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Microreactors

Lithiation of 1,2-Dichloroethene in Flow Microreactors: Versatile Synthesis of Alkenes and Alkynes by Precise Residence-Time Control**

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Although a variety of methods for the synthesis of alkenes and alkynes have been developed, the pursuit of new and versatile methods remains topical. Reactions that involve 2-halovinyl metals serve as powerful methods in this context.[1] For example, the β-elimination of 2-halovinyl metals is one of the most straightforward methods for making a carbon–carbon triple bond.[2] In contrast, the direct use of 2-halovinyl metals without β-elimination serves as a method for synthesizing substituted alkenes that contain a halogen atom,[3] which can be used for further reactions.[4] 2-Halovinyllithium compounds are especially attractive intermediates because of their high reactivity relative to other 2-halovinyl metals. However, the use of 2-halovinyllithium is often problematic as a result of competing β-elimination.

In flash chemistry[5] in a flow microreactor system,[6–8] a highly reactive and unstable intermediate can be generated and used in a subsequent reaction before it decomposes by virtue of precise control of the reaction time.[9] Herein, we report that flash chemistry enables the versatile synthesis of alkenes and alkynes from *trans*-1,2-dichloroethene.

The first step in the synthesis is the generation of 1,2-dichlorovinyllithium[10] by deprotonation of *trans*-1,2-dichloroethene. It is well known that the reaction should be conducted at −78 °C or below in a batch macroreactor. To confirm this, the reaction of *trans*-1,2-dichloroethene with *n*BuLi (1.05 equiv) and subsequent treatment with benzaldehyde was examined at 0 °C in a conventional batch macroreactor. The desired product, (*E*)-2,3-dichloro-1-phenylprop-2-en-1-ol (**1a**, Table 1, below) was not obtained at all because a significant amount of 3-chloro-1-phenyl-prop-2-yn-1-ol (**2a**) was produced. In contrast the reaction at −78 °C gave **1a** in 81 % yield (See the Supporting Information for details).

We examined the reaction in a flow microreactor system that consists of two T-shaped micromixers (M1 and M2) and two microtube reactors (R1 and R2), as shown in Figure 1.

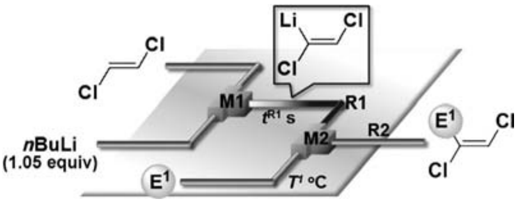

Figure 1. A flow microreactor system for the lithiation of *trans*-1,2-dichloroethene with *n*BuLi and subsequent reaction with electrophiles. T-shaped micromixers: M1 and M2; microtube reactors: R1 and R2.

The reaction was carried out over various residence times (t^{R1}) in R1, and at various temperatures (T^1). The results are summarized in Figure 2, in which the yield of **1a** is plotted against T^1 and t^{R1} as a contour map with scattered overlay. High yields (greater than 80 %) were obtained with a short t^{R1}, such as 0.055 s at 0 °C. An increase in t^{R1} caused a decrease in the yield, presumably because of β-elimination of *trans*-1,2-dichlorovinyllithium. At low temperatures, the yield was low after a short t^{R1} because of incomplete deprotonation. It is important to note that *trans*-1,2-dichlorovinyllithium could be used for the subsequent reaction at 0 °C. In fact, under the optimized conditions ($T^1 = 0$ °C, $t^{R1} = 0.055$ s), reactions with various electrophiles were successfully carried out to obtain the corresponding alkenes, which contain two chlorine atoms,

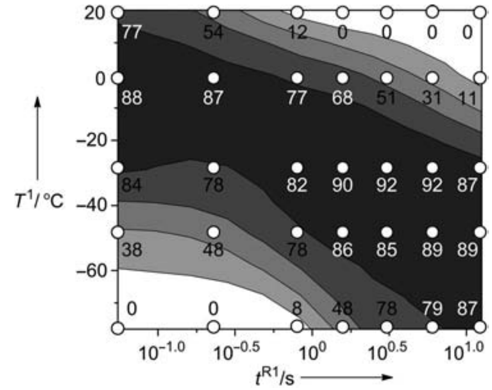

Figure 2. A contour map with scatter overlay of the effects of temperature (T^1) and residence time (t^{R1}) on the yield [%] of (*E*)-2,3-dichloro-1-phenylprop-2-en-1-ol (**1a**) from the lithiation of *trans*-1,2-dichloroethene with *n*BuLi (1.05 equiv) and subsequent reaction with benzaldehyde in the flow microreactor system.

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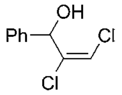
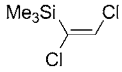
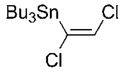
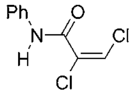
in high yields (Table 1). The two chlorine atoms could be used for further transformations to obtain a variety of substituted alkenes.[11]

Table 1: Reactions of lithiated *trans*-1,2-dichloroethene with various electrophiles.[a]

Electrophile	Product	Yield [%]
PhCHO	 **1a**	88
Me_3SiCl Me_3SiOTf	 **1b**	91 92
Bu_3SnCl	 **1c**	85[b]
PhNCO	 **1d**	93

[a] $T^1 = 0\,°C$, $t^{R1} = 0.055$ s. Determined by GC analysis with an internal standard. [b] Yield of isolated product.

We examined sequential reactions in an integrated flow microreactor system that consists of four micromixers (M1, M2, M3, and M4) and four microtube reactors (R1, R2, R3, and R4), as shown in Figure 3. *Trans*-1,2-dichlorovinyllithium was generated in M1 and R1 at 0 °C ($t^{R1} = 0.055$ s). The reaction with the electrophile was carried out in M2 and R2 at the same temperature ($t^{R2} = 8.2$ s). The desired product 2,3-dichloro-3-trimethylsilyl-1-phenyl-prop-(2*E*)-en-1-ol (**3ab**, Table 2) was obtained in a high yield (greater than 70%) from the reaction with Me_3SiOTf (Tf = trifluoromethanesulfonate) only at low temperatures and by adjusting the residence time ($t^{R3} = 4.6$ s, $T^2 = -78\,°C$), presumably because β-elimination of the monosubstituted *trans*-1,2-dichlorovinyllithium intermediate is very fast. Reactions with various electrophiles were performed under the optimized conditions to obtain the corresponding alkenes, which bear two chlorine atoms, in high yields (Table 2).

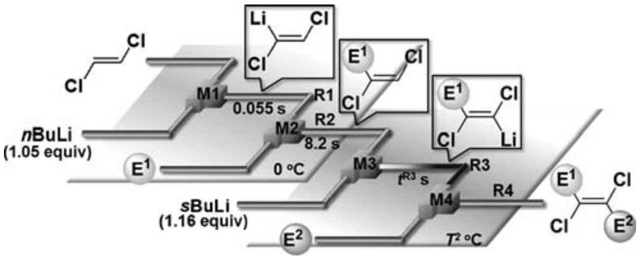
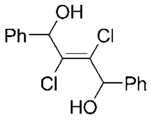
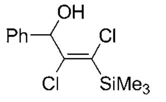
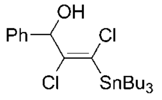
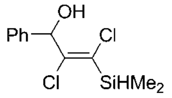


Figure 3. An integrated flow microreactor system for the synthesis of disubstituted dichloroalkenes by sequential introduction of two electrophiles. T-shaped micromixers: M1, M2, M3, and M4, microtube reactors: R1, R2, R3, and R4.

Table 2: Synthesis of disubstituted 1,2-dichloroethenes.[a]

Electrophile	Product	Yield [%]
E^1: PhCHO E^2: PhCHO	 **3aa**	71
E^1: PhCHO E^2: Me_3SiOTf	 **3ab**	72
E^1: PhCHO E^2: Bu_3SnCl	 **3ac**	73[b]
E^1: PhCHO E^2: Me_2SiHCl	 **3ad**	62[b]

[a] $T^1 = 0\,°C$, $t^{R1} = 0.055$ s, $T^2 = -78\,°C$, $t^{R3} = 4.6$ s. Determined by GC analysis with an internal standard. [b] Yield of isolated product.

We examined the synthesis of asymmetric disubstituted alkynes from *trans*-1,2-dichloroethene (Figure 4). 1,2-Dichlorovinyllithium undergoes β-elimination with a longer residence time at 0 °C to give chloroacetylene. The use of 2.10 equiv of *n*BuLi gave rise to deprotonation, and the subsequent reaction with benzaldehyde gave 3-chloro-1-phenylprop-2-yn-1-ol (**2a**) in 90% yield ($t^{R1} = 50$ s, see the Supporting Information for details). This result demonstrates that precise control of the residence-time is quite effective for the selective synthesis of either an alkene or an alkyne at will. Furthermore, asymmetric disubstituted alkynes **4** could be synthesized based on the Cl–Li exchange reaction of substituted chloroacetylenes shown in Figure 5. The results are summarized in Table 3. Furthermore, asymmetric disubstituted alkynes could also be synthesized by another route. As shown in Figure 5a, lithiation of 1,2-dichloroethene and

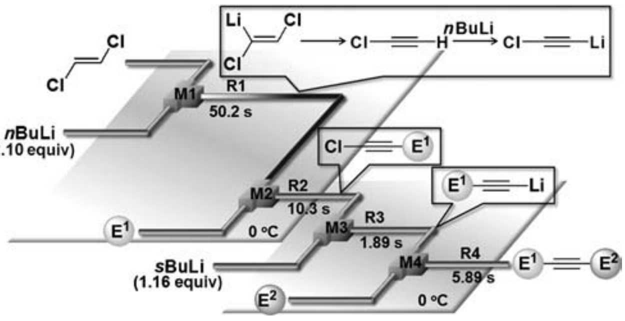


Figure 4. An integrated flow microreactor system for the synthesis of asymmetric disubstituted alkynes.

subsequent reaction with an electrophile gave **1**. Further lithiation, β-elimination, Cl–Li exchange, and reaction with an electrophile gave the corresponding asymmetric disubstituted alkynes **4**. Some examples are shown in Figure 5b.

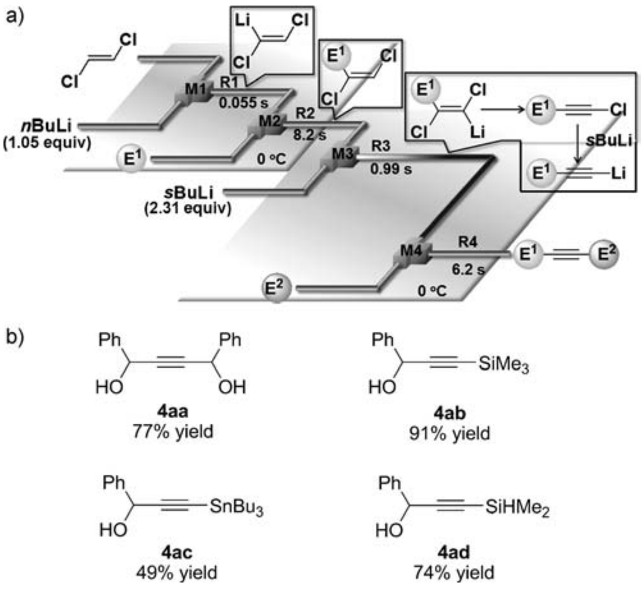
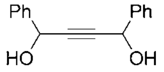
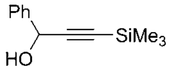
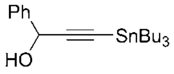
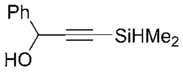
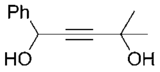
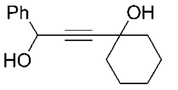
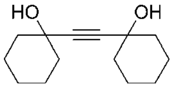
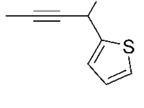
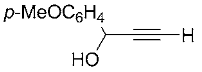
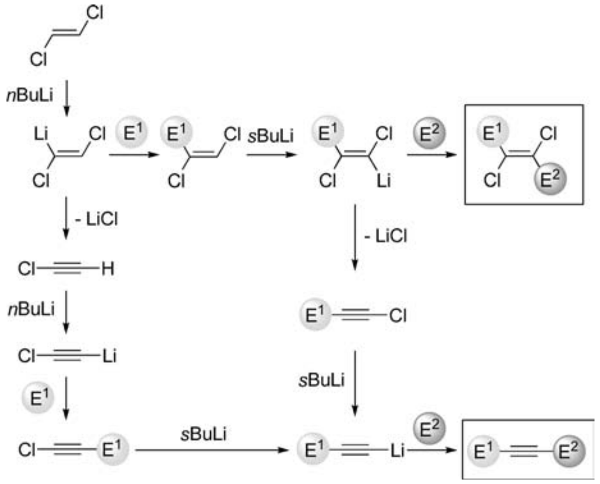


Figure 5. a) An integrated flow microreactor system for an alternative synthesis of asymmetric disubstituted alkynes. b) The structures and the yields of the disubstituted alkynes obtained.

Table 3: Synthesis of asymmetric disubstituted alkynes.

Electrophile	Product	Yield [%][a]
E^1: PhCHO E^2: PhCHO	 **4aa**	78
E^1: PhCHO E^2: Me_3SiOTf	 **4ab**	66(78)[b]
E^1: PhCHO E^2: Bu_3SnCl	 **4ac**	28(48)[c]
E^1: PhCHO E^2: Me_2SiHCl	 **4ad**	73(77)[b]
E^1: PhCHO E^2: $(CH_3)_2CO$		74
E^1: PhCHO E^2: $(CH_2)_5CO$		79
E^1: $(CH_2)_5CO$ E^2: $(CH_2)_5CO$		71
E^1: MeOTf E^2: 2-thiophenaldehyde		84
E^1: Ph_2PCl E^2: Ph_2PCl	$Ph_2P{\equiv}PPh_2$	49
E^1: p-$MeOC_6H_4CHO$ E^2: H_2O		89

[a] Yield of isolated product. [b] Determined by GC analysis with an internal standard. [c] Determined by ^1H NMR analysis with an internal standard.



Scheme 1. Versatile synthesis of alkenes and alkynes from *trans*-1,2-dichloroethene.

In conclusion, we have demonstrated that precise control of the residence time enables the reaction pathway of a 1,2-dichlorovinyllithium intermediate to be switched. Based on this switch, versatile syntheses of alkenes and alkynes from *trans*-1,2-dichloroethene were developed by space integration[12] (Scheme 1).

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[1] a) R. F. Cunico, Y. 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.

[2] 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. Rachoh, 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.* **1998**, *110*, 444; *Angew. Chem. Int. Ed.* **1998**, *37*, 430.

[3] a) G. Köbrich, *Angew. Chem.* **1967**, *79*, 15; *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 41; b) G. Köbrich, *Angew. Chem.* **1972**, *84*, 557; *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 473.

[4] a) J. Barluenga, P. Moriel, F. Aznar, C. Valdés, *Adv. Synth. Catal.* **2006**, *348*, 347; b) J. Barluenga, M. A. Fernández, F. Aznar, C. Valdés, *Chem. Commun.* **2002**, 2362; c) J. Barluenga, M. A. Fernández, F. Aznar, C. Valdés, *Chem. Eur. J.* **2004**, *10*, 494; d) J. Barluenga, M. A. Fernández, F. Aznar, C. Valdés, *Chem. Commun.* **2004**, 1400; e) J. Barluenga, F. Aznar, P. Moriel, C. Valdés, *Adv. Synth. Catal.* **2004**, *346*, 1697.

[5] a) J. Yoshida, *Flash Chemistry. Fast Organic Synthesis in Microsystems*, Wiley-Blackwell, Hoboken, **2008**; b) J. Yoshida, *Chem. Commun.* **2005**, 4509; c) J. Yoshida, A. Nagaki, T. Yamada, *Chem. Eur. J.* **2008**, *14*, 7450; d) J. Yoshida, *Chem. Rec.* **2010**, *10*, 332.

[6] a) W. Ehrfeld, V. Hessel, H. Löwe, *Microreactors*, Wiley-VCH, Weinheim, **2000**; b) V. Hessel, S. Hardt, H. Löwe, *Chemical Micro Process Engineering*, Wiley-VCH, Weinheim, **2004**; c) V. Hessel, A. Renken, J. C. Schouten, J. Yoshida, *Micro Process Engineering*, Wiley-Blackwell, Hoboken, **2009**.

[7] Reviews on microreactors: a) K. Jähnisch, V. Hessel, H. Löwe, M. Baerns, *Angew. Chem.* **2004**, *116*, 410; *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) T. Fukuyama, M. T. Rahman, M. Sato, I. Ryu, *Synlett* **2008**, 151; d) R. L. Hartman, K. F. Jensen, *Lab Chip* **2009**, *9*, 2495; e) J. P. McMullen, K. F. Jensen, *Annu. Rev. Anal. Chem.* **2010**, *3*, 19; f) J. Yoshida, H. Kim, A. Nagaki, *ChemSusChem* **2011**, *4*, 331.

[8] Some recent examples: a) A. Nagaki, M. Togai, S. Suga, N. Aoki, K. Mae, J. Yoshida, *J. Am. Chem. Soc.* **2005**, *127*, 11666; b) P. He, P. Watts, F. Marken, S. J. Haswell, *Angew. Chem.* **2006**, *118*, 4252; *Angew. Chem. Int. Ed.* **2006**, *45*, 4146; c) K. Tanaka, S. Motomatsu, K. Koyama, S. Tanaka, K. Fukase, *Org. Lett.* **2007**, *9*, 299; d) H. R. Sahoo, J. G. Kralj, K. F. Jensen, *Angew. Chem.* **2007**, *119*, 5806; *Angew. Chem. Int. Ed.* **2007**, *46*, 5704; e) C. H. Hornung, M. R. Mackley, I. R. Baxendale, S. V. Ley, *Org. Process Res. Dev.* **2007**, *11*, 399; f) T. Fukuyama, M. Kobayashi, M. T. Rahman, N. Kamata, I. Ryu, *Org. Lett.* **2008**, *10*, 533; g) C. Wiles, P. Watts, *Org. Process Res. Dev.* **2008**, *12*, 1001; h) A. Nagaki, E. Takizawa, J. Yoshida, *Chem. Lett.* **2009**, *38*, 486; i) I. C. Wienhofer, A. Studer, M. T. Rahman, T. Fukuyama, I. Ryu, *Org. Lett.* **2009**, *11*, 2457; j) A. R. Bogdan, S. L. Poe, D. C. Kubis, S. J. Broadwater, D. T. McQuade, *Angew. Chem.* **2009**, *121*, 8699; *Angew. Chem. Int. Ed.* **2009**, *48*, 8547; k) T. Tricotet, D. F. O'Shea, *Chem. Eur. J.* **2010**, *16*, 6678.

[9] a) H. Usutani, Y. Tomida, A. Nagaki, H. Okamoto, T. Nokami, J. Yoshida, *J. Am. Chem. Soc.* **2007**, *129*, 3046; b) A. Nagaki, Y. Tomida, H. Usutani, H. Kim, N. Takabayashi, T. Nokami, H. Okamoto, J. Yoshida, *Chem. Asian J.* **2007**, *2*, 1513; c) A. Nagaki, N. Takabayashi, Y. Tomida, J. Yoshida, *Org. Lett.* **2008**, *18*, 3937; d) A. Nagaki, H. Kim, J. Yoshida, *Angew. Chem.* **2008**, *120*, 7951; *Angew. Chem. Int. Ed.* **2008**, *47*, 7833; e) A. Nagaki, N. Takabayashi, Y. Tomida, J. Yoshida, *Beilstein J. Org. Chem.* **2009**, *5*, 16; f) Y. Tomida, A. Nagaki, J. Yoshida, *Org. Lett.* **2009**, *11*, 3614; g) A. Nagaki, H. Kim, J. Yoshida, *Angew. Chem.* **2009**, *121*, 8207; *Angew. Chem. Int. Ed.* **2009**, *48*, 8063; h) A. Nagaki, H. Kim, C. Matsuo, J. Yoshida, *Org. Biomol. Chem.* **2010**, *8*, 1212; i) A. Nagaki, E. Takizawa, J. Yoshida, *Chem. Eur. J.* **2010**, *16*, 14149; j) A. Nagaki, H. Kim, Y. Moriwaki, C. Matsuo, J. Yoshida, *Chem. Eur. J.* **2010**, *16*, 11167; k) Y. Tomida, A. Nagaki, J. Yoshida, *J. Am. Chem. Soc.* **2011**, *133*, 3744; l) H. Kim, A. Nagaki, J. Yoshida, *Nat. Commun.* **2011**, *2*, 264; m) A. Nagaki, S. Yamada, M. Doi, Y. Tomida, N. Takabayashi, J. Yoshida, *Green Chem.* **2011**, *13*, 1110.

[10] a) G. Köbrich, H. Trapp, I. Hornke, *Tetrahedron Lett.* **1964**, *5*, 1130; b) G. Köbrich, K. Flory, *Tetrahedron Lett.* **1964**, *5*, 1137; c) G. Köbrich, *Angew. Chem.* **1967**, *79*, 15; *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 41; d) H. G. Viehe, *Chem. Ber.* **1959**, *92*, 1950; e) B. B. Sinder, D. M. Roush, *J. Am. Chem. Soc.* **1979**, *101*, 1906.

[11] 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.

[12] Integration of a sequence of reactions in a flow by adding reaction components at different places: 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.* **2010**, *122*, 7705; *Angew. Chem. Int. Ed.* **2010**, *49*, 7543; c) J. Yoshida, K. Saito, T. Nokami, A. Nagaki, *Synlett* **2011**, 1189.