 1-chloroalkynes followed by reaction with electrophiles enables the synthesis of unsymmetrically disubstituted ethynes (Figure 1).

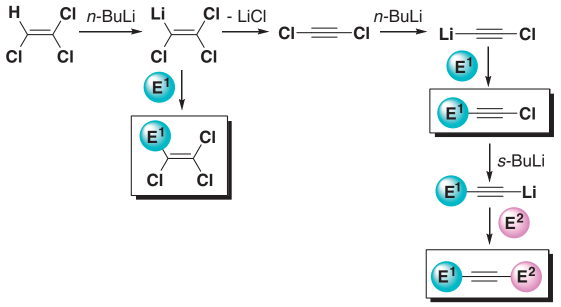
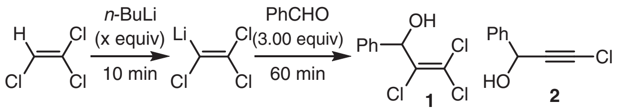


Figure 1. Synthesis of chloroalkenes and alkynes from trichloroethene.

Table 1. H/Li exchange of trichloroethene with *n*-BuLi followed by reaction with benzaldehyde in a batch macroreactor



Temperature /°C	x/equiv	Yield/%[a] 1	2
−78	1.05	0	44
	2.00	0	89
0	1.05	0	48
	2.00	0	75

[a] Determined by GC analysis with an internal standard.

First, we examined the H/Li exchange of trichloroethene with *n*-BuLi (1.05 or 2.00 equiv) followed by reaction with benzaldehyde in a conventional batch macroreactor. As shown in Table 1, 2,3,3-trichloro-1-phenylprop-2-en-1-ol (**1**) was not obtained at all. A significant amount of 3-chloro-1-phenylprop-2-yn-1-ol (**2**) was produced in all cases, presumably because of the extremely fast elimination of LiCl from trichlorovinyllithium under these conditions.

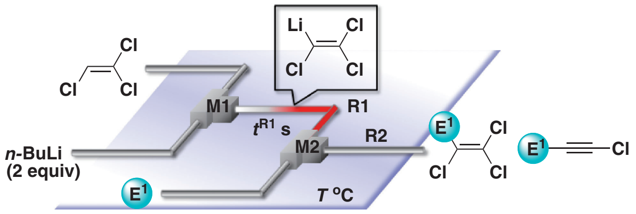


Figure 2. A flow microreactor system for the H/Li exchange of trichloroethene with *n*-BuLi (2.00 equiv) and the subsequent reaction with electrophiles. T-shaped micromixers: **M1** and **M2**, microtube reactors: **R1** and **R2**.

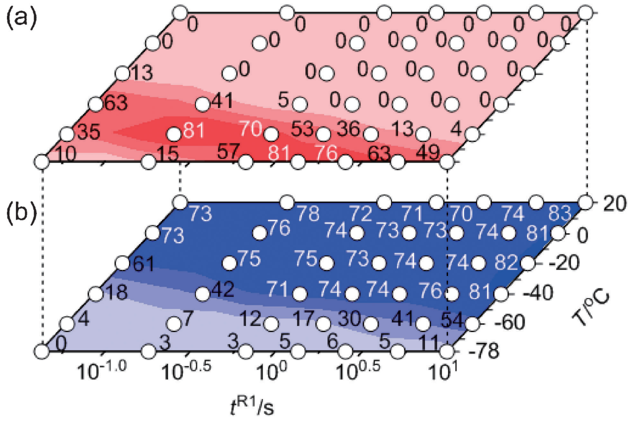


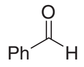
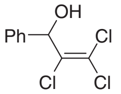
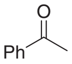
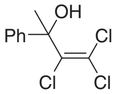
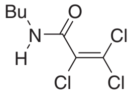
Figure 3. Effects of temperature (T) and residence time (t^{R1}) for H/Li exchange of trichloroethene with *n*-BuLi (2.00 equiv) followed by the reaction with benzaldehyde using the flow microreactor system. (a) Contour map with scattered overlay of the yield of 2,3,3-trichloro-1-phenylprop-2-en-1-ol (**1**), and (b) contour map with scattered overlay of the yield of 3-chloro-1-phenylprop-2-yn-1-ol (**2**).

Next, the reaction was examined using a flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2**) and two microtube reactors (**R1** and **R2**), shown in Figure 2, with varying residence time (t^{R1}) in **R1**, and temperature (T).

The results are summarized in Figure 3, in which the yields of **1** and **2** are plotted against T and t^{R1} as a contour map with a scattered overlay. As shown in Figure 3a, high yields of **1** (>80%) were obtained with short t^{R1} such as 0.18 s at −60 °C. The increase in t^{R1} and T caused a decrease in the yield of **1** because of the elimination of LiCl from trichlorovinyllithium. In fact, trichlorovinyllithium undergoes β-elimination in the high temperature–long residence time region to give **2**. Presumably, the initially formed dichloroethyne undergoes Cl/Li exchange and the subsequent reaction with benzaldehyde gives **2** (Figure 3b). These results demonstrate that high-resolution residence time control enables the control of β-elimination and that the present method is effective for the selective synthesis of either alkene **1** or alkyne **2** at will.

Under optimized conditions ($T = -60$ °C, $t^{R1} = 0.18$ s) for the synthesis of **1**, the reactions with various electrophiles such as benzaldehyde, acetophenone, and butyl isocyanate were successfully carried out to obtain the corresponding 1,1,2-trichloroalkenes in good yields (Table 2). The three chlorine atoms could be used for further transformations to give a variety of substituted alkenes.[13]

Table 2. Reactions of trichlorovinyllithium with various electrophiles

Electrophile	Product	Yield/%[a]
		81[a] (64)[b]
		46[b]
Bu−N=C=O		57[b]

[a]GC yield. [b]Yield of isolated product.

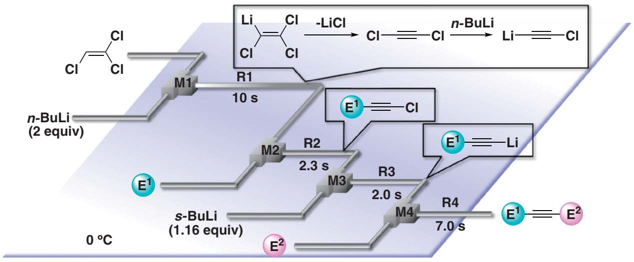
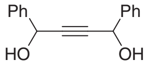
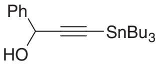
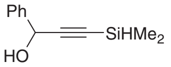
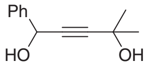
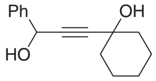
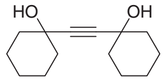
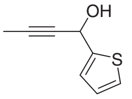
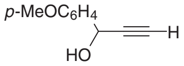


Figure 4. An integrated flow microreactor system for the synthesis of unsymmetrically disubstituted ethynes by sequential introduction of two electrophiles. T-shaped micromixers: **M1**, **M2**, **M3**, and **M4**, microtube reactors: **R1**, **R2**, **R3**, and **R4**.

Table 3. Synthesis of unsymmetrically disubstituted ethynes from trichloroethene via sequential lithiations followed by reactions with various electrophiles

Electrophile	Product	Yield/%[a]
E^1: PhCHO E^2: PhCHO		88
E^1: PhCHO E^2: Bu_3SnCl		79
E^1: PhCHO E^2: Me_2SiHCl		74
E^1: PhCHO E^2: $(CH_3)_2CO$		56
E^1: PhCHO E^2: $(CH_2)_5CO$		67
E^1: $(CH_2)_5CO$ E^2: $(CH_2)_5CO$		56
E^1: MeOTf E^2: 2-thiophenaldehyde		48
E^1: p-$MeOC_6H_4CHO$ E^2: H_2O		52

[a]Yield of isolated product.

Next, we focused on the synthesis of unsymmetrically disubstituted ethynes via β-elimination using an integrated flow microreactor system consisting of four micromixers (**M1**, **M2**, **M3**, and **M4**) and four microtube reactors (**R1**, **R2**, **R3**, and **R4**), as shown in Figure 4. The use of two equivalents of *n*-BuLi led to the

Cl/Li exchange of the initially formed dichloroethyne. The resulting chloroethynyllithium was reacted with electrophile E^1 in **M2** and **R2**. The second Cl/Li exchange with *s*-BuLi in **M3** and **R3**, followed by reactions with electrophile E^2 in **M4** and **R4**, gave unsymmetrically disubstituted ethynes, as shown in Table 3. It is important to note that the whole transformation can be performed at 0 °C.

In conclusion, we demonstrated that flash chemistry using flow microreactor systems enables the switching of the reaction pathways of trichlorovinyllithium and that a variety of 1,1,2-trichloroalkenes, 1-chloroalkynes, and unsymmetrically disubstituted ethynes can be selectively synthesized from a single starting material, trichloroethene, at will by changing the residence time and temperature.

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Supporting Information is available electronically on J-STAGE.

References and Notes

1 a) M. M. Midland, R. L. Halterman, *J. Org. Chem.* **1981**, *46*, 1227. b) A. J. Laurent, S. Leniak, *Tetrahedron Lett.* **1992**, *33*, 3311. c) N. Dyatkina, B. Costisella, F. Theil, M. von Janta-Lipinski, *Tetrahedron Lett.* **1994**, *35*, 1961. d) S. Kobayashi, T. Hayashi, *J. Org. Chem.* **1995**, *60*, 1098. e) K. Hiroya, N. Suzuki, A. Yasuhara, Y. Egawa, A. Kasano, T. Sakamoto, *J. Chem. Soc., Perkin Trans. 1* **2000**, 4339. f) C. Feng, X. Wang, B.-Q. Wang, K.-Q. Zhao, P. Hu, Z.-J. Shi, *Chem. Commun.* **2012**, *48*, 356.

2 a) A.-L. Marshall, P. J. Alaimo, *Chem.—Eur. J.* **2010**, *16*, 4970. b) P. Gallezot, *Chem. Soc. Rev.* **2012**, *41*, 1538. c) D. M. Alonso, S. G. Wettstein, J. A. Dumesic, *Green Chem.* **2013**, *15*, 584. d) P. A. Wilbon, F. Chu, C. Tang, *Macromol. Rapid Commun.* **2013**, *34*, 8.

3 a) J. Yoshida, *Chem. Commun.* **2005**, 4509. b) J. Yoshida, A. Nagaki, T. Yamada, *Chem.—Eur. J.* **2008**, *14*, 7450. c) P. J. Nieuwland, K. Koch, N. van Harskamp, R. Wehrens, J. C. M. van Hest, F. P. J. T. Rutjes, *Chem.—Asian J.* **2010**, *5*, 799. d) J. Yoshida, *Chem. Rec.* **2010**, *10*, 332. e) J. Yoshida, Y. Takahashi, A. Nagaki, *Chem. Commun.* **2013**, *49*, 9896.

4 Books on flow chemistry and flow microreactor synthesis: a) W. Ehrfeld, V. Hessel, H. Löwe, *Microreactors: New Technology for Modern Chemistry*, Wiley-VCH, Weinheim, **2000**. doi:10.1002/3527601953. b) V. Hessel, S. Hardt, H. Löwe, *Chemical Micro Process Engineering: Fundamentals, Modelling and Reactions*, Wiely-VCH Verlag, Weinheim, **2004**. doi:10.1002/3527603042. c) *Micro Precess Engineering: A Comprehensive Handbook*, ed. by V. Hessel, A. Renken, J. C. Schouten, J. Yoshida, Wiley-Blackwell, **2009**. doi:10.1002/9783527631445. d) *Microreactors in Organic Chemistry and Catalysis*, 2nd ed., ed. by T. Wirth, Wiely, **2013**. doi:10.1002/9783527659722.

5 Reviews on flow chemistry and flow microreactor synthesis: a) K. Jähnisch, V. Hessel, H. Löwe, M. Baerns, *Angew. Chem., Int. Ed.* **2004**, *43*, 406. 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. 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.

6 Some selected recent examples: a) D. Cantillo, M. Baghbanzadeh, C. O. Kappe, *Angew. Chem., Int. Ed.* **2012**, *51*, 10190. b) W. Shu, S. L. Buchwald, *Angew. Chem., Int. Ed.* **2012**, *51*, 5355. 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. e) K. C. Basavaraju, S. Sharma, R. A. Maurya, D.-P. Kim, *Angew. Chem., Int. Ed.* **2013**, *52*, 6735. 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) A. Nagaki, D. Ichinari, J. Yoshida, *Chem. Commun.* **2013**, *49*, 3242. l) L. Guetzoyan, N. Nikbin, I. R. Baxendale, S. V. Ley, *Chem. Sci.* **2013**, *4*, 764. m) S. Fuse, Y. Mifune, T. Takahashi, *Angew. Chem., Int. Ed.* **2014**, *53*, 851. n) Z. He, T. F. Jamison, *Angew. Chem., Int. Ed.* **2014**, *53*, 3353. o) A. Nagaki, Y. Takahashi, J. Yoshida, *Chem.—Eur. J.* **2014**, *20*, 7931.

7 a) H. Usutani, Y. Tomida, A. Nagaki, H. Okamoto, T. Nokami, J. Yoshida, *J. Am. Chem. Soc.* **2007**, *129*, 3046. b) A. Nagaki, H. Kim, J. Yoshida, *Angew. Chem., Int. Ed.* **2008**, *47*, 7833. c) A. Nagaki, H. Kim, J. Yoshida, *Angew. Chem., Int. Ed.* **2009**, *48*, 8063. d) A. Nagaki, E. Takizawa, J. Yoshida, *J. Am. Chem. Soc.* **2009**, *131*, 1654. e) A. Nagaki, A. Kenmoku, Y. Moriwaki, A. Hayashi, J. Yoshida, *Angew. Chem., Int. Ed.* **2010**, *49*, 7543. f) Y. Tomida, A. Nagaki, J. Yoshida, *J. Am. Chem. Soc.* **2011**, *133*, 3744. g) H. Kim, A. Nagaki, J. Yoshida, *Nat. Commun.* **2011**, *2*, 264. h) A. Nagaki, N. Takabayashi, Y. Moriwaki, J. Yoshida, *Chem.—Eur. J.* **2012**, *18*, 11871. i) A. Nagaki, D. Ichinari, J. Yoshida, *J. Am. Chem. Soc.* **2014**, *136*, 12245.

8 Reports on 1-metalated 2-haloalkenes: a) R. F. Cunico, Y.-K. Han, *J. Organomet. Chem.* **1978**, *162*, 1. b) F. G. Drakesmith, R. D. Richardson, O. J. Stewart, P. Tarrant, *J. Org. Chem.* **1968**, *33*, 286. c) G. Boche, J. C. W. Lohrenz, *Chem. Rev.* **2001**, *101*, 697.

9 The synthesis of alkynes from 1-metalated 2-haloalkenes: a) G. Köbrich, K. Flory, *Tetrahedron Lett.* **1964**, *5*, 1137. b) F. G. Drakesmith, O. J. Stewart, P. Tarrant, *J. Org. Chem.* **1968**, *33*, 472. c) H. Hart, K. Shahlai, *Tetrahedron Lett.* **1987**, *28*, 5437. The synthesis of alkynes from 1-metalated 1-haloalkenes: d) M. Topolski, *J. Org. Chem.* **1995**, *60*, 5588. e) M. Topolski, M. Duraisamy, J. Rachoń, J. Gawronski, K. Gawronska, V. Goedken, H. M. Walborsky, *J. Org. Chem.* **1993**, *58*, 546. f) D. Y. Curtin, E. W. Flynn, *J. Am. Chem. Soc.* **1959**, *81*, 4714. g) T. Okuyama, H. Yamataka, *Can. J. Chem.* **1999**, *77*, 577. h) D. J. Nelson, *J. Org. Chem.* **1984**, *49*, 2059. i) M. Braun, *Angew. Chem., Int. Ed.* **1998**, *37*, 430.

10 a) H. G. Viehe, *Chem. Ber.* **1959**, *92*, 1950. b) G. Köbrich, H. Trapp, I. Hornke, *Tetrahedron Lett.* **1964**, *5*, 1130. c) G. Köbrich, A. Akhtar, F. Ansari, W. E. Breckoff, H. Büttner, W. Drischel, R. H. Fischer, K. Flory, H. Fröhlich, W. Goyert, H. Heinemann, I. Hornke, H. R. Merkle, H. Trapp, W. Zündorf, *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 41. d) G. Köbrich, *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 473. e) B. B. Snider, D. M. Roush, *J. Am. Chem. Soc.* **1979**, *101*, 1906.

11 A. Nagaki, C. Matsuo, S. Kim, K. Saito, A. Miyazaki, J. Yoshida, *Angew. Chem., Int. Ed.* **2012**, *51*, 3245.

12 a) R. West, L. C. Quass, *J. Organomet. Chem.* **1969**, *18*, 55. b) A. S. Kende, P. Fludzinski, *Synthesis* **1982**, 455. c) S. Sekigawa, T. Shimizu, W. Ando, *Tetrahedron* **1993**, *49*, 6359. d) J. Balsells, A. Moyano, M. A. Pericàs, A. Riera, *Tetrahedron: Asymmetry* **1997**, *8*, 1575. e) S. J. Blanksby, D. Schröder, S. Dua, J. H. Bowie, H. Schwarz, *J. Am. Chem. Soc.* **2000**, *122*, 7105. f) Y. Yokoyama, T. Sagisaka, Y. Yamaguchi, Y. Yokoyama, J. Kiji, T. Okano, A. Takemoto, S. Mio, *Chem. Lett.* **2000**, 220. g) J. Kiji, Y. Kondou, M. Asahara, Y. Yokoyama, T. Sagisaka, *J. Mol. Catal. A: Chem.* **2003**, *197*, 127. h) Y. K. Kang, P. Deria, P. J. Carroll, M. J. Therien, *Org. Lett.* **2008**, *10*, 1341. i) O. Ekkert, G. Kehr, R. Fröhlich, G. Erker, *J. Am. Chem. Soc.* **2011**, *133*, 4610. j) A. E. Brown, B. E. Eichler, *Tetrahedron Lett.* **2011**, *52*, 1960.

13 a) D. Naskar, S. Chowdhury, S. Roy, *Tetrahedron Lett.* **1998**, *39*, 699. b) S. C. Roy, C. Guin, G. Maiti, *Tetrahedron Lett.* **2001**, *42*, 9253. c) C. Kuang, H. Senboku, M. Tokuda, *Synlett* **2000**, 1439. d) T. J. Barton, G. T. Burns, *Organometallics* **1982**, *1*, 1455.