A Continuous Homologation of Esters: An Efficient Telescoped Reduction—Olefination Sequence
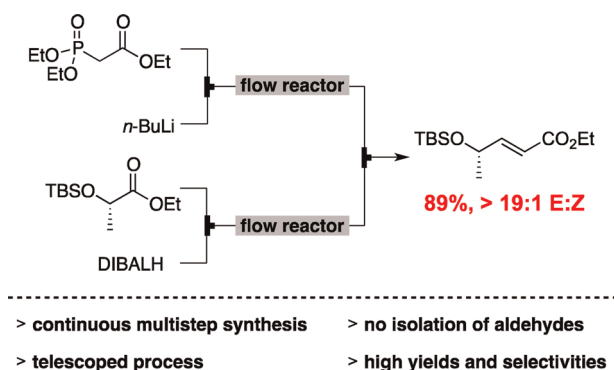
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ABSTRACT

> **continuous multistep synthesis**   > **no isolation of aldehydes**

> **telescoped process**   > **high yields and selectivities**

A continuous protocol for the two-carbon homologation of esters to α,β-unsaturated esters is described. This multireactor homologation telescopes an ester reduction, phosphonate deprotonation, and Horner—Wadsworth—Emmons olefination, thus converting a three-operation procedure into a single, uninterrupted system that eliminates the need for isolation or purification of the aldehyde intermediates. The homologated products are obtained in high yield and selectivity.

The two-carbon homologation of esters to α,β-unsaturated esters is a ubiquitous sequence in synthetic organic chemistry. This fundamental assembly exercise can be achieved in two synthetic steps that comprise the Horner—Wadsworth—Emmons olefination[1] of an aldehyde that is prepared by the partial reduction of an ester using diisobutylaluminum hydride[2] (DIBALH) (Figure 1a). However, the capriciousness often observed for the DIBALH reduction step has conferred such a notorious reputation upon this transformation that this sequence is rarely used.[3] Accordingly, one often resorts to a multistep alternative: reduction of the ester to a primary alcohol and then oxidation to the aldehyde, followed by the olefination step (Figure 1b). This three-step approach is undesirable as it generates additional waste, in addition to requiring the

isolation—and often purification—of aldehydes that may be troublesome to handle.

Although one-pot procedures for this homologation sequence have been reported,[4] this approach has not been widely used. Moreover, the requirement for cryogenic temperatures renders this method undesirable for use on a large scale. Recently, continuous flow methods[5,6] have emerged as an enabling tool, particularly for the execution

(1) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863–927.

(2) Zakharkin, L. I.; Khorlina, I. M. *Tetrahedron Lett.* **1962**, 619–620.

(3) Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 2854–2867.

(4) For one-pot DIBALH reduction/olefination sequences, see: (a) Takacs, J. M.; Helle, M. A.; Seely, F. L. *Tetrahedron Lett.* **1986**, *27*, 1257–1260. (b) Hoye, T. R.; Kopel, L. C.; Ryba, T. D. *Synthesis* **2006**, 1572–1574.

(5) For recent general reviews on continuous-flow chemistry, see: (a) Wirth, T. *Microreactors in Organic Synthesis and Catalysis*; Wiley-VCH: Weinheim, 2008. (b) Hartman, R. L.; Jensen, K. F. *Lab Chip* **2009**, *9*, 2495. (c) Mason, B. P.; Price, K. E.; Steinbacher, J. L.; Bogdan, A. R.; McQuade, D. T. *Chem. Rev.* **2007**, *107*, 2300. (d) Geyer, K.; Gustafsson, T.; Seeberger, P. H. *Synlett* **2009**, 2382. (e) Kirschning, A.; Solodenko, W.; Mennecke, K. *Chem.—Eur. J.* **2006**, *12*, 5972. (f) Wiles, C.; Watts, P. *Eur. J. Org. Chem.* **2008**, *10*, 1655. (g) Ley, S. V.; Baxendale, I. R. *Proc. Bosen Symp., Systems Chem.* **2008**, 65. (h) Jähnisch, K.; Hessel, V.; Löwe, H.; Baerns, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 406.
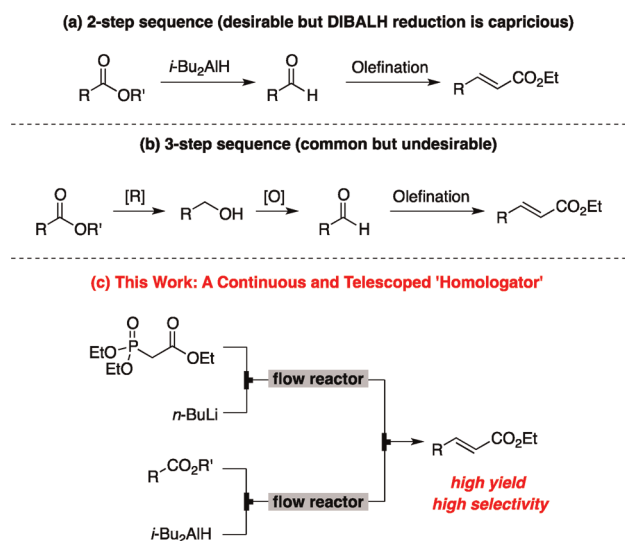
Figure 1. Strategies for the two-carbon homologation of esters to α,β-unsaturated esters.

Figure 2. General experimental setup for the continuous flow homologation. **P1**, **P2**: precooling loops. **M1**, **M2**: T-shaped mixers. **R1**, **R2**: reactors.

of highly exothermic and fast chemical reactions involving organometallic reagents.[7] In this regard, we reported a simple flow system for the continuous DIBALH reduction of esters that facilitated the rapid optimization of multiple reaction parameters and was successfully applied to yield a selective and reproducible synthesis of aldehydes from esters.[8] In this paper, we disclose the development of a continuous multistep process[9] wherein the aldehyde generated from the DIBALH reduction is not isolated or purified but undergoes a subsequent olefination transformation in a concatenated reactor (Figure 1c).[10] This telescoped[11] multistep synthesis ("one-flow" synthesis) of α,β-unsaturated esters from esters affords the products in high yields and with excellent E/Z selectivity and avoids the need to isolate or purify the aldehyde intermediates.

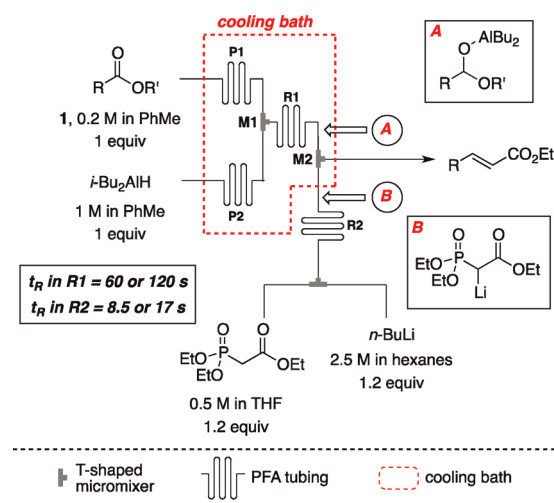Our easily configured multireactor network (Figure 2) was assembled from standard PFA (perfluoroalkoxy alkane)

tubing and T-shaped mixers (Tefzel, 0.02 in. inner diameter).[12] The reagent streams were introduced to the system by syringe pump devices, and a cooling bath was used to control the temperature (−78 or −42 °C).

In our initial study of the DIBALH reduction of esters, we focused on developing a fast and reliable system for aldehyde synthesis. Consequently, many of our previously reported conditions employed an excess of DIBALH as this enabled extremely fast conversion to the aldehyde products. Considering the multistep homologation sequence holistically, we recognized that excess DIBALH from the reduction step would negatively impact on the Horner−Wadsworth−Emmons olefination. As a result, using the extensive amount of data we had collected previously,[8] we rapidly established a general set of flow conditions that resulted in complete and selective reduction of the ester using only a stoichiometric quantity of DIBALH (−42 or −78 °C with an ester flow-rate of 2.5 or 5 mL·min^{-1} corresponding to a residence time (t_R) of 60 or 120 s, respectively). Similarly, our preliminary experiments revealed that deprotonation of the phosphonate using n-BuLi was fast (t_R = 8.5, or 17 s) and could be conducted at room temperature. It should also be emphasized that no precipitation was observed using this reagent combination.

The experimental procedure is summarized as follows (Figure 2): A solution of DIBALH and a solution of ester are mixed and flowed through the first reactor (R1) at low temperature, wherein the controlled partial reduction occurs. Solutions of the phosphonate and n-BuLi are mixed and flowed through a second reactor (R2), wherein the phosphonate deprotonation occurs. The outlets of R1 (a solution of aluminated hemiacetal **A**[13]) and R2

(6) For recent reports from our laboratory, see: (a) Bedore, M. W.; Zaborenko, N.; Jensen, K. F.; Jamison, T. F. *Org. Process Res. Dev.* **2010**, *14*, 432−440. (b) Sniady, A.; Bedore, M. W.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 2155−2158. (c) Palde, P. B.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 3525−3528. (d) Zhang, Y.; Jamison, T. F.; Patel, S. J.; Mainofli, N. *Org. Lett.* **2010**, *13*, 280−283. (e) Gutierrez, A. C.; Jamison, T. F. *Org. Lett.* **2011**, *13*, 6414−6417.

(7) For recent examples demonstrating the large-scale use of organometallic reagents, see: (a) Browne, D. L.; Baumann, M.; Harji, B. H.; Baxendale, I. R.; Ley, S. V. *Org. Lett.* **2011**, *13*, 3312−3315. (b) Fandrick, D. R. *Org. Process Res. Dev.* **2012**10.1021/op200180t. (c) Grongsaard, P. *Org. Process Res. Dev.* **2012**10.1021/op300031r. (d) Gustafsson, T.; Sörensen, H.; Pontén, F. *Org. Process Res. Dev.* **2012**10.1021/op200340c.

(8) Webb, D.; Jamison, T. F. *Org. Lett.* **2012**, *14*, 568−571.

(9) For a review, see:Webb, D.; Jamison, T. F. *Chem. Sci.* **2010**, *1*, 675−680.

(10) For the first report of a telescoped flow process that involves the preparation and use of an aldehyde of a single substrate using a segmented flow approach, see: Carter, C. F.; Lange, H.; Sakai, D.; Baxendale, I. R.; Ley, S. V. *Chem.—Eur. J.* **2011**, *17*, 3398−3405.

(11) Anderson, N. G. *Practical Process Research & Development*; Academic Press: San Diego, 2000; Chapter 2.

(12) See the Supporting Information for full experimental details.

(13) (a) Polt, R.; Peterson, M. A.; DeYoung, L. *J. Org. Chem.* **1992**, *57*, 5469−5480. (b) Kiyooka, S.; Shirouchi, M.; Kaneko, Y. *Tetrahedron Lett.* **1993**, *34*, 1491−1494.

Table 1. Continuous Telescoped Homologation of Esters to α,β-Unsaturated Esters

entry	starting ester	temp (°C)	product	yield (%)[a]	E/Z[b]
1	**1a**	−42	**4a**	86	> 19:1
2	**1b**	−78	**4b**	84	> 19:1
3	**1c**	−78	**4c**	81	> 19:1
4	**1d**	−42	**4d**	89	> 19:1
5	**1e**	−78	**4e**	96	> 19:1
6	**1f**	−78	**4f**	86	> 19:1
7	**1g**	−78	**4g**	89	> 19:1
8	**1h**	−78	**4h**	99	> 19:1
9	**1a**	−78	**4i**	90	8:1
10	**1g**	−42	**4j**	93	7:1

[a] All yields are isolated yields (1 mmol scale) after flash chromatography with silica gel. [b] Determined by ^1H NMR spectroscopic analysis of the crude product.

(a solution of lithio-phosphonate **B**) are then combined in a third mixer (which is held at low temperature). After a steady state is reached, the final eluting stream is deposited into a collection vessel and stirred until TLC analysis indicates full conversion.

Using this setup, a variety of esters were investigated as starting materials for the multistep flow process (Table 1). In all cases, the desired products were obtained in high yield and with high levels of selectivity for the newly formed alkene. For example, the synthetically useful ethyl 3-hydroxy-2-methylpropanoate **1e** was transformed to the homologated product **4e** in high isolated yield with > 95% selectivity for the *trans*-alkene (Table 1, entry 5). The use of caprolactone **1h** as starting material (Table 1, entry 8) afforded the corresponding hydroxy ester product **4h** almost quantitatively. The procedure was also successful in providing the *E*-trisubstituted olefins **4i** and **4j** when the phosphonopropionate **3** was employed. In all of the examples, the amount of unwanted overreduction to the alcohol product was negligible owing to the well-controlled nature of the reduction step.[8]

It is interesting to note that, in addition to an increase in yield, the selectivity in the olefination step was considerably higher than those reported previously using batch methods with similar reagents.[14] Also worthy of note is the use of volatile and sensitive aldehydes, which are experimentally challenging to handle when isolated prior to the olefination step. For example, the aldehyde obtained from the silyl ether of ethyl lactate (Table 1, entry 4) is volatile and prone to racemization when purified.[15] In our system, this ester underwent partial reduction and subsequent olefination without incident to give the desired product **4d** in high yield and selectivity.

In conclusion, an efficient protocol has been developed for the highly selective and high-yielding continuous synthesis of α,β-unsaturated esters from esters. The mediation of two organometallic reactions in a telescoped flow format means the aldehyde intermediates do not have to be isolated or purified, which greatly minimizes the amount of waste generated for the sequence. Our future research endeavors are focused on the evaluation and development of other telescoped transformations.

(14) For example, see ref 6a and:Claridge, T. D. W.; Davies, S. G.; Lee, J. A.; Nicholson, R. L.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Toms, S. M. *Org. Lett.* **2008**, *10*, 5437–5440.
(15) Marshall, J. A.; Yanik, M. M.; Adams, N. A.; Ellis, K. C.; Chobanian, H. R. *Org. Synth.* **2009**, *11*, 615–625.