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Revitalized: A Fast, Robust, and Selective
Continuous Flow System for Aldehyde Synthesis*

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Diisobutylaluminum Hydride Reductions Revitalized: A Fast, Robust, and Selective Continuous Flow System for Aldehyde Synthesis

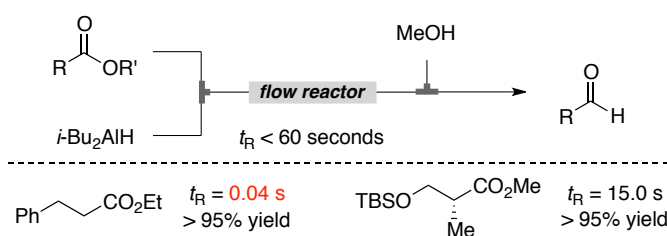
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ABSTRACT



A continuous flow system for the multiparameter (flow rate, temperature, residence time, stoichiometry) optimization of the DIBALH reduction of esters to aldehydes is described. Incorporating an in-line quench (MeOH), these transformations are generally complete in fewer than 60 seconds. Mixing of the DIBALH and ester solutions was observed to be an exceptionally critical parameter for optimum results. This system thus provides general guidelines based on the structure of the ester for selective reduction of an ester without overreduction.

Aldehydes play a prominent role in synthetic organic chemistry and reliable methods to prepare this versatile functional group are consequently of great importance. The partial reduction of esters using diisobutylaluminum hydride (DIBALH) at low temperatures is particularly appealing conceptually; it converts widely available and inexpensive esters directly to the corresponding aldehyde, often proceeding in high yield.¹ However, the capriciousness often observed from experiment to experiment has conferred such a notorious reputation upon this transformation that it is rarely used.² Notably, only four examples of selective DIBALH reduction of an ester to an aldehyde are described in *Organic Syntheses*, and three of these indicate that overreduction is a

significant problem. Additionally, the requirement for cryogenic temperatures and a slow addition rate of DIBALH has deterred the use of this method on large scale.³ Accordingly, one often resorts to a multi-step alternative: Reduction of the ester to a primary alcohol and oxidation to the aldehyde.

With these challenges in mind, and as part of our interest in continuous flow synthesis,⁴ we envisaged that a

³ For representative examples in which the use of DIBALH was explicitly stated to be unsuitable on large scale: (a) Liu, C.; Ng, J. S.; Behling, J. R.; Yen, C. H.; Campbell, A. L.; Fuzail, K. S.; Yonan, E. E.; Mehrotra, D. V. *Org. Process Res. Dev.* **1997**, *1*, 45–54. (b) Botteghi, C.; Corrias, T.; Marchetti, M.; Paganelli, S.; Piccolo, O. *Org. Process Res. Dev.* **2002**, *6*, 379–383. (c) Brock, S.; Hose, D. R. J.; Moseley, J. D.; Parker, A. J.; Patel, I.; Williams, A. J. *Org. Process Res. Dev.* **2008**, *12*, 496–502. (d) Bio, M. M.; Hansen, K. B.; Gipson, J. *Org. Process Res. Dev.* **2008**, *12*, 892–895. (e) Haycock-Lewandowski, S. J.; Wilder, A.; Åhman, J. *Org. Process Res. Dev.* **2008**, *12*, 1094–1103.

⁴ (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.

¹ Zakharkin, L. I.; Khorlina, I. M. *Tetrahedron Lett.* **1962**, 619–620.

² Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem. Int. Ed.* **2009**, *48*, 2854–2867.

continuous flow method for the DIBALH reduction of esters would provide an effective and reliable protocol for this most useful of transformations (Figure 1).⁵ Although the benefits of continuous flow methods and microreactor technology have been well documented,⁶ increasing the knowledge base for flow-based chemical transformations is imperative to maximize the impact of this potentially disruptive technology.⁷

In this *Letter* we disclose the use of a simple flow reactor – easily assembled from commercially available parts – for a rapid, multiparameter investigation leading to an improved protocol for the synthesis of aldehydes from a wide variety of esters. Our results clearly demonstrate the benefits of this approach and identify the crucial experimental parameters required for optimum results: flow rate (A), residence time (t_R), temperature (T), and stoichiometry.

Our simply configured continuous system comprised three pre-cooling loops (P1, P2 and P3) and two reactors (R1 and R2), each constructed from standard PFA (perfluoroalkoxy alkane, 0.03” inner diameter⁸) tubing (Table 1).⁹ T-shaped mixers (M1 and M2, Tefzel®, 0.02” inner diameter) were used to combine the streams that were introduced by syringe pump devices, and the entire assembly was submerged in a cooling bath held at the desired reaction temperature.

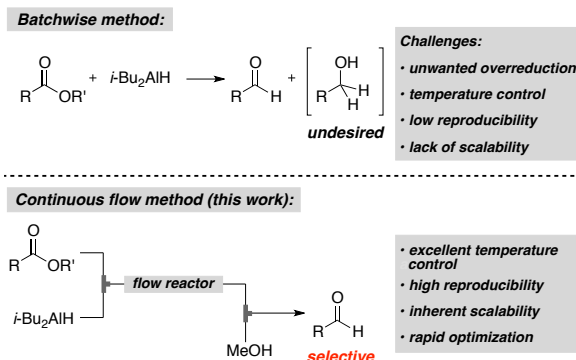


Figure 1. The continuous DIBALH reduction of esters to aldehydes using a continuous flow system.

An often-overlooked aspect of flow chemistry is the impact of the flow rate on the mixing and consequently conversion and selectivity.¹⁰ This is especially pertinent when the transformation being investigated has a high reaction rate and is thus likely to be influenced by the mixing process. Therefore, our initial continuous flow experiments were designed to investigate and understand the effect of varying the residence time (t_R) as both a function of R1 volume (constant flow rate) and as a function of flow rate (constant R1 volume), at a constant temperature ($-78\text{ }^\circ\text{C}$). It was quickly discovered that a key component for evaluation of the system was the incorporation of an in-line quench (neat methanol¹¹) that was necessary to avoid overreduction to the alcohol, even at $-78\text{ }^\circ\text{C}$ (Table 1, entry 4).

With this important modification the flow system allowed for the selective DIBALH reduction of ethyl hydrocinnamate **1** at $-78\text{ }^\circ\text{C}$ (Table 1).¹² Interestingly, at a higher flow rate (at a constant R1 volume) higher conversion and yield of the desired aldehyde was observed, despite the shorter residence time (for example compare Table 1, entries 1, 2 and 3). This observation indicates that the reaction is very fast and that the mixing heavily influences the outcome. As the flow rate is increased, additional energy is provided for mixing,⁹ thus explaining the *higher conversion* observed at *shorter* residence times.¹³ At very fast flow rates the outcome of the reaction was independent of residence time (compare Table 1, entries 3, 6 and 9), indicating that mixing was

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.; Mainolfi, N. *Org. Lett.* **2010**, *13*, 280–283. (e) Gutierrez, A. C.; Jamison, T. F. *Org. Lett.* **2011**, *13*, 6414–6417.

⁵ For a previous evaluation of the performance of commercial micromixers in a single specific example, see: (a) Ducry, L.; Roberge, D. M. *Org. Process Res. Dev.* **2008**, *12*, 163–167. For a recent report of a single substrate using a segmented flow approach, see: (b) Carter, C. F.; Lange, H.; Sakai, D.; Baxendale, I. R.; Ley, S. V. *Chem. Eur. J.* **2011**, *17*, 3398–3405.

⁶ For recent general reviews on continuous flow chemistry see: (a) Wirth, T. *Micromixers 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. *Proceedings of Bosen Symposium, Systems Chemistry* **2008**, 65. (h) Jähnisch, K.; Hessel, V.; Löwe, H.; Baerns, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 406.

⁷ Hartman, R. L.; McMullen, J. P.; Jensen, K. F. *Angew. Chem. Int. Ed.* **2011**, *50*, 2–20.

⁸ Increasing the inner diameter of the R1 reactor to 0.04” had a negligible effect on the outcome under otherwise identical conditions.

⁹ See the Supporting Information for full experimental details.

¹⁰ For example see: Dolman, S. J.; Nyrop, J. L.; Kuethe, J. T. *J. Org. Chem.* **2011**, *76*, 993–996. For a recent report comparing the performance of different micromixers see: Falk, L.; Commenge, J. M. *Chem. Eng. Sci.* **2009**, *65*, 405–411.

¹¹ It is essential to use pre-dried methanol to avoid clogging of the system. Methanol was dried according to: Williams, D. B. G.; Lawton, M. J. *Org. Chem.* **2010**, *75*, 8351–8354.

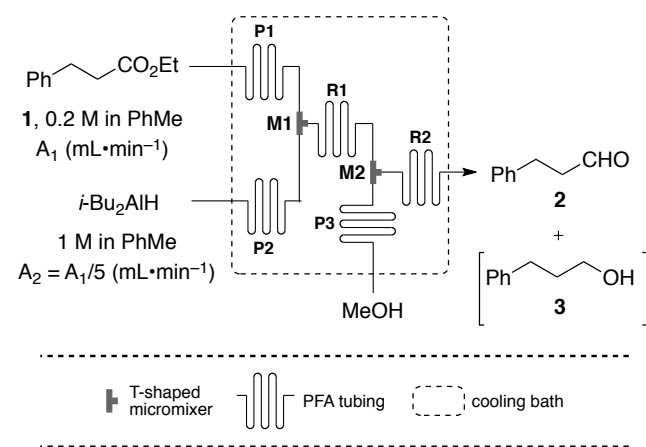
¹² As expected, the batch reduction of ethyl hydrocinnamate (2 mmol scale) to hydrocinnamaldehyde, using one equivalent of DIBALH in a variety of solvents, is strongly dependent on the reaction temperature and often results in some overreduction to hydrocinnamyl alcohol, even at $-78\text{ }^\circ\text{C}$. At elevated temperatures ($-42\text{ }^\circ\text{C}$ and above) overreduction is unavoidable with **3** becoming the major product of the reaction.

¹³ When a Y-shaped mixer (M1) was employed a notable decrease in conversion was observed compared to the use of the T-shaped mixer. It is known that Y-shaped mixers afford poorer mixing than T-shaped mixers in these kind of flow systems (see Falke *et al.* ref. 10).

very fast under these conditions. Remarkably, even at very short residence times (<50 ms), essentially full conversion and complete selectivity was obtained (Table 1, entry 3). The extrapolated throughput using the fastest flow rate examined is 10.4 moles (>1.8 kg) of starting material per day using the 23 μL reactor.¹⁴

To further our understanding of this transformation, we conducted a systematic study of the interdependence of three reaction variables: flow rate, R1 volume, and reaction temperature. Due to the speed of the reaction and flexibility of the system, this investigation required fewer than 5 h, and the results of the 45 experiments were best analyzed with contour plots (Figure 2).

Table 1. Evaluation of the Effect of Residence Time on the Continuous DIBALH Reduction of Ethyl Hydrocinnamate **1** using a Continuous Flow System^a.



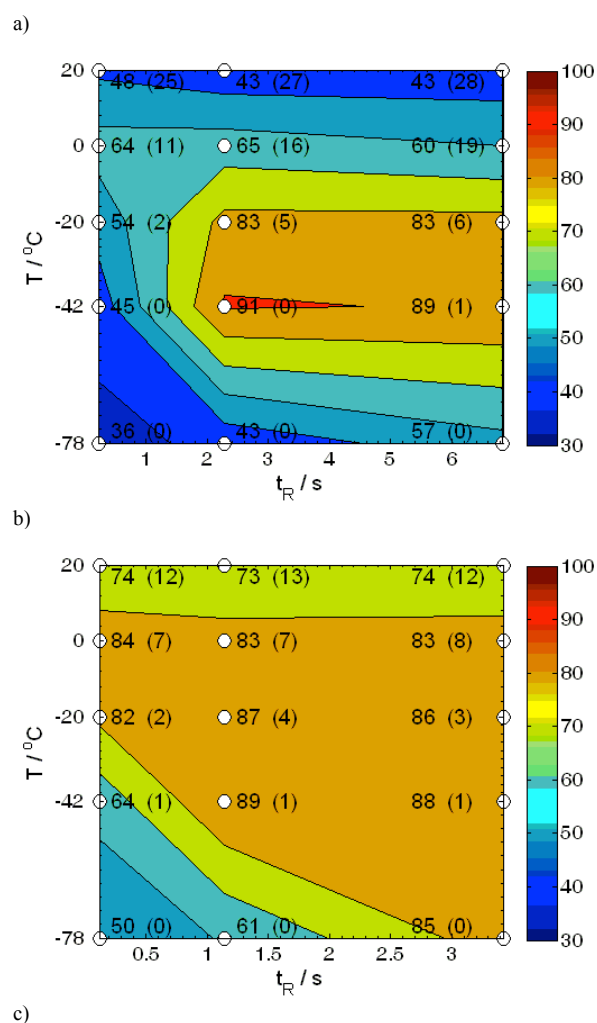
entry	R1 (μL)	A_1 (mL·min ⁻¹)	t_r (s)	selectivity ^b		
				2	1	3
1	23	5	0.23	36	64	0
2	23	10	0.11	50	50	0
3	23	30	0.04	96	4	0
4 ^c	228	5	2.28	43	57	0
5	228	10	1.14	61	39	0
6	228	30	0.38	97	3	0
7	684	5	6.84	57	43	0
8	684	10	3.42	85	15	0
9	684	30	1.14	96	3	1

^a P1, P2, P3: pre-cooling loops; M1, M2: T-shaped mixers; R1, R2: reactors; A = flow rate (mL·min⁻¹). ^b Selectivity determined by GC. ^c >5% **3** was formed if the in-line methanol quench was omitted.

As expected, the selectivity for partial reduction of **1** to aldehyde **2** decreases with increasing reaction temperature (Figures 2a, 2b and 2c). However, the degree of overreduction is significantly reduced when compared to the corresponding batch reaction at the same temperature. For example, overreduction is negligible at -42°C at all flow rates, which is not the case in the batchwise format

of this reaction.¹⁵ This effect is most pronounced at the faster flow rates (Figure 2c) where even at room temperature the yield of aldehyde is 80% with less than 10% overreduction to alcohol **3**. In contrast, at room temperature in batch, only 14% of aldehyde **2** was obtained, along with 43% overreduction to alcohol **3**.

The increased selectivity at higher flow rates is most likely a result of improved mixing and more rapid quenching of the organoaluminum intermediate, thereby preventing aldehyde release and overreduction. At -20°C and higher the experimental outcome is largely independent of residence time, indicating that the reaction is very fast at these temperatures and that higher flow rates are necessary for selectivity.^{5a} Our results are a further indication that mixing devices that approach ideal mixing¹⁶ could improve selective transformations in synthetic organic chemistry.



¹⁴ For a review on the large-scale use of organometallic reagents in microreactors under flow conditions see: ref. 6(a), p211, and references cited therein. For a recent example see: Browne, D. L.; Baumann, M.; Harji, B. H.; Baxendale, I. R.; Ley, S. V. *Org. Lett.* **2011**, *13*, 3312–3315.

¹⁵ In batch at -42°C , 7% of alcohol **3** was formed.

¹⁶ For a review see: Yoshida, J. *Flash Chemistry. Fast Organic Synthesis in Microsystems*; Wiley-Blackwell, 2008; Chapter 6, pp 69–104 and references cited within.

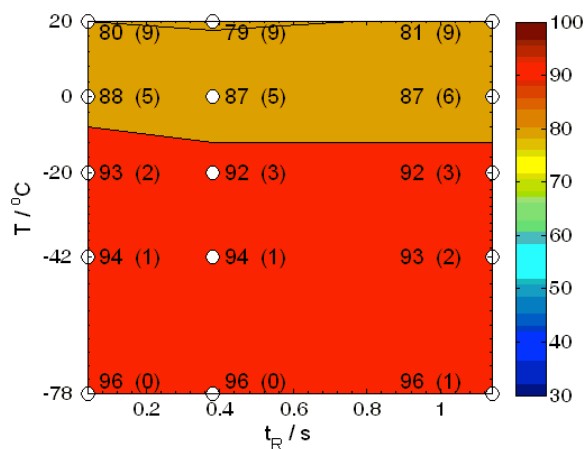
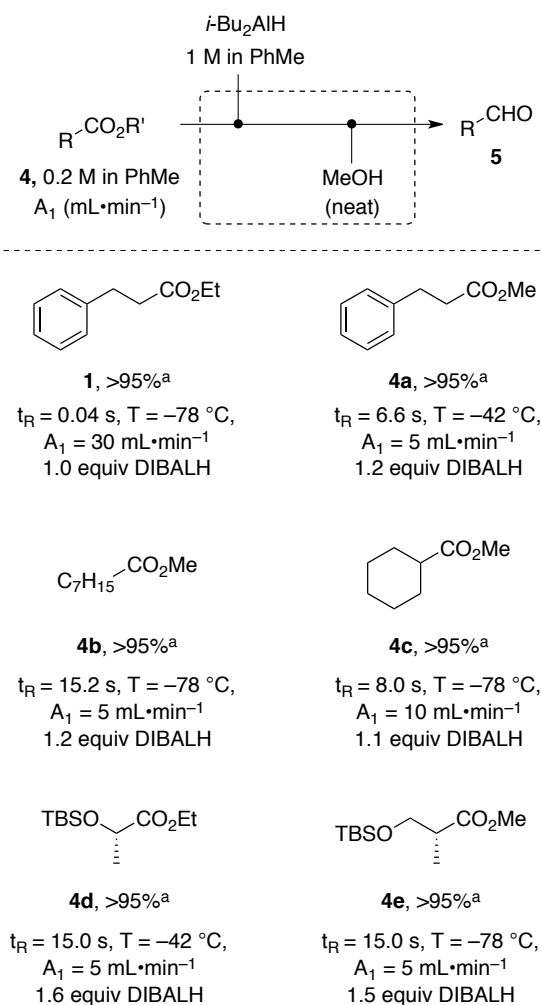


Figure 2. Contour plots showing the effect of reaction temperature (T) and residence time (t_R) on the amount of aldehyde **2** at different flow rates: a) $A_1 = 5 \text{ mL}\cdot\text{min}^{-1}$, b) $A_1 = 10 \text{ mL}\cdot\text{min}^{-1}$, c) $A_1 = 30 \text{ mL}\cdot\text{min}^{-1}$, using the continuous flow apparatus depicted in Table 1. Numbers in parenthesis are the amount of alcohol **3**.

Scheme 1. Representative conditions for the selective reduction of various commonly used esters.



^a Yield of aldehyde and alcohol determined by GC using an internal standard.⁹ The yield of alcohol is 0% in all cases except **1** (1%), **4a** (2%) and **4b** (2%).

To the best of our knowledge this is the first systematic investigation of these reaction parameters for the venerable DIBALH reduction and further demonstrates that flow systems are ideally suited for such studies.

We also performed similar optimization studies (temperature, flow rate, residence time, stoichiometry) for a number of substrates that are typical of the most commonly used esters, and representative results and conditions are outlined in Scheme 1.⁹ These reductions could be rapidly optimized to afford $>95\%$ GC yield of the desired aldehyde **5** in all cases. Additionally, a number of useful observations were made during these experiments. Both ethyl- and methyl hydrocinnamate **1** and **4a** could be reduced selectively to hydrocinnamaldehyde **2**. However, the methyl ester was more prone to overreduction. Methyl cyclohexanecarboxylate **4b** proved more prone to overreduction than **4a** and required a reaction temperature of $-78 \text{ }^\circ\text{C}$ to enable high selectivity. The synthetically useful lactate derivative **4d** could be reduced selectively to the desired aldehyde, even at elevated temperatures (up to $-20 \text{ }^\circ\text{C}$) and when using an excess of DIBALH. Previously reported yields vary greatly for this transformation.

Similarly, propanoate derivative **4e** could be transformed to the desired aldehyde although this substrate required the reaction temperature to be $-78 \text{ }^\circ\text{C}$, suggesting β -O-Al chelation is more easily ruptured than the α -O-Al chelation involved for substrate **4d**. Interestingly, using a slower flow rate for this substrate ($A_1 = 0.1 \text{ mL}\cdot\text{min}^{-1}$) resulted in significant unwanted overreduction of **4e** ($>5\%$) at incomplete conversion, even at this cryogenic temperature, further emphasizing the importance of understanding the mixing requirements of this transformation.^{5b} Finally, given the lack of operator bias in executing these flow reactions, it seems this experimental approach is ideal for delineating which substrates are unsuitable for this transformation. For example, overreduction of ethyl benzoate could not be avoided under a variety of conditions, indicating that simple aromatic esters are unlikely candidates for a selective reduction until a more efficient mixing device is developed.¹⁶

In conclusion, a simple continuous flow system has been developed for the continuous DIBALH reduction of esters. The flow format has facilitated the rapid optimization of multiple reaction parameters and has been successfully applied to yield a selective and reproducible synthesis of aldehydes from esters. Additionally, the data generated in our study should be of considerable use to those who wish to conduct DIBALH reductions on larger scales and/or wish to incorporate this transformation into

a multi-step sequence.¹⁷ We are currently engaged in the development one-flow multi-step processes wherein the aldehyde is not isolated or purified but undergoes a subsequent reaction in a concatenated flow reactor.¹⁸

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Supporting Information Available Experimental procedures and analytical data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

¹⁷ For representative one-pot multi-step transformations employing DIBALH see: (a) Takacs, J. M.; Helle, M. A.; Seely, F. L. *Tetrahedron Lett.* **1986**, *27*, 1257–1260. (b) Burke S. D.; Deaton, D. N.; Olsen, R. J.; Armistead, D. M.; Blough, B. E. *Tetrahedron Lett.* **1987**, *28*, 3905–3906. (c) Polt, R.; Peterson, M. A.; DeYoung, L. *J. Org. Chem.* **1992**, *57*, 5469–5480. (d) Dickson, H. D.; Smith, S. C.; Hinkle, K. W. *Tetrahedron Lett.* **2004**, *45*, 5597–5599. (e) Sasaki, M.; Yudin, A. K. *Synlett* **2004**, 2443–2444. (f) Hoye, T. R.; Kopel, L. C.; Ryba, T. D. *Synthesis* **2006**, 1572–1574.

¹⁸ For a review see: Webb, D.; Jamison, T. F. *Chem. Sci.* **2010**, *1*, 675–680.