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Beilstein Journal of Organic Chemistry

# Chemistry in flow systems

Andreas Kirschning

Editorial

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Address:
Institut für Organische Chemie and Zentrum für Biomolekulare Wirkstoffe (BMWZ), Leibniz Universität Hannover, Schneiderberg 1B, D-30167 Hannover, Germany

Email:
Andreas Kirschning - andreas.kirschning@oci.uni-hannover.de

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The environment in which synthesis is conducted has hardly changed over the last centuries: reactions are still typically performed batchwise in standardized glassware which has commonly been in use since the time of Justus von Liebig. In contrast, the use of flow-through processes is still rather restricted to the production site. Only recently have chemists in industry as well as in academia begun to focus on the development of flow devices for laboratory use and hence for industrial applications. An important field of research is the optimization and adaptation of known reactions and reaction sequences for use in flow systems. Advantageously, continuous-flow processes can be further improved by techniques that originate from high-throughput chemistry laboratories as they can be combined with the use of immobilized reagents or catalysts, or by using fixed bed reactors in parallel. These developments in flow techniques using mini and micro flow reactors have initiated changes that will pave the way for a technological step forward in chemical synthesis similar to that which took place in analytical chemistry and purification when chromatography started to conquer laboratories several decades ago, finally taking them by storm.

This **thematic series** on **chemistry in flow systems**, which includes original research papers and a review, mainly from the organic chemist's perspective, will become part of this development, and we are happy to have assembled research by the leading research groups in this area from all over the world. I have to thank all contributing authors and colleagues who made this thematic series possible. It has been a great privilege and honour to assemble this magnificent crew of outstanding scientists, who worked to deadlines to put a lot of effort into the production of excellent and illustrative manuscripts. Particular thanks are directed to the Beilstein Journal of Organic Chemistry editorial and production team for their support and encouragement.

Hannover, April 2009

Andreas Kirschning

Guest Editor

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Beilstein Journal of Organic Chemistry

# Synthesis of unsymmetrically substituted biaryls via sequential lithiation of dibromobiaryls using integrated microflow systems

Aiichiro Nagaki, Naofumi Takabayashi, Yutaka Tomida and Jun-ichi Yoshida*

Full Research Paper

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Address:
Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Kyotodaigakukatsura, Nishikyo-ku, Kyoto, 615-8510, Japan

Email:
Jun-ichi Yoshida* - yoshida@sbchem.kyoto-u.ac.jp

* Corresponding author

Keywords:
dibromobiaryls; fast mixing; integrated microflow system; selective lithiation; unsymmetrically substituted biaryls

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## Abstract

A microflow system consisting of micromixers and microtube reactors provides an effective method for the introduction of two electrophiles onto dibromobiaryls. Selective monolithiation of dibromobiaryls, such as 2,2′-dibromobiphenyl, 4,4′-dibromobiphenyl, 2,7-dibromo-9,9-dioctylfluorene, 2,2′-dibromo-1,1′-binaphthyl, and 2,2′-dibromobibenzyl with 1 equiv of *n*-butyllithium followed by the reaction with electrophiles was achieved using a microflow system by virtue of fast micromixing and precise temperature control. Sequential introduction of two different electrophiles was achieved using an integrated microflow system composed of four micromixers and four microtube reactors to obtain unsymmetrically substituted biaryl compounds.

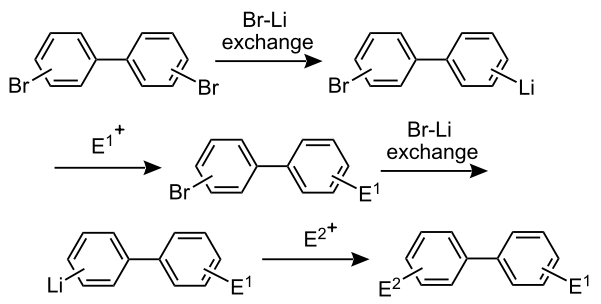
## Introduction

Unsymmetrical biaryls have received significant research interest because of the frequent occurrence of such structures in natural products, pharmaceuticals, agrochemicals, and functional organic materials [1]. Transition metal-catalyzed cross-coupling of arylmetal compounds with aryl halides or triflates serves as a useful method for preparation of such unsymmetrical biaryls [2-9]. Selective monolithiation of dihalobiaryls also seems to be useful for synthesis of unsymmetrically substituted biaryls because the remaining halogen atom can be utilized for further transformations [10-12]. However, halogen-lithium exchange reactions of dihalobiaryls usually give a mixture of mono- and dilithiated compounds in a conventional macrobatch reactor, even when one equivalent of butyllithium is used.

Recent investigations revealed that microflow systems [13-26] serve as useful method for improving product selectivity in fast competitive consecutive reactions. If a reaction is faster than mixing, the reaction takes place before the homogeneity of the

solution is achieved. This often happens in macrobatch reactors such as flasks. In such cases, arguments based on kinetics do not work, and product selectivity is determined by the manner of mixing (disguised chemical selectivity) [27,28]. To obtain a predictable selectivity close to kinetically based one, extremely fast mixing is necessary. Micromixing based on short diffusion paths proved to be quite effective for this purpose [29-33]. Fast heat transfer by virtue of high surface-to-volume ratios in microspaces is also important for conducting fast reactions, because fast reactions are often highly exothermic. Fast reactions often involve unstable short-lived intermediates. In such cases residence time control in microflow system is effective for conducting reactions without decomposing such intermediates [34-40]. Moreover, microflow systems serve as effective ways of integrating chemical reactions, in which an initial product is used for a subsequent transformation [41-51]. For example, sequential introduction of two electrophiles to *p*-, *m*-, and *o*-dibromobenzenes based on Br-Li exchange reactions has been accomplished using an integrated microflow system at much higher temperatures than those for conventional macrobatch systems by virtue of residence time control and temperature control [52,53].

Recently, we reported that selective monolithiation can be achieved by extremely fast 1:1 micromixing of dibromobiaryls and *n*-butyllithium using microflow systems [54]. The successful results prompted us to perform a study on the synthesis of unsymmetrically substituted biaryls via sequential lithiation of dibromobiaryls using an integrated microflow system. These observations may open a new aspect of the synthesis of unsymmetrically substituted biaryls (Scheme 1), and herein we report full details of this study.



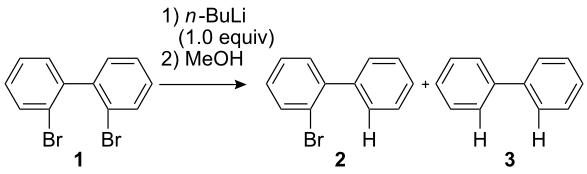

**Scheme 1:** Sequential introduction of two electrophiles onto dibromobiaryls using Br-Li exchange reactions.

# Results and Discussion

## Br-Li Exchange Reaction of 2,2′-Dibromobiphenyl

First, we focused on Br-Li exchange reaction of 2,2′-dibromobiphenyl (**1**) to generate (2-bromobiphenyl-2′-yl)lithium. It is known that Br-Li exchange reaction of 2,2′-dibromobiphenyl (**1**) gives a significant amount of dilithiated product in a conventional macrobatch system [55,56]. In order to confirm this, we reexamined the Br-Li exchange reaction of **1** with 1 equiv of *n*-BuLi in a conventional macrobatch reactor (Scheme 2). A hexane solution of *n*-BuLi was added dropwise (1 min) to a THF solution of **1** in a 20 mL round-bottomed flask at *T* °C (*T* = −78, −48, −27, 0, and 24) to generate (2-bromobiphenyl-2′-yl)lithium. After stirring methanol was added, and the mixture was stirred for 10 min. Then, the solution was analyzed by gas chromatography (GC) to determine the yields of 2-bromobiphenyl (**2**, product derived from monolithiation) and biphenyl (**3**, product derived from dilithiation).

As shown in Table 1, **2** was obtained with high selectivity at −78 °C, but the yield was not very high. Moreover, the requirement of such low temperatures like −78 °C causes severe limita-




**Scheme 2:** Br-Li exchange reaction of 2,2′-dibromobiphenyl (**1**) with *n*-BuLi using a conventional macrobatch reactor.

**Table 1:** Br-Li exchange reaction of 2,2′-dibromobiphenyl (**1**) using a conventional macrobatch system.[a]

| temperature (°C) | reaction time (min) | **1** conversion (%)[b] | **2** yield (%)[b] | **3** yield (%)[b] | **4** yield (%)[b] |
|---|---|---|---|---|---|
| −78 | 60 | 94 | 76 | 4 | 0 |
| −48 | 10 | 86 | 69 | 4 | 0 |
| −27 | 10 | 81 | 48 | 18 | 0 |
| 0 | 10 | 75 | 36 | 25 | 2 |
| 24 | 10 | 66 | 14 | 34 | 3 |

[a]A solution of **1** (0.10 M, 6.0 mL) in THF was stirred in a flask (20 mL). A solution of *n*-BuLi (0.50 M, 1.2 mL) in hexane was added dropwise for 1.0 min. After stirring, methanol (neat, 3.0 mL) was added dropwise for 1.0 min. After stirring for 10 min, the mixture was analyzed. [b]Determined by GC.

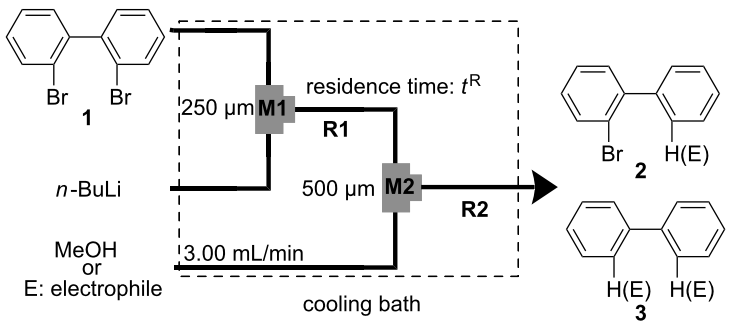



**Figure 1:** Microflow system for Br-Li exchange reaction of 2,2′-dibromobiphenyl (**1**). T-shaped micromixer: **M1** (ø = 250 µm) and **M2** (ø = 500 µm), microtube reactor: **R1** and **R2** (ø = 1000 µm, *l* = 50 cm), a solution of 2,2′-dibromobiphenyl (**1**): 0.10 M in THF, a solution of *n*-BuLi: 0.50 M in hexane, a solution of electrophile: 0.30 M in THF.

tions in the industrial application. The selectivity decreased with an increase in the temperature, and a significant amount of **3** was produced at higher temperatures. The major side product was 2-bromo-2′-butylbiphenyl (**4**), which seemed to be produced by the reaction of (2-bromobiphenyl-2′-yl)lithium with 1-bromobutane that was produced by Br-Li exchange reaction.

In the next step, the same reaction was examined using a microflow system composed of two T-shaped micromixers (**M1** and **M2**) and two microtube reactors (**R1** and **R2**) shown in Figure 1. A solution of 2,2′-dibromobiphenyl (**1**) (0.10 M) in THF (flow rate: 6.00 ml·min$^{-1}$, 0.60 mmol min$^{-1}$) and a solution of *n*-BuLi (0.50 M) in hexane (flow rate: 1.20 ml·min$^{-1}$, 0.60 mmol min$^{-1}$) were introduced to **M1** (ø = 250 µm) by syringe pumping. The mixture was passed through **R1** (residence time = $t^R$ s) and was introduced to **M2** (ø = 500 µm), where methanol (neat, flow rate: 3.00 ml·min$^{-1}$) was introduced. The resulting mixture was passed through **R2** (ø = 1000 µm, *l* = 50 cm, $t^R$ = 2.3 s). The temperature for the Br-Li exchange reaction and that for the quenching with methanol were controlled by adjusting the temperature of a cooling bath. The residence time ($t^R$) was adjusted by changing the length of the microtube reactor **R1** with a fixed flow rate. After a steady state was reached, an aliquot of the product solution was taken for 60 s. The amount of 2-bromobiphenyl (**2**) and that of biphenyl (**3**) were determined by GC.

The results obtained with varying temperature (−78 to 24 °C) and residence time ($t^R$) in **R1** (0.057–13 s) are shown in Figure 2 (see the Supporting Information for details). High yields and high selectivities were obtained even at 0 °C ($t^R$ = 0.057 s: **2** (88%) and **3** (3%)), and 24 °C ($t^R$ = 0.057 s: **2** (85%) and **3** (4%)), demonstrating a significant advantage of the microflow system. Extremely fast heat transfer of the microflow system seems to be responsible for these results. In other words, Br-Li exchange reaction can be inherently conducted at 0 °C and 24 °C, while the reaction in macrobatch reactors suffers from insufficient heat removal, and therefore, over-cooling is necessary. At −48 °C and −78 °C, the Br-Li exchange reaction was not complete within 0.1 s. At higher temperatures, however, the Br-Li exchange reaction was complete within 0.1 s.

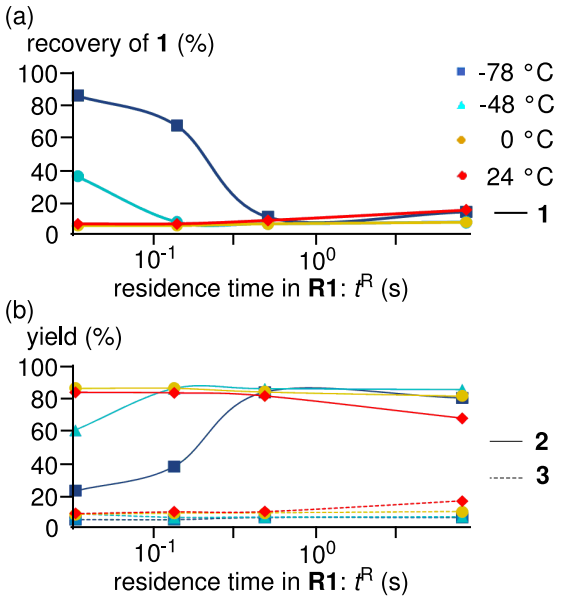



**Figure 2:** Effect of temperature and residence time in Br-Li exchange reaction of 2,2′-dibromobiphenyl (**1**) using the microflow system; (a) plots of recovery of **1** against the residence time, (b) plots of yields of **2** and **3** against the residence time. Flow rate of a solution of 2,2′-dibromobiphenyl (**1**): 6.00 ml·min$^{-1}$, flow rate of *n*-BuLi: 1.20 ml·min$^{-1}$, flow rate of methanol: 3.00 ml·min$^{-1}$. Yields of **1**, **2** and **3** were determined by GC.

As shown in Table 2, the selectivity increased with a decrease in the diameter of **M1**, presumably because faster mixing can be achieved with a mixer of a smaller diameter. The selectivity also increased with an increase in the flow rate. It is known that

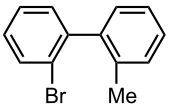
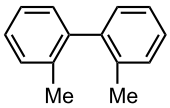
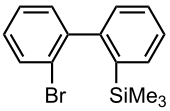
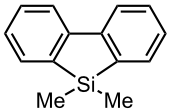
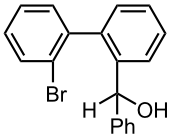
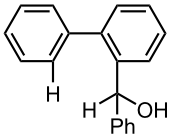
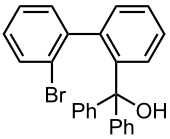
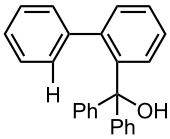
**Table 2:** Effect of flow rate and inner diameter of **M1** at 0 °C.[a]

| flow rate of **1**/THF (mL/min) | flow rate of *n*-BuLi/hexane (mL/min) | inner diameter of **M1** (μm) | **1** conversion (%)[b] | **2** yield (%)[b] | **3** yield (%)[b] |
|---|---|---|---|---|---|
| 6.00 | 1.20 | 250 | 97 | 88 | 3 |
| 3.00 | 0.600 | 250 | 90 | 80 | 7 |
| 1.50 | 0.300 | 250 | 76 | 57 | 15 |
| 0.600 | 0.120 | 250 | 69 | 41 | 19 |
| 6.00 | 1.20 | 500 | 93 | 77 | 7 |
| 6.00 | 1.20 | 800 | 79 | 62 | 9 |

[a]**R1**: ø = 500 μm, *l* = 3.5 cm, flow rate of methanol: 3.00 ml·min$^{-1}$. [b] Determined by GC.

the mixing rate increases with an increase in the flow rate for other types of micromixers [57]. These observations indicate that extremely fast 1:1 mixing in the microflow system is responsible for selective monolithiation at much higher temperatures such as 0 °C and 24 °C than those required for a conventional macrobatch processes.

**Table 3:** Br-Li exchange reaction of 2,2′-dibromobiphenyl (**1**) followed by reaction with an electrophile using the microflow system.[a]

| electrophile | yield (%)[c] monosubstituted product | yield (%)[c] major byproduct |
|---|---|---|
| MeI[b] |  **5** 89 |  **6** Trace |
| $Me_3SiCl$[b] |  **7** 80 |  **8** 3 |
| PhCHO |  **9** 90 |  **10** Trace |
| PhCOPh |  **11** 93 |  **12** 2 |

[a]Flow rate of a solution of **1**: 6.00 ml·min$^{-1}$, flow rate of *n*-BuLi/hexane: 1.20 ml·min$^{-1}$, **R1**: ø = 500 μm, *l* = 3.5 cm ($t^R$ = 0.057 s). The conversion was higher than 95% in all cases. [b] **R2**: ø = 1000 μm, *l* = 200 cm, flow rate of a solution of an electrophile: 4.00 ml·min$^{-1}$. [c]Determined by GC.

Under the optimized reaction conditions (reaction temperature: 0 °C, $t^R$: 0.057 s), reactions using other electrophiles (0.30 M in THF) were examined. In all cases, the conversion of **1** was higher than 95%. As summarized in Table 3, the reaction with iodomethane gave 2-bromo-2′-methylbiphenyl (**5**) in 89% yield with high selectivity. Chlorotrimethylsilane, benzaldehyde, and benzophenone were also effective as electrophiles, and the corresponding products derived from the monolithiated species were obtained selectively in high yields. These results show that the microflow system serves as an useful method for selective monolithiation of 2,2′-dibromobiphenyl (**1**) followed by the reaction with electrophiles.

## Synthesis of Unsymmetrically Substituted Biaryls from 2,2′-Dibromobiphenyl (**1**) by Sequential Introduction of Two Electrophiles

With successful monolithiation of 2,2′-dibromobiphenyl (**1**) followed by the reaction with an electrophile using the microflow system in hand, sequential introduction of two electrophiles ($E^1$ and $E^2$) onto 2,2′-dibromobiphenyl (**1**) was examined using an integrated microflow system composed of four T-shaped micromixers (**M1**, **M2**, **M3** and **M4**) and four microtube reactors (**R1**, **R2**, **R3** and **R4**) shown in Figure 3. In this case, T-shaped micromixers **M3** and **M4** having the inside diameter of 500 μm were used to suppress the pressure increase because an increase in the numbers of micromixers and microtube reactors in the system causes a signficant pressure increase.

A solution of 2,2′-dibromobiphenyl (**1**) (0.10 M) in THF (flow rate: 6.00 ml·min$^{-1}$, 0.60 mmol min$^{-1}$) and a solution of *n*-BuLi (0.50 M) in hexane (flow rate: 1.20 ml·min$^{-1}$, 0.60 mmol·min$^{-1}$) were introduced to **M1** (ø = 250 μm) by syringe pumping. The mixture was passed through **R1** (ø = 500 μm, *l* = 3.5 cm, $t^R$ = 0.057 s) and the resulting solution was introduced to **M2** (ø = 500 μm), where a solution of a first electrophile ($E^1$)

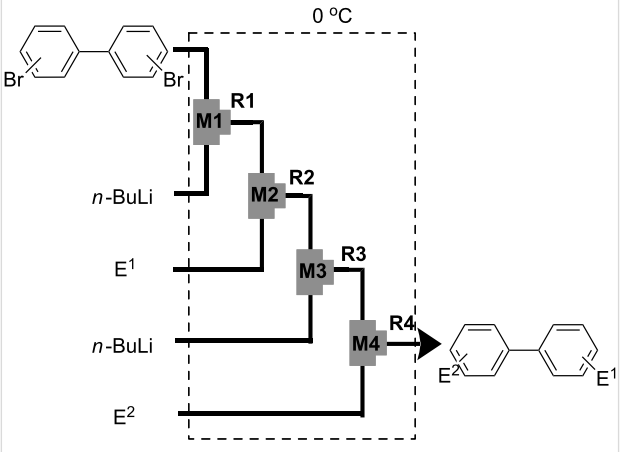



**Figure 3:** A microflow system for sequential introduction of two electrophiles. T-shaped micromixer: **M1** (ø = 250 μm), **M2** (ø = 500 μm), **M3** (ø = 500 μm), and **M4** (ø = 500 μm), microtube reactor: **R1** (ø = 500 μm, *l* = 3.5 cm ($t^R$: 0.057 s)), **R2** (ø = 1000 μm, *l* = 200 cm ($t^R$: 9.8 s)), **R3** (ø = 1000 μm, *l* = 200 cm ($t^R$: 8.5 s)), and **R4** (ø = 1000 μm, *l* = 50 cm ($t^R$: 1.8 s)). Flow rate of a solution of a dibromobiaryl (0.10 M in THF): 6.00 ml·min$^{-1}$, flow rate of *n*-BuLi (0.50 M in hexane): 1.20 ml·min$^{-1}$, flow rate of a solution of a first electrophile ($E^1$) (0.50 M in THF): 2.40 ml·min$^{-1}$. flow rate of *n*-BuLi (1.00 M in hexane): 1.44 ml·min$^{-1}$, flow rate of a solution of a second electrophile ($E^2$) (0.90 M in THF): 2.00 ml·min$^{-1}$.

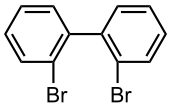
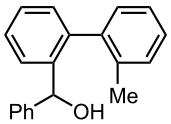
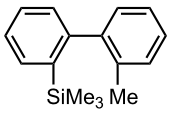
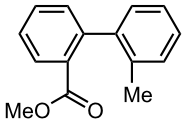
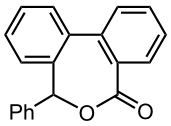
(0.50 M) in THF (flow rate: 2.40 ml·min$^{-1}$, 1.20 mmol·min$^{-1}$) was introduced. The mixture was passed through **R2** (ø = 1000 μm, *l* = 200 cm, $t^R$ = 9.8 s) and the resulting solution containing a monobromo compound was introduced to **M3** (ø = 500 μm), where a solution of *n*-BuLi (1.0 M) in hexane (flow rate: 1.44 ml·min$^{-1}$, 1.44 mmol·min$^{-1}$) was introduced. The mixture was passed through **R3** (ø = 1000 μm, *l* = 200 cm, $t^R$ = 8.5 s) and the resulting solution containing a second aryllithium intermediate was introduced to **M4** (ø = 500 μm), where a solution of a second electrophile ($E^2$) (0.90 M) in THF (flow rate: 2.00 mL·min$^{-1}$, 1.80 mmol·min$^{-1}$) was introduced. Themixture was passed through **R4** (ø = 1000 μm, *l* = 50 cm, $t^R$ = 1.8 s). The all processes were conducted at 0 °C.

As summarized in Table 4, the sequential introductions of two electrophiles were achieved successfully with various combinations of electrophiles without isolation of monobromo biaryl compound. It is interesting to note that the use of an aldehyde ($E^1$) and methyl chlorocarbonate ($E^2$) as electrophiles led to effective formation of a seven-membered ring lactone. This integrated microflow synthesis serves as a straightforward and powerful method for synthesizing unsymmetrically substituted biaryls from 2,2′-dibromobiphenyl (**1**) and two electrophiles.

## Br-Li Exchange Reaction of 4,4′-Dibromobiphenyl

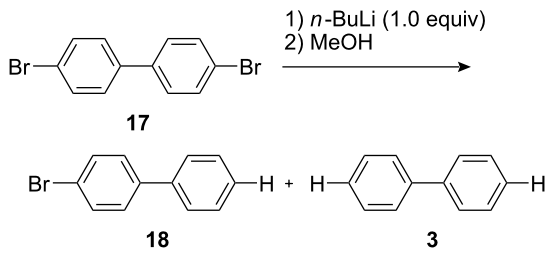
Next, we examined Br-Li exchange reaction of 4,4′-dibromobiphenyl (**17**) with *n*-BuLi. The temperature effect for a macrobatch reaction was studied (Scheme 3) and the results are summarized in Table 5.

**Table 4:** Synthesis of unsymmetrically substituted biaryls from 2,2′-dibromobiphenyl (**1**) by sequential introduction of two electrophiles.[a]

| dibromobiaryl | electrophile | yield (%) |
|---|---|---|
|  **1** | $E^1$: MeI $E^2$: PhCHO |  **13** 70 [b,e] |
| | $E^1$: MeI $E^2$: $Me_3SiCl$ |  **14** 82 [c,f] |
| | $E^1$: MeI $E^2$: MeOCOCl |  **15** 76 [f] |
| | $E^1$: PhCHO $E^2$: MeOCOCl |  **16** 75 [d,f] |

[a]Reactions were conducted in the microflow system shown in Figure 3 unless otherwise stated. [b]2-Methylbiphenyl was also produced as a byproduct. [c]**R4**: ø = 1000 μm, *l* = 200 cm [d]**R2**: ø = 1000 μm, *l* = 50 cm, benzaldehyde (0.30 M), methyl chlorocarbonate (0.30 M) [e]Isolated yield. [f]Determined by GC.

4-Bromobiphenyl (**18**) was obtained with high yield and selectivity at −78 °C. However, the yield and selectivity decreased with an increase in the temperature. At higher temperatures 4-bromo-4′-butylbiphenyl (**19**) was produced presumably by the reaction of (4-bromobiphenyl-4′-yl)lithium




**Scheme 3:** Br-Li exchange reaction of 4,4′-dibromobiphenyl (**17**) with *n*-BuLi using a conventional macrobatch reactor.

**Table 5:** Br-Li exchange reaction of 4,4′-dibromobiphenyl (**17**) using a conventional macrobatch system.[a]

| temperature (°C) | reaction time (min) | **17** conversion (%)[b] | **18** yield (%)[b] | **3** yield (%)[b] | **19** yield (%)[b] |
|---|---|---|---|---|---|
| −78 | 60 | 95 | 87 | 5 | 0 |
| −48 | 10 | 90 | 49 | 5 | 0 |
| −27 | 10 | 81 | 56 | 5 | 2 |
| 0 | 10 | 86 | 47 | 6 | 13 |
| 24 | 10 | 87 | 25 | 2 | 26 |

[a]A solution of **17** (0.10 M, 6.0 mL) in THF was stirred in a flask (20 mL). A solution of *n*-BuLi (0.50 M, 1.2 mL) in hexane was added dropwise for 1.0 min. After stirring, methanol (neat, 3.0 mL) was added dropwise for 1.0 min. After stirring for 10 min, the mixture was analyzed. [b]Determined by GC.

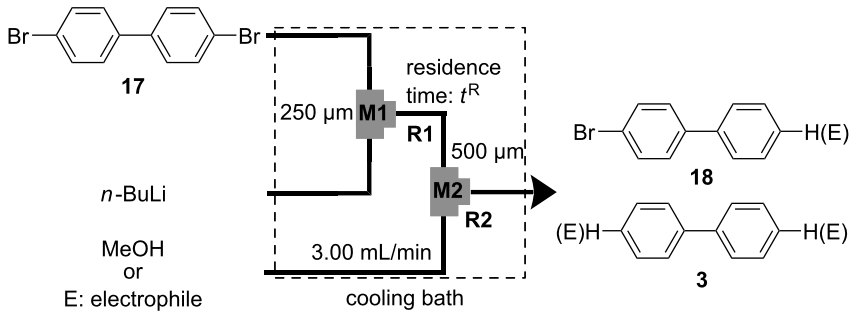



**Figure 4:** Microflow system for Br-Li exchange reaction of 4,4′-dibromobiphenyl (**17**). T-shaped micromixer: **M1** (ø = 250 μm) and **M2** (ø = 500 μm), microtube reactor: **R1** and **R2** (ø = 1000 μm, *l* = 50 cm), a solution of 4,4′-dibromobiphenyl (**17**): 0.10 M in THF, a solution of *n*-BuLi: 0.50 M in hexane, a solution of an electrophile: 0.30 M in THF.

with 1-bromobutane that was produced by Br-Li exchange reaction.

In the next step, the reaction was carried out using a microflow system composed of two T-shaped micromixers (**M1** and **M2**) and two microtube reactors (**R1** and **R2**) shown in Figure 4. A solution of 4,4′-dibromobiphenyl (**17**) (0.10 M) in THF (flow rate: 6.00 mL·min$^{-1}$, 0.60 mmol·min$^{-1}$) and a solution of *n*-BuLi (0.50 M) in hexane (flow rate: 1.20 mL·min$^{-1}$, 0.60 mmol·min$^{-1}$) were introduced to **M1** (ø = 250 μm) by syringe pumping. The mixture was passed through **R1** (residence time = $t^R$ sec) and was introduced to **M2** (ø = 500 μm), where methanol (neat, flow rate: 3.00 ml·min$^{-1}$) was introduced. The resulting mixture was passed through **R2** (ø = 1000 μm, *l* = 50 cm, $t^R$ = 2.3 s). The temperature for the Br-Li exchange reaction and the quenching with methanol was controlled by adjusting the temperature of a cooling bath. The residence time was adjusted by changing the length of the microtube reactor **R1** with a fixed flow rate. After a steady state was reached, an aliquot of the product solution was taken for 60 s. The amount of 4-bromobiphenyl (**18**, product derived from monolithiation) and biphenyl (**3**, product derived from dilithiation) was determined by GC.

The results obtained with varying temperature (−78 to 24 °C) and residence time in **R1** (0.057–13 s) are shown in Figure 5

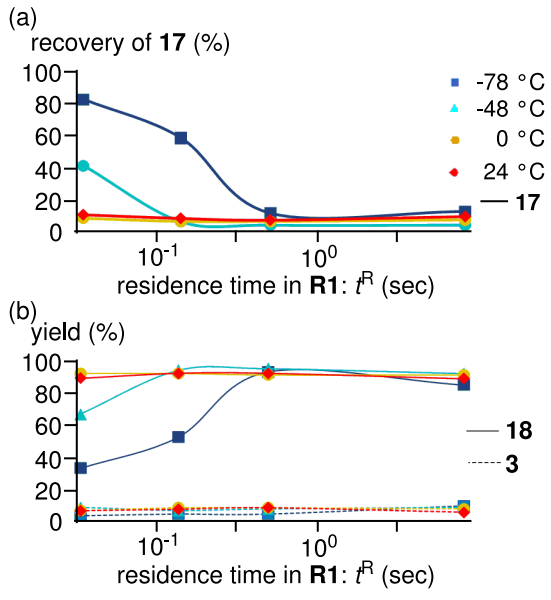
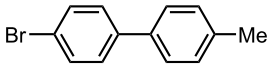
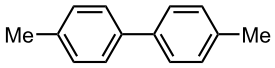
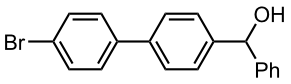
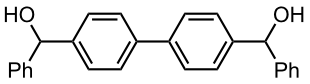
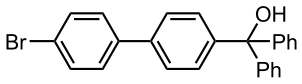
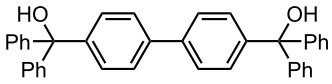



**Figure 5:** Effect of temperature and residence time in Br-Li exchange reaction of 4,4′-dibromobiphenyl (**17**) using the microflow system; (a) Plots of recovery of **17** against residence time, (b) Plots of yields of **18** and **3** against residence time. Flow rate of a solution of 4,4′-dibromobiphenyl (**17**): 6.00 mL·min$^{-1}$, flow rate of *n*-BuLi/hexane: 1.20 mL·min$^{-1}$, flow rate of methanol: 3.00 mL·min$^{-1}$. Yields of **3**, **17** and **18** were determined by GC.

**Table 6:** Br-Li exchange reaction of 4,4′-dibromobiphenyl (**17**) followed by the reaction with an electrophile using the microflow system.[a]

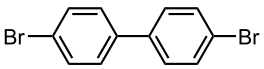
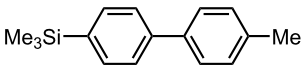
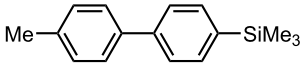
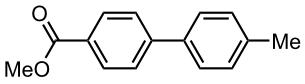
| electrophile | yield (%) | |
|---|---|---|
| | monosubstituted product | disubstituted product |
| MeI[b] |  **20** 85 [c] |  **21** 4 [c] |
| PhCHO |  **22** 83 [d] |  **23** 6 [d] |
| PhCOPh |  **24** 84 [d] |  **25** 5 [d] |

[a] Flow rate of a solution of **17**: 6.00 mL·min$^{-1}$, flow rate of *n*-BuLi/hexane: 1.20 mL·min, **R1**: ø = 500 μm, *l* = 3.5 cm ($t^R$ = 0.057 s). [b] **R2**: ø = 1000 μm, *l* = 200 cm, flow rate of a solution of an electrophile: 4.00 mL·min$^{-1}$. [c]Determined by GC. [d]Isolated yield.

(see the Supporting Information for details). High yields and high selectivities were obtained even at 0 °C (residence time of **R1** = 0.057 s: **18** (88%) and **3** (4%)) and 24 °C (residence time of **R1** = 0.057 s: **18** (85%) and **3** (4%)). At −48 °C and −78 °C, the Br-Li exchange reaction was not complete within 0.1 s. At higher temperatures, however, the Br-Li exchange reaction was complete within 0.1 s. These tendencies are quite similar to those for the 2,2′-dibromobiphenyl (**1**) case. Therefore, it is reasonable to consider that (2-bromobiphenyl-2′-yl)lithium and (4-bromobiphenyl-4′-yl)lithium have similar thermal stability.

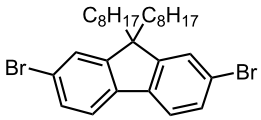
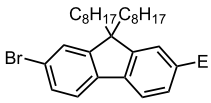
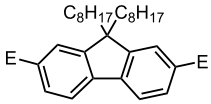
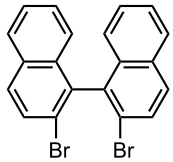
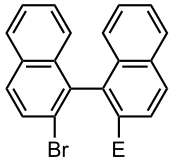
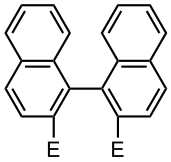
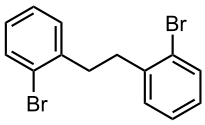
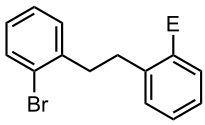
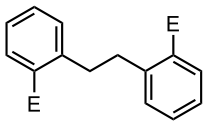
Under the optimized reaction conditions (reaction temperature: 0 °C, $t^R$: 0.057 s), reactions using other electrophiles (0.30 M in THF) such as iodomethane, benzaldehyde, and benzophenone were examined to obtain the corresponding products in good yields at 0 °C as shown in Table 6. These results show that microflow system serves as an useful method for selective monolithiation of 4,4′-dibromobiphenyl (**17**) followed by the reaction with electrophiles.

**Table 7:** Synthesis of unsymmetrically substituted biaryls from 4,4′-diboromobiphenyl (**17**).[a]

| dibromobiaryl | electrophile | yield (%)[b] |
|---|---|---|
|  **17** | $E^1$: MeI $E^2$: $Me_3SiCl$ |  **26** 71 [c] |
| | $E^1$: $Me_3SiCl$ $E^2$: MeI |  **26** 75 [d] |
| | $E^1$: MeI $E^2$: MeOCOCl |  **27** 56 |

[a]Reactions were conducted in the microflow system shown in Figure 3 unless otherwise stated. [b]Determined by GC. [c]**R4**: ø = 1000 μm, *l* = 200 cm. [d]**R4**: ø = 1000 μm, *l* = 200 cm, flow rate of a solution of chlorotrimethylsilane (0.30 M): 2.00 mL·min$^{-1}$, flow rate of a solution of iodomethane (0.50 M): 2.40 mL·min$^{-1}$.

**Table 8:** Br-Li exchange reaction of other dibromobiaryls (**28**, **36**) and 2,2′-dibromobibenzyl (**43**) followed by reactions with electrophiles.

| dibromo compound | reaction system[a] | temp. (°C) | electrophile | | yield (%) | |
|---|---|---|---|---|---|---|
| | | | | | monosubstituted product | disubstituted product |
|  **28** | | | | |  |  |
| | macrobatch[b,c] | −78 | MeOH | E: -H | 89 | 6 |
| | | | | | (**29**) | (**30**) |
| | macrobatch[c,d] | 0 | MeOH | E: -H | 54[f] | 5 |
| | microflow | 0 | MeOH | E: -H | 95 | 4 |
| | microflow | 24 | MeOH | E: -H | 92 | 5 |
| | microflow [e] | 0 | MeI | E: -Me | 93 | 3 |
| | | | | | (**32**) | (**33**) |
| | microflow | 0 | PhCHO | E: | 90[g] | 2[g] |
| | | | | -CH(OH)Ph | (**34**) | (**35**) |
|  **36** | | | | |  |  |
| | macrobatch[b,c] | −78 | MeOH | E: -H | 90 | 10 |
| | | | | | (**37**) | (**38**) |
| | macrobatch[c,d] | 0 | MeOH | E: -H | 86 | 13 |
| | microflow | 0 | MeOH | E: -H | 93 | 1 |
| | microflow | 24 | MeOH | E: -H | 92 | 2 |
| | microflow[e] | 0 | MeI | E: -Me | 85 | Trace |
| | | | | | (**39**) | (**40**) |
| | microflow | 0 | PhCHO | E: | 82[g] | trace[g] |
| | | | | -CH(OH)Ph | (**41**) | (**42**) |
|  **43** | | | | |  |  |
| | macrobatch[b,c] | −78 | MeOH | E: -H | 85 | 10 |
| | | | | | (**44**) | (**45**) |
| | macrobatch[c,d] | 0 | MeOH | E: -H | 27 | 15 |
| | microflow | 0 | MeOH | E: -H | 80 | 10 |
| | microflow | 24 | MeOH | E: -H | 77 | 11 |
| | microflow[e] | 0 | MeI | E: -Me | 81 | 4 |
| | | | | | (**46**) | (**47**) |
| | microflow | 0 | PhCHO | E: | 66[g] | 7[g] |
| | | | | -CH(OH)Ph | (**48**) | (**49**) |

[a]Microflow reactions were carried out under the following conditions unless otherwise stated. **R1**: ø = 500 μm, *l* = 3.5 cm, **R2**: ø = 1000 μm, *l* = 50 cm, flow rate of a solution of a dibromobiaryl compound: 6.00 mL·min$^{-1}$, flow rate of *n*-BuLi/hexane: 1.20 mL·min$^{-1}$, flow rate of a solution of an electrophile: 3.00 mL·min$^{-1}$. Yields were determined by GC otherwise stated. [b]Reaction time: 60 min. [c]A solution of dibromo compound (0.10 M, 6.0 mL) in THF was stirred in a flask (20 mL). A solution of *n*-BuLi (0.50 M, 1.2 mL) in hexane was added dropwise for 1.0 min. After stirring, methanol (neat, 3.0 mL) was added dropwise for 1.0 min. After stirring for 10 min, the mixture was analyzed. [d]Reaction time: 10 min. [e]**R2**: ø = 1000 μm, *l* = 200 cm, flow rate of a solution of an electrophile: 4.00 mL·min$^{-1}$. [f] 2-Bromo-7-butyl-9,9-dioctylfluorene (**31**) was also produced as a byproduct. [g]Isolated yield.

## Synthesis of Unsymmetrically Substituted Biaryls from 4,4′-Dibromobiphenyl (**17**) by Sequential Introduction of Two Electrophiles

With successful monolithiation of 4,4′-dibromobiphenyl (**17**) followed by the reaction with an electrophile using the microflow system in hand, sequential introduction of two electrophiles ($E^1$ and $E^2$) onto 4,4′-dibromobiphenyl (**17**) was carried out using an integrated microflow system composed of four T-shaped micromixers and four microtube reactors shown in Figure 3. As summarized in Table 7, the sequential introductions of two electrophiles were achieved successfully without isolation of a monobromo biaryl compound.

## Br-Li Exchange Reaction of Other Dibromobiaryls and 2,2′-Dibromobibenzyl (**43**)

We next examined the reactions of other dibromobiaryls such as 2,7-dibromo-9,9-dioctylfluorene (**28**), and 2,2′-dibromo-1,1′-binaphthyl (**36**) [58] using the microflow system. As summarized in Table 8, monolithiation was achieved with high selectivity even at 0 °C and 24 °C. Such high selectivity is difficult to obtain with macrobatch reactors at similar temperatures such as 0 °C. It is also noteworthy that monolithiation of 2,2′-dibromobibenzyl (**43**) can be achieved with high selectivity even at 0 °C and 24 °C. The resulting organolithium intermediate reacted with various electrophiles to give the corresponding products in high yields with high selectivity.

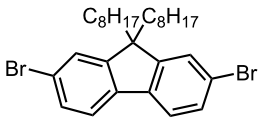
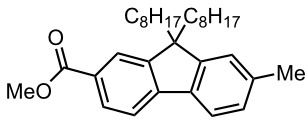
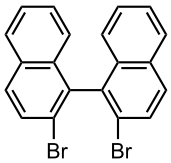
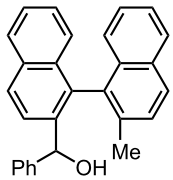
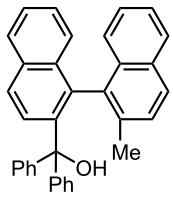
## Synthesis of Unsymmetrically Substituted Biaryls by Sequential Introduction of Two Electrophiles

With successful monolithiation of dibromobiaryls such as 2,7-dibromo-9,9-dioctylfluorene (**28**) and 2,2′-dibromobinaphthyl (**36**) followed by the reaction with an electrophile using the microflow system in hand, sequential introduction of two electrophiles ($E^1$ and $E^2$) onto dibromobiaryls was carried out using an integrated microflow system composed of four T-shaped micromixers and four microtube reactors shown in Figure 3.

As summarized in Table 9, the sequential introductions of two electrophiles were achieved successfully with various combinations of electrophiles without isolation of monobromo biaryl compounds. This integrated microflow synthesis serves as a straightforward and powerful method for synthesizing unsymmetrically substituted biaryls from dibromobiaryls and two electrophiles.

In conclusion, we have developed an efficient method for selective monolithiation of dibromobiaryls at 0 °C by virtue of

**Table 9:** Synthesis of unsymmetrially substituted biaryls from dibromobiaryls by sequential introduction of two electrophiles.[a]

| dibromobiaryl | electrophile | yield (%) |
|---|---|---|
|  **28** | $E^1$: MeI $E^2$: MeOCOCl |  **50** 51 [b] |
|  **36** | $E^1$: MeI $E^2$: PhCHO |  **51** 71 [c] |
| | $E^1$: MeI $E^2$: PhCOPh |  **52** 78 [c] |

[a]Reactions were conducted in the microflow system shown in Figure 3 unless otherwise stated. [b]Determined by GC. [c]Isolated yield.

fast mixing in microflow systems. Electrophiles was introduced on one of the aromatic rings with high selectivity. Sequential introduction of two electrophiles by repeating the sequence have also been achieved using the integrated microflow systems. Unsymmetrically substituted biaryls were obtained in high selectivity. The results obtained in this study speak well for the potential of integrated microflow systems in multi-step synthesis in flash chemistry [59-61], and the method adds a new dimension to the synthesis of unsymmetrically substituted biaryls.

## Supporting Information

Experimental procedures and full spectroscopic data for all new compounds are provided as supporting information.

### Supporting Information File 1

Experimental procedures for compounds **1**–**52**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-5-16-S1.pdf]

### Supporting Information File 2

$^{1}$H NMR spectra and $^{13}$C NMR spectra of compounds **4**, **5**, **9**–**16**, **19**, **22**–**26**, **31**–**35**, **39**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-5-16-S2.pdf]

### Supporting Information File 3

$^{1}$H NMR spectra and $^{13}$C NMR spectra of compounds **41**, **42**, **46**, **48**–**52**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-5-16-S3.pdf]

## Acknowledgments

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# A biphasic oxidation of alcohols to aldehydes and ketones using a simplified packed-bed microreactor

Andrew Bogdan[1] and D. Tyler McQuade[*,2]

Full Research Paper

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Address:
[1]Department of Chemistry and Chemical Biology, Cornell University, Ithaca, NY, 14853 USA and [2]Department of Chemistry and Biochemistry, Florida State University, Tallahassee, FL 32306, USA. Fax (850) 644-8281

Email:
D. Tyler McQuade[*] - mcquade@chem.fsu.edu

* Corresponding author

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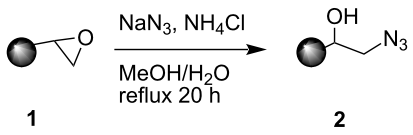
## Abstract

We demonstrate the preparation and characterization of a simplified packed-bed microreactor using an immobilized TEMPO catalyst shown to oxidize primary and secondary alcohols via the biphasic Anelli-Montanari protocol. Oxidations occurred in high yields with great stability over time. We observed that plugs of aqueous oxidant and organic alcohol entered the reactor as plugs but merged into an emulsion on the packed-bed. The emulsion coalesced into larger plugs upon exiting the reactor, leaving the organic product separate from the aqueous by-products. Furthermore, the microreactor oxidized a wide range of alcohols and remained active in excess of 100 trials without showing any loss of catalytic activity.

## Introduction

Microreactors have gained attention because they can help run chemical transformations more efficiently, more selectively, and with a higher degree of safety [1-12]. Alcohol oxidations are well suited for microreactors due to high by-product formation, catalyst contamination and safety concerns often associated with scale-up in batch reactors [13]. Recent developments in microreactor technology and solid-supported catalysis have aimed to solve these issues. Numerous flow oxidations have been presented in the literature [13-16], however many rely on stoichiometric reagents [17,18], suffer from catalyst deactivation [19,20], or rely on soluble catalysts [21], all of which limit their potential as continuous flow processes. Realizing this, we developed a catalytic packed-bed microreactor that could be used for the continuous flow oxidation of alcohols to aldehydes or ketones.

Oxidations that do not require transition metal catalysts are particularly appealing since there is neither leaching nor the need for catalyst regeneration [22]. Nitroxyl radicals, such as 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), immobilized on silicates [23-32], fluorous supports [33], soluble and insoluble polymers [22,34-36], magnetic nanoparticles [37], and ionic liquids [38] have been extensively studied and are useful because the oxidation conditions are mild, selective, and the




**Scheme 1:** Preparation of azide-modified AO resin **2**.

catalysts do not require regeneration. TEMPO, however, is expensive and difficult to remove from reaction mixtures. For these reasons, TEMPO immobilization is an important goal because it enables facile removal and recycling.

We recently reported the development of an effective solid support for use in packed-bed microreactors [39], AMBERZYME® Oxirane (AO, **1**), a commercially available resin with pendant epoxide functionalities designed for enzyme immobilization. AO is readily functionalized with a range of catalysts and works well as packing material for flow chemistry [39]. In this report, we demonstrate the immobilization of TEMPO and its use in a flow system using the Anelli-Montanari protocol for the oxidation of primary and secondary alcohols [30,40]. Our simplified reactor is advantageous because the reactions not only run continuously, but since the microreactor is made of cheap, disposable fluoroelastomeric tubing, wall oxidation that is commonplace with metal microchannels is not observed [21]. The narrow dimensions of the microreactor also allow excellent heat transfer, increasing the safety of large-scale oxidations. Furthermore, it was determined that the use of a packed-bed microreactor facilitates efficient mixing of a biphasic system without destroying the solid support, a common problem with stirred systems [4].

## Results and Discussion

Previously we reported that catalysts functionalized with an acetylene moiety can be tethered to AO using a Huisgen cycloaddition [39]. Azide-functionalized AO resin (AO-$N_3$, **2**) was prepared by treating AO with sodium azide (Scheme 1) [41]. The coupling of 4-hydroxy-TEMPO **3** with propargyl bromide (**4**) using sodium hydride yielded the acetylene-modified TEMPO species **5** [33,34,37]. TEMPO derivative **5** was then covalently bound to AO-$N_3$ using copper(I) iodide [42-45], yielding the TEMPO-functionalized resin (AO-TEMPO, **6**, Scheme 2, 0.46 mmol TEMPO/g resin).

Using a simplified procedure developed by ourselves and others [39,46-49], flow reactions were performed by packing fluoroelastomeric tubing (60 cm, 1.6 mm i.d.) with the

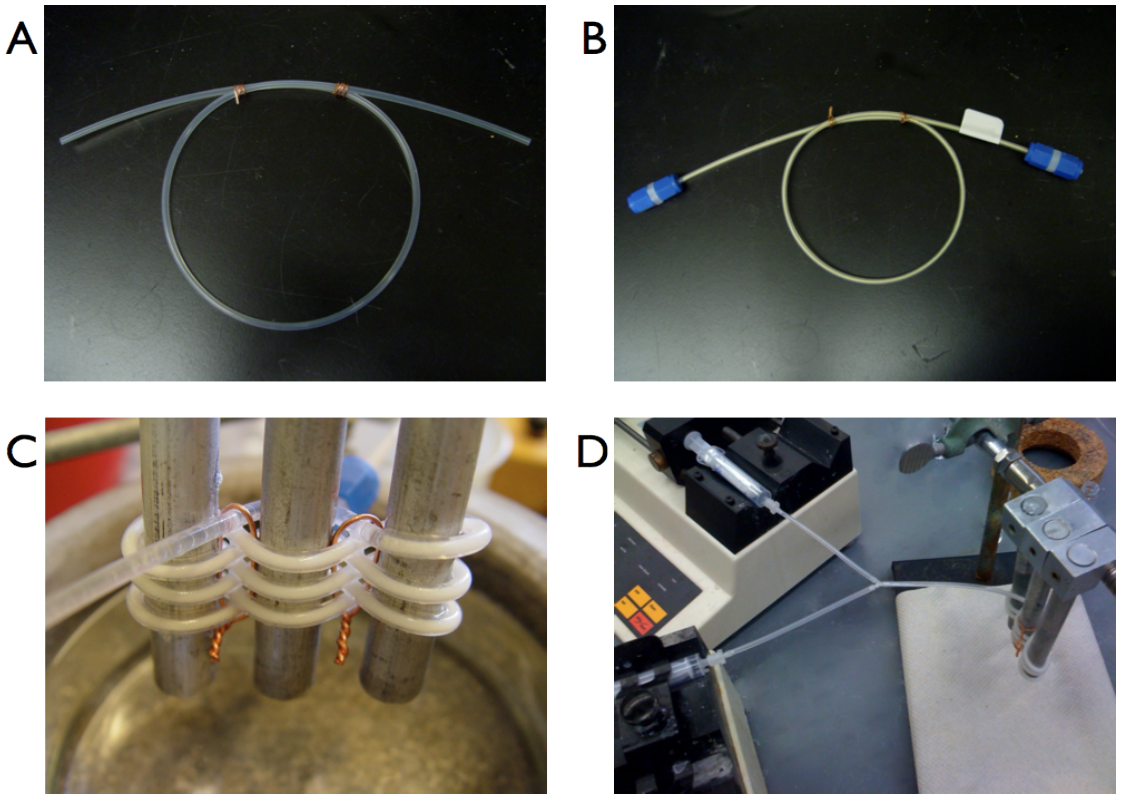
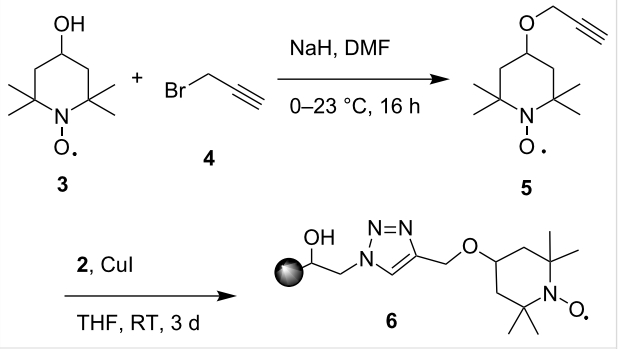


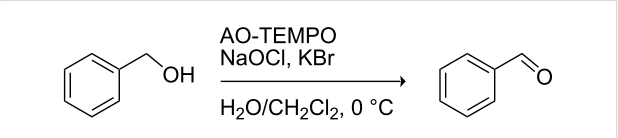

**Figure 1:** The simplified microreactor setup. Empty tubing (A) is packed with functionalized AO resin and attached to caps (B). The packed bed is woven between metal bars (C) and connected to syringe pumps (D).




**Scheme 2:** Preparation of AO-TEMPO **6**.

AO-TEMPO resin. The tubing was subsequently woven between metal bars, to improve mixing and to enable facile microreactor cooling (Figure 1). A Y-junction placed at the inlet of the microreactor allowed the immiscible bleach (adjusted to pH 9.1 using $NaHCO_3$) and organic alcohol solutions to form plugs before reaching the packed bed (Figure 2A). When passing through the AO-TEMPO catalyst bed, the plugs emulsified, as indicated by visual inspection and by the plug coalescence at the microchannel outlet (Figure 2B). The effective mixing was later supported by the high yields and conversions that were achieved for this biphasic reaction.

Preliminary reactions were performed using benzyl alcohol as the test substrate in order to establish the optimal flow conditions (Scheme 3). A solution of benzyl alcohol in $CH_2Cl_2$ (0.2 M), an aqueous NaOCl solution (0.25 M, adjusted to pH 9.1 using $NaHCO_3$), and an aqueous KBr solution (0.5 M) were prepared. The organic phase was loaded into one syringe and a mixture of NaOCl and KBr (30 µL KBr solution per mL NaOCl solution) was added to another. The syringes were placed on separate syringe pumps and the flow rates were regulated such that 1.0 equiv alcohol $min^{-1}$, 1.5 equiv NaOCl $min^{-1}$, and 0.10 equiv KBr $min^{-1}$ were delivered to the packed bed. Various flow rates were examined to determine the optimal flow conditions for the oxidation. For data relating flow rate to residence time, see Supporting Information File 1. During our optimization studies, it was shown that a total flow rate of 100 µL $min^{-1}$ (aqueous flow rate 56 µL $min^{-1}$ and organic flow rate 44 µL $min^{-1}$, approximately 4.8 min residence time) afforded quantitative conversion of benzyl alcohol to benzaldehyde, indicating that efficient mixing was occurring in the




**Scheme 3:** The AO-TEMPO-catalyzed oxidation of benzyl alcohol.

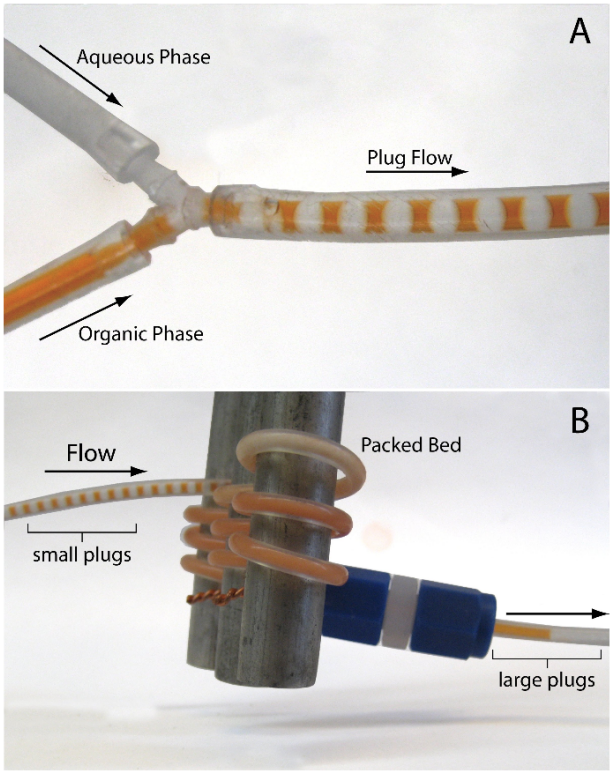
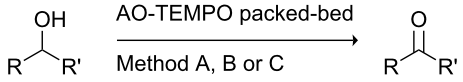


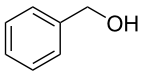
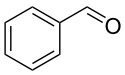
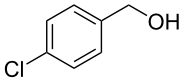
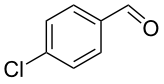
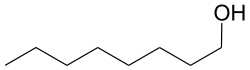
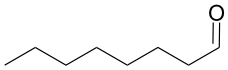
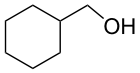
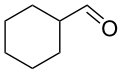
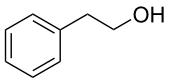
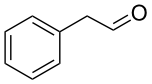
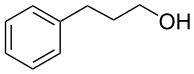
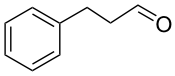
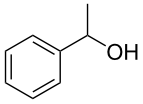
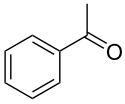
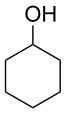
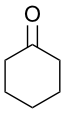
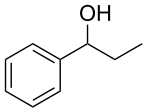
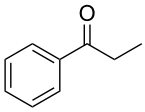
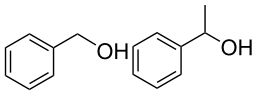
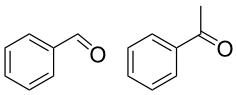
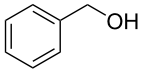
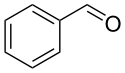

**Figure 2:** The organic (colored solution) and aqueous phases (colorless solution) forming plugs at the Y-junction (A). The phases mix upon reaching the packed bed, leading to a coalescence of drops at the outlet of the microchannel (B).

column at this flow rate. Faster flow rates (200 or 400 µL $min^{-1}$) could also be used to obtain higher outputs of benzaldehyde, however these reaction conditions did not provide complete conversion of starting material.

Using these optimized flow conditions for the benzyl alcohol oxidation, a number of different substrates were examined to test the generality of the AO-TEMPO packed-bed microreactor. High conversions were achieved when using both aromatic and aliphatic alcohols (Table 1, Entries 1–6). Secondary alcohols, which are known to be oxidized at a slower rate than primary alcohols, could effectively be oxidized to ketones by increasing the equivalents of NaOCl with respect to the alcohol concentration (Table 1, Entries 7–9). Primary alcohols were shown to be oxidized selectively over secondary alcohols (Table 1, Entry 10). Interestingly, it was also demonstrated that ethyl acetate was almost as effective a solvent as methylene chloride, opening the possibility of making this process "green" (Table 1, Entry 11). While reactions range from modest to high yields, systems that do not perform as efficiently could readily be optimized to afford higher conversions and yields. For the purposes of this paper however, we were solely testing the generality of the method and, therefore, did not optimize every

**Table 1:** Oxidation of alcohols using AO-TEMPO packed-bed microreactor.




| Entry | Alcohol | Method | Solvent | Product | Conversion[d] | Yield[d] |
|---|---|---|---|---|---|---|
| 1 |  | A[a] | $CH_2Cl_2$ |  | >99% | 95% |
| 2 |  | A | $CH_2Cl_2$ |  | >99% | 93% (86%)[e] |
| 3 |  | A | $CH_2Cl_2$ |  | 88% | 85% |
| 4 |  | A | $CH_2Cl_2$ |  | 89% | 86% |
| 5 |  | A | $CH_2Cl_2$ |  | 88% | 71% |
| 6 |  | A | $CH_2Cl_2$ |  | 80% | 74% |
| 7 |  | B[b] | $CH_2Cl_2$ |  | >99% | 95% |
| 8 |  | B | $CH_2Cl_2$ |  | 95% | 84% |
| 9 |  | B | $CH_2Cl_2$ |  | 89% | 85% |
| 10 |  1:1 mixture | C[c] | $CH_2Cl_2$ |  | 79%/16% | 71%/11% |
| 11 |  | A | EtOAc |  | 84% | 81% |

[a]Method A: Organic Phase – Alcohol (0.2 M) in $CH_2Cl_2$ or EtOAc set to 44 μL $min^{-1}$ (8.8 μmol alcohol $min^{-1}$, 1.0 equiv $min^{-1}$). Aqueous Phase – Aqueous NaOCl (0.25 M), adjusted to pH 9.1 with $NaHCO_3$, mixed with aqueous KBr (0.5 M, 30 μL per mL NaOCl) set to 56 μL $min^{-1}$ (1.5 equiv NaOCl $min^{-1}$, 0.10 equiv KBr $min^{-1}$). The phases combined at a Y-junction and passed through a 60 cm channel packed with AO-TEMPO (300 mg, 0.138 mmol TEMPO) submerged in an ice bath. [b]Method B: Organic Phase – Alcohol (0.1 M) in $CH_2Cl_2$ set to 44 μL $min^{-1}$ (4.4 μmol alcohol $min^{-1}$, 1.0 equiv $min^{-1}$). Aqueous Phase – Aqueous NaOCl (0.25 M), adjusted to pH 9.1 with $NaHCO_3$, mixed with aqueous KBr (0.5 M, 30 μL per mL NaOCl) set to 56 μL $min^{-1}$ (3.0 equiv NaOCl $min^{-1}$, 0.20 equiv KBr $min^{-1}$). The phases combined at a Y-junction and passed through a 60 cm channel packed with AO-TEMPO (300 mg, 0.138 mmol TEMPO) submerged in an ice bath. [c]Method C: Organic Phase – Benzyl alcohol (0.2 M) and 1-phenylethanol (0.2 M) in $CH_2Cl_2$ set to 44 μL $min^{-1}$ (8.8 μmol alcohol $min^{-1}$, 1.0 equiv $min^{-1}$). Aqueous Phase – Aqueous NaOCl (0.20 M), adjusted to pH 9.1 with $NaHCO_3$, mixed with aqueous KBr (0.5 M, 30 μL per mL NaOCl) set to 56 μL $min^{-1}$ (1.25 equiv NaOCl $min^{-1}$, 0.10 equiv KBr $min^{-1}$). The phases combined at a Y-junction and passed through a 60 cm channel packed with AO-TEMPO (300 mg, 0.138 mmol TEMPO) submerged in an ice bath. [d]Conversions and yields determined by GC using cyclooctane as an internal standard. [e]Number in parentheses corresponds to isolated yield.

substrate. Similar to our previous packed-bed systems, these AO-TEMPO microchannels showed a high degree of recyclability, in some cases being used in excess of 100 trials without any apparent loss of catalytic activity. Channels also maintained a high activity after three months of not being used.

To test the long-term activity of the AO-TEMPO packed beds, the oxidation of 4-chlorobenzyl alcohol to 4-chlorobenzaldehyde was run continuously and sampled periodically to monitor its activity. As seen in Figure 3, the activity of the catalyst bed remained high even after hours of use. Furthermore, the work-up of this simplified oxidation scale-up comprised only of phase separation followed by concentration, yielding a white crystalline solid with greater than 95% purity by $^1$H NMR.

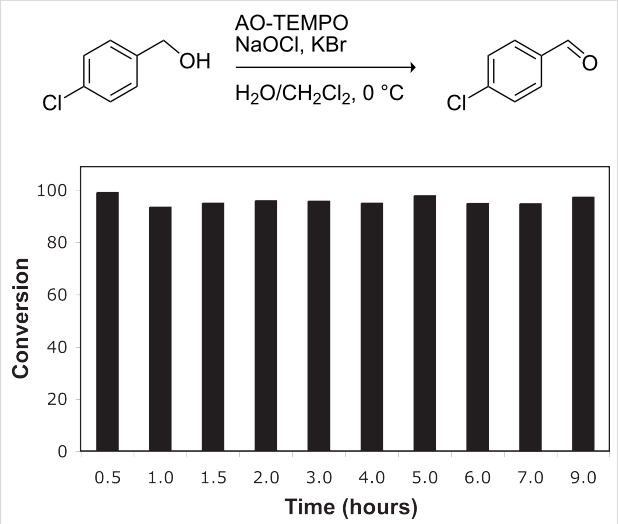



**Figure 3:** The long-term activity of AO-TEMPO packed beds in the oxidation of 4-chlorobenzyl alcohol. A solution of 4-chlorobenzyl alcohol (0.2 M in $CH_2Cl_2$) set to 44 µL min$^{-1}$ (8.8 µmol min$^{-1}$, 1.0 equiv min$^{-1}$) and an aqueous solution consisting of NaOCl (0.25 M), adjusted to pH 9.1 with $NaHCO_3$, and KBr (0.5 M, 30 µL per mL NaOCl) set to 56 µL min$^{-1}$ (1.5 equiv NaOCl min$^{-1}$, 0.10 equiv KBr min$^{-1}$) were passed through the AO-TEMPO packed bed for 9 h. Fractions were collected and analyzed by GC using an internal standard.

## Conclusion

We have demonstrated that using supported TEMPO is an efficient method to oxidize alcohols using a simplified packed-bed microreactor. A biphasic mixture was thoroughly mixed by passing the immiscible liquids through the catalytic packed-bed, leading to no disruptions or degradation of the packing material. Thus, the AO-TEMPO resins are recyclable, showing no loss of catalytic activity and a substrate scope that encompasses many primary and secondary alcohols. The devices presented are predicted to be readily scaled-up to achieve the desired output of a reaction and is of higher throughput than other reported packed-bed microreactors.

## Experimental

### General

Solvents were purified by standard procedures. All other reagents were used as received, unless otherwise noted. Sodium hypochlorite solution (reagent grade, available chlorine 10–15%) was purchased from Aldrich and titrated before use. $^1$H NMR and $^{13}$C NMR spectra were recorded in $CDCl_3$ on Varian Mercury 300 MHz operating at 300.070 MHz and 75.452 MHz, respectively, using the residual solvent peak as reference. ATR-IR was performed on a Nicolet Avatar DTGS 370 infrared spectrometer with Avatar OMNI sampler and OMNIC software. Elemental analysis was performed by Robertson Microlit Laboratories, Inc., in Madison, New Jersey. Gas chromatographic (GC) analyses were performed using an Agilent 7890A GC equipped with an Agilent 7683B autosampler, a flame ionization detector (FID), and a J&W Scientific 19091J-413 column (length = 30 m, inner diameter = 320 µm, and film thickness = 250 µm). The temperature program for GC analysis held the temperature constant at 80 °C for 1 min, heated samples from 80 to 200 °C at 20 °C/min and held at 200 °C for 1 min. Inlet and detector temperatures were set constant at 220 and 250 °C, respectively. Cyclooctane was used as an internal standard to calculate reaction conversion and yield. Gas chromatography-mass spectrometry (GC/MS) analyses were performed using a Hewlett Packard HP 6890 Series Gas Chromatograph, a Hewlett Packard HP 5973 Mass Spectrometer Detector (MSD), and a J&W Scientific DB*-5 Column (length = 30 m, inner diameter = 0.325 mm, film thickness = 1.0 µm, catalog number 123-5033). The temperature program for the analyses held the temperature constant at 50 °C for 3 min, heated samples from 50 to 80 °C at 30 °C/min, holding at 80 °C for 2 min, then heating samples from 80 to 200 °C at 17 °C/min, and holding at 200 °C for 1.94 min. The MSD temperature was held at 300 °C for 15 min.

### Azide modified AMBERZYME® Oxirane (AO-$N_3$, **2**)

Sodium azide (5.26 g, 81 mmol, 8.1 equiv) and ammonium chloride (2.27 g, 42.4 mmol, 4.2 equiv) were dissolved in 500 mL 90:10 v/v water in methanol. AMBERZYME® Oxirane (10.0 g, 1.0 mmol epoxide/g resin, 10.0 mmol, 1.0 equiv) was suspended in the azide solution and the reaction mixture refluxed overnight with gentle stirring. The resin was filtered using a Buchner funnel, washed with deionized $H_2O$ (2 × 50 mL), MeOH (2 × 50 mL), $Et_2O$ (1 × 25 mL), and dried under vacuum. Elemental analysis afforded a loading of 1.0 mmol $N_3$/g resin.

### Propargyl ether TEMPO **5**

Sodium hydride (150 mg, 6.3 mmol, 1.1 equiv) was added to DMF (10 mL) and stirred at RT. 4-hydroxy-TEMPO (1.02 g,

5.9 mmol, 1.0 equiv) in DMF (10 mL) was added drop wise to the sodium hydride suspension at 0 °C and stirred until gas evolution ceased. Propargyl bromide (80% in toluene, 800 μL, 7.4 mmol, 1.3 equiv) in DMF (10 mL) was added at 0 °C and the reaction was allowed to warm up to RT and stirred overnight. The reaction was quenched with water and the aqueous phase was extracted with ethyl acetate (3 × 50 mL) and the combined organic extracts dried over $MgSO_4$, concentrated and dried under vacuum. The product was purified using column chromatography (silica gel, 1:1 → 1:2 hexanes/ethyl acetate, $R_f$ = 0.40) to yield a dark orange solid (841 mg, 68%). $\delta_C$ (75 MHz, $CDCl_3$): 20.619, 32.199, 44.530, 55.298, 59.198, 69.905, 74.238; MS *m/z* 210 ($M^+$). To obtain NMR spectra, a few drops of phenylhydrazine were added to the NMR tube to reduce the product to the corresponding hydroxylamine.

## AO-TEMPO **6**

**5** (450 mg, 2.14 mmol, 1.3 equiv) and CuI (40 mg, 0.2 mmol, 0.13 equiv) were dissolved in anhydrous THF (20 mL). **2** (1.64 g, 1.0 mmol $N_3$/g resin, 1.64 mmol, 1.0 equiv) was added to the solution and placed under a $N_2$ atmosphere. The suspension was shaken for 3 d. The resin was washed with THF (2 × 10 mL), MeOH (1 × 10 mL), 1 M HCl (2 × 10 mL), deionized $H_2O$ (1 × 10 mL), sat. $NaHCO_3$ (2 × 10 mL), deionized $H_2O$ (1 × 10 mL), MeOH (1 × 10 mL) and $CH_2Cl_2$ (1 × 10 mL), and dried under vacuum to yield the white AO-TEMPO resin (1.81 g, 0.46 mmol TEMPO/g resin). The loading was calculated by mass difference.

## Supporting Information

### Supporting Information File 1

Experimental methods and spectral data
[http://beilstein-journals.org/bjoc/content/supplementary/1860-5397-5-17-S1.pdf]

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# Oxidative cyclization of alkenols with Oxone using a miniflow reactor

Yoichi M. A. Yamada[1,2], Kaoru Torii[2] and Yasuhiro Uozumi[*,1,2]

Preliminary Communication

Open Access

Address:
[1]RIKEN, Hirosawa, Wako, Saitama 351-0198, Japan and [2]Institute for Molecular Science (IMS), Myodaiji, Okazaki, Aichi 444-8787, Japan

Email:
Yasuhiro Uozumi* - uo@ims.ac.jp

* Corresponding author

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## Abstract

A miniflow system for oxidative cyclization of alkenols with Oxone was developed. Thus, the oxidative cyclization of (*Z*)- and (*E*)-alkenols in *i*-PrOH with an aqueous solution of Oxone proceeded smoothly and safely in a PTFE tube without any exogenous catalytic species, and was subsequently quenched in a flow-reaction manner to afford the corresponding furanyl and pyranyl carbinols quantitatively within 5 or 10 min of residence time.

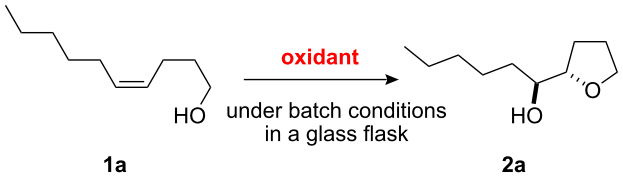
## Introduction

The development of flow-reaction systems for molecular transformations is an important goal in organic syntheses. Recently, innovative devices such as micro- and miniflow reactors that offer many fundamental as well as practical advantages for efficient organic transformations have been gaining ground in chemical experimentation [1-15]. Extensive investigations have revealed that the large interfacial area and the short molecular diffusion path in narrow space reactors often drastically improve the efficiency of a given chemical reaction. As a case in point, we have previously developed a catalyst-installed microflow reactor where a membranous polymeric palladium catalyst was deposited inside a micro-channel reactor at the laminar flow interface [16], resulting in the instantaneous production of biaryls (quantitative yield within 4 s of residence time) via a palladium-catalyzed Suzuki-Miyaura reaction under microflow conditions. An additional advantage of micro- and minireactors is the small heat capacity of the micro- and miniflow systems thus rendering exothermic and/or potentially explosive reactions safe and practical. Consequently, oxidative transformations with potentially explosive oxidants would be ideal target reactions for miniflow systems. We wish to report the oxidative construction of furanyl and pyranyl alkyl carbinols with Oxone via a miniflow reaction system.

## Results and Discussion

Furanyl and pyranyl carbinols have generated considerable interest due to their presence in a number of therapeutically and biologically active compounds [17-31]. We therefore decided to

**Table 1:** The oxidative cyclization of an alkenol **1a** with Oxone under batch conditions.




**1a** **2a**

| oxidant | conditions | yield of **2a** (%) |
|---|---|---|
| aq Oxone | 80 °C, 5 min | 99 |
| 30% aq $H_2O_2$ | 80 °C, 60 min | no reaction |
| polymeric $PW_{12}O_{40}^{3-}$ (cat) with 30% aq $H_2O_2$ (see [32]) | 50 °C, 24 h | 99 |

turn our attention to developing an oxidative cyclization of alkenols [32,33] for the preparation of furanyl and pyranyl alkyl carbinols. During our investigation, we found that the oxidative cyclization of (*Z*)-4-decen-1-ol (**1a**) with Oxone ($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$) proceeded at 80 °C without any exogenous catalysts under small-scale batch conditions (up to 50 mmol of **1a**) to give *threo*-1-(2-tetrahydrofuranyl)hexan-1-ol (**2a**) in 99% yield within 5 min (Table 1) [34]. When a mixture of an aqueous solution of Oxone (100 mM, 1 mL, 2 equiv vs **1a**) and a 2-propanol solution of **1a** (50 mM, 1 mL) was stirred at 80 °C for 5 min, the cyclization took place very smoothly to afford *threo*-1-(2-tetrahydrofuranyl)hexan-1-ol (**2a**) in 99% yield as a single racemic diastereoisomer. Yet when 30% aq $H_2O_2$ was used as the oxidant at 80 °C, the cyclization hardly proceeded at all, even with a longer reaction time [32]. We had previously found that a polymeric phosphotungstate catalyst promoted the cyclization of **1a** with 30% aq $H_2O_2$ at 50 °C with a much longer reaction time (24 h). Thus, Oxone was found to be the most efficient oxidant to promote the cyclization of (*Z*)-4-decen-1-ol (**1a**). Although a powerful and inexpensive oxidant for this transformation [35-42], Oxone however is also a known fire and explosion hazard [43] essentially rendering its large-scale use impractical. To avoid these potentially dangerous and hazardous conditions in a large-scale batch oxidation, we switched the conventional batch system to a miniflow system.

The miniflow reaction system is composed of poly(tetrafluoroethylene) (PTFE) tubes of ø = 1 mm, T-shaped connectors, and syringes with syringe pumps as shown in Figure 1. When the miniflow reaction of the alkenols **1** in *i*-PrOH with an aqueous solution of Oxone was carried out in the miniflow reactor with 5 min of residence time at 80 °C, we were pleased to see that the reaction proceeded smoothly to afford the corresponding cyclic ethers **2** in high conversion. Thus, a solution of an alkenol **1** in *i*-PrOH (50 mM) and Oxone in water (100 mM) were oppositely injected with a flow rate of 4.0 µl/min each by using syringe pumps from the individual inlets. The mixed solution passed through a PTFE tube reactor (length = 50 mm) at 80 °C, and then was quenched with 30% aq $Na_2S_2O_3$ solution injected into the flow tube with a flow rate of 4.0 µl/min. The resulting organic/aqueous outflow was collected in a glass vial. The chemical conversion and structure of the products were determined by GC and $^1$H NMR analysis. As shown in Table 2,

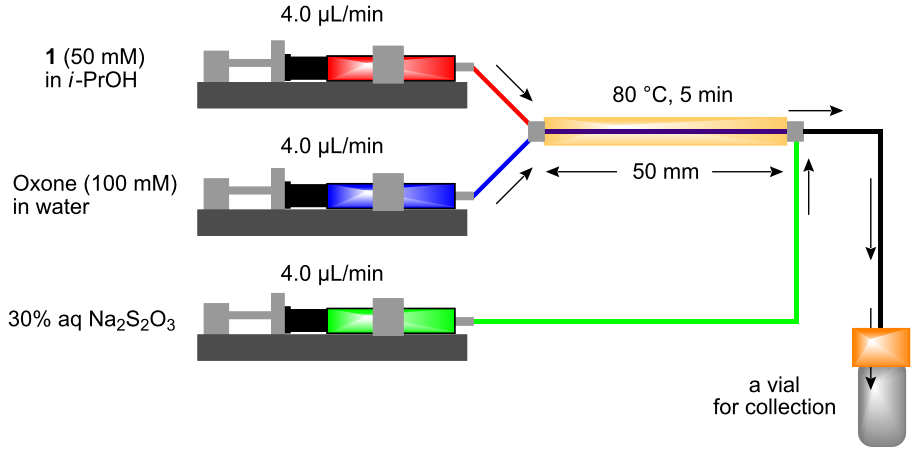
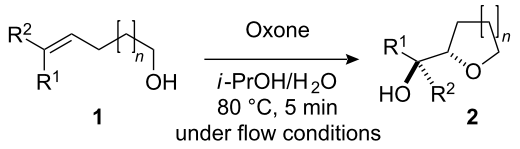
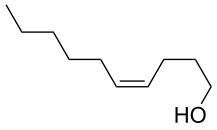
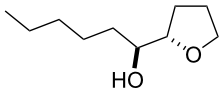
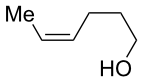
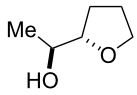
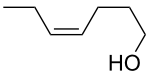
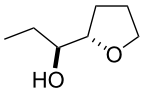
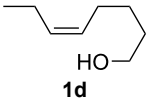
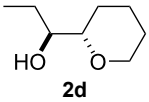
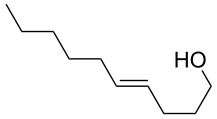
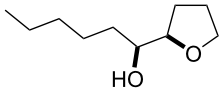



**Figure 1:** Miniflow reaction system of oxidative cyclization.

**Table 2:** Oxidative cyclization of alkenols with Oxone through a miniflow reactor.[a]




| Entry | Substrate | Product | Conversion (%) |
|---|---|---|---|
| 1 |  **1a** |  **2a** | 99 |
| 2 |  **1b** |  **2b** | 90 |
| 3 |  **1c** |  **2c** | 88 |
| 4[b] |  **1d** |  **2d** | 90 |
| 5[b] |  **1e** |  **2e** | 70 |

[a]alkenol (50 mM in *i*-PrOH), Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) (100 mM in $H_2O$), flow rate: 4.0 μL/min each, 80 °C, residence time = 5 min; several fractions were collected for each reaction shown to demonstrate the stable and high reactive performance of the miniflow reactor; the product **2a** was obtained in 0.12 mmol/h. [b]flow rate: 2.0 μL/min each, 80 °C, residence time = 10 min.

entry 1, the oxidative cyclization of (*Z*)-4-decen-1-ol (**1a**) with Oxone was performed within 5 min of residence time to afford *threo*-1-(2-tetrahydrofuranyl)hexan-1-ol (**2a**) in 99% conversion. The cyclization of (*Z*)-4-hexen-1-ol (**1b**) and (*Z*)-4-hepten-1-ol (**1c**) proceeded smoothly to give the *threo*-tetrahydrofuranyl alcohols **2b** and **2c** in 90% and 88% conversion, respectively (entries 2 and 3). This flow reaction system was also utilized for the formation of six-membered cyclic ethers. Thus, the oxidation of (*Z*)-5-octen-1-ol (**1d**) was carried out with a flow rate of 2.0 μL/min (residence time: 10 min) to give 90% conversion of the *threo*-tetrahydropyranyl alcohol **2d** (entry 4). (*E*)-4-Decen-1-ol (**1e**) underwent oxidative cyclization with 10 min residence time to afford the *erythro*-product **2e** in 70% conversion (entry 5). These stereochemical observations indicate that the cyclization involves a stereospecific reaction pathway. The reaction pathway of the present oxidative cyclization should proceed via the epoxidation of the alkene **1** with Oxone and subsequent oxirane ring opening with the intramolecular oxygen nucleophile (an intramolecular $S_N2$ reaction) to afford the product **2** stereospecifically [44,45]. It should be noted that the miniflow cyclization of **1a** was continuously carried out to give a quantitative conversion of **2a** over 2 h.

## Conclusion

In conclusion, we have developed a miniflow reaction system for the oxidative cyclization of alkenols with Oxone, affording the corresponding cyclic ethers in high conversion, where potentially explosive Oxone was used and quenched safely. Development of instantaneous flow reaction systems for the oxidation reactions with a retention time of several seconds is currently in progress.

## Acknowledgments

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Beilstein Journal of Organic Chemistry

# Asymmetric reactions in continuous flow

Xiao Yin Mak, Paola Laurino and Peter H. Seeberger*

Review

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Address:
Department of Biomolecular Systems, Max Planck Institute of Colloids and Interfaces, Research Campus Golm, D-14424 Potsdam, Germany

Email:
Peter H. Seeberger* - peter.seeberger@mpikg.mpg.de

* Corresponding author

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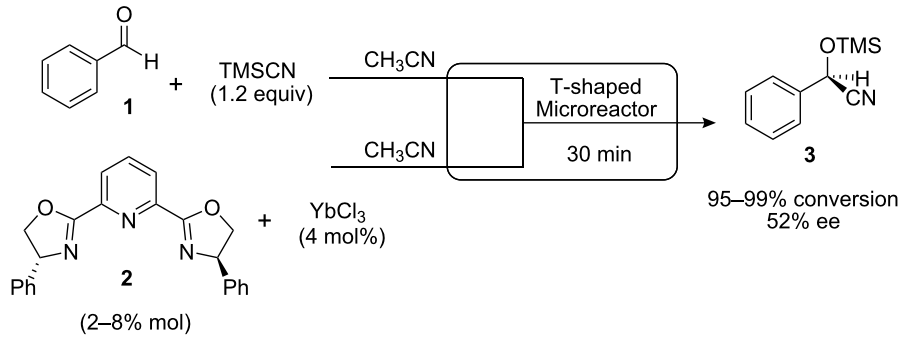
## Abstract

An overview of asymmetric synthesis in continuous flow and microreactors is presented in this review. Applications of homogeneous and heterogeneous asymmetric catalysis as well as biocatalysis in flow are discussed.

## Introduction

While many technological advancements have been made over the years in order to facilitate the day-to-day endeavors of the laboratory chemist, an aspect that has been reconsidered only recently is the *format* in which organic transformations are carried out. Continuous (micro)flow systems are gaining recognition as good, and in some cases, even better alternatives to the traditional 'round-bottomed flask' concept, which is still typically widely used for most chemical reactions [1-8]. Many advantages have been attributed to the use of flow devices, such as improved heat and mass transfer as well as mixing, and also easier scale-up and reproducibility due to the precise control over reaction conditions in these devices. Continuous flow technology has excellent potential for the integration of a high level of automation and for the incorporation of on-demand reaction analysis. This can be advantageous for applications such as high-throughput screening and synthesis, as well as for the continuous production of significant quantities of compound at higher efficiency and lower costs [1-8].

Stereoselective transformations are among the many different classes of reactions that have been investigated using continuous flow technology. The development of new methods for the synthesis of enantiopure building blocks and intermediates is important. Asymmetric catalysis, in particular, has come to the forefront as a highly economical and efficient means for the generation of chiral compounds, whereby achiral starting materials are transformed directly into enantioenriched products using only minute amounts of a renewable chiral component [9]. The potential applications of continuous flow technology as a valuable tool for asymmetric synthesis has been demonstrated in terms of fast optimization studies, improved control of reaction conditions and in the case of heterogeneous catalysis,




**Scheme 1:** Enantioselective addition of trimethylsilyl cyanide to benzaldehyde.

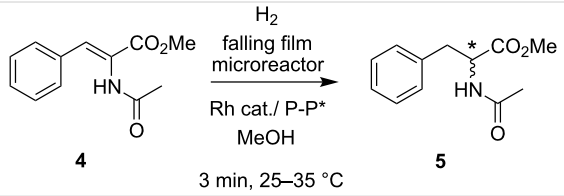
potential long term use of the catalysts. This review will highlight some of the continuous flow asymmetric reactions described to date.

# Review

## Homogeneous catalysis

Only a few examples of homogeneous enantioselective reactions in continuous flow have been reported, and these have been performed in microfluidic flow systems [10,11] consisting usually of micro-scale channels. The use of microreactors has been found to be especially useful for catalyst/ligand screening, as only low loading of reagents is required. The enantioselective silyl-cyanation of benzaldehyde (**1**) catalyzed by lanthanide(III)-PyBox complexes was investigated using a T-shaped borosilicate microreactor and electroosmotic flow (Scheme 1) [12]. The reaction was initially screened with different lanthanide (III) complexes such as Ce(III), Yb(III) and Lu(III). Further efforts were focused on screening the effect of diverse additives and also the applied voltages, in order to maximize the enantioselectivity and conversion of the reaction. While enantioselectivities for formation of cyanohydrin **3** were found to be comparable to analogous batch reactions, reactivity was observed to be higher in the microreactor.

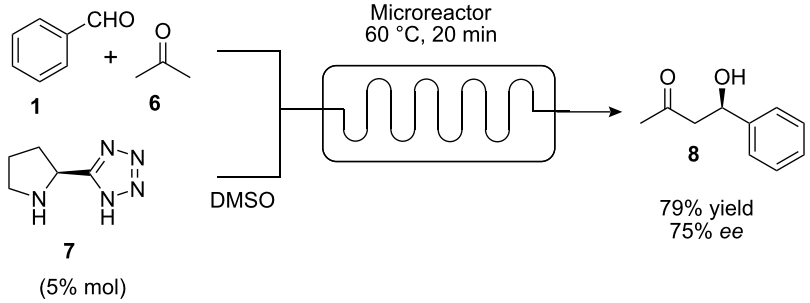
A single-channel, falling film microreactor designed specifically for efficient gas-liquid phase contact was used to screen the




**Scheme 2:** Asymmetric catalytic hydrogenation in a falling-film microreactor.

asymmetric hydrogenation of (*Z*)-methyl acetamidocinnamate **4** and related substrates (Scheme 2) [13,14]. Seventeen chiral phosphines were screened for reactivity and enantioselectivity with the rhodium catalyst $[Rh(COD)_2]BF_4$ within a 3 min residence time. With this device, very low catalyst/ligand loadings were used per run (ca. 0.1 μg of Rh catalyst), providing reliably reproducible results. Reactivity in the microreactor was found to be significantly higher when compared to a carousel-type reactor typically used for parallel synthesis.

Organocatalytic asymmetric aldol reactions in microflow devices were recently reported by our laboratory [15]. The aldol condensation of various aromatic aldehydes with acetone was carried out at higher temperatures than previously reported in batch, resulting in shorter reaction times and lower loadings of the organocatalyst **7** (Scheme 3). Slightly higher yields and selectivities, compared to reactions in both batch and in the



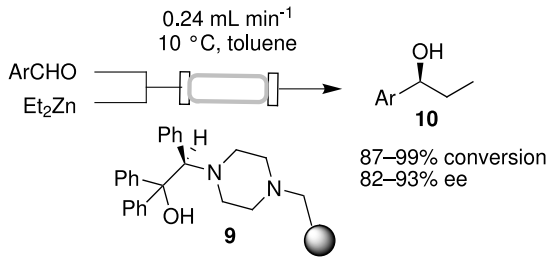

**Scheme 3:** Aldol reaction catalyzed by 5-(pyrrolidine-2-yl)tetrazole.

microwave were obtained. This study was extended to an example using cyclohexanone as donor, and subsequently to a Mannich reaction with α-iminoglyoxylate.

## Supported and heterogeneous catalysis

Chiral catalysts and ligands are often expensive and the complete separation of these components from reaction products can frequently be quite challenging. Degradation products and leaching (in the case of transition metal-catalyzed reactions) also can be problematic in large-scale syntheses, especially in pharmaceutical applications. Consequently, reactions based on the use of supported catalysts are in many ways a more attractive option for the stereoselective synthesis of chiral compounds. Supported catalysts are in principle recoverable and, ideally, recyclable. With potential longer term usage, chemical processes can become more economically and environmentally friendly [16,17].

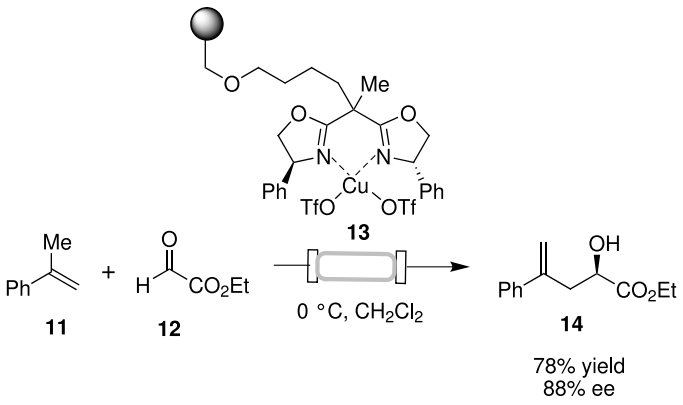
In conjunction with continuous flow, the reaction and separation of catalysts can be performed simultaneously. The mechanical degradation of the support material can lead to significantly shortened lifetimes of the supported reagent. In flow no mechanical stirring or agitation is required, thus avoiding this problem, and this can lead to higher overall productivity. However, one of the main difficulties of asymmetric synthesis using solid-supported catalysts is the development of an immobilization strategy that maintains both good stereoselectivity and catalyst activity. Selectivities obtained using homogeneous catalysts that work well in solution phase can often be significantly reduced when heterogenized [18]. Soluble supported catalysts have also been developed, particularly in form of dendrimers that can be separated from the reaction mixture via membrane filtration, a process that is also applicable in continuous flow [19-22]. This following section summarizes some recent developments in continuous flow asymmetric reactions using immobilized catalyst systems.



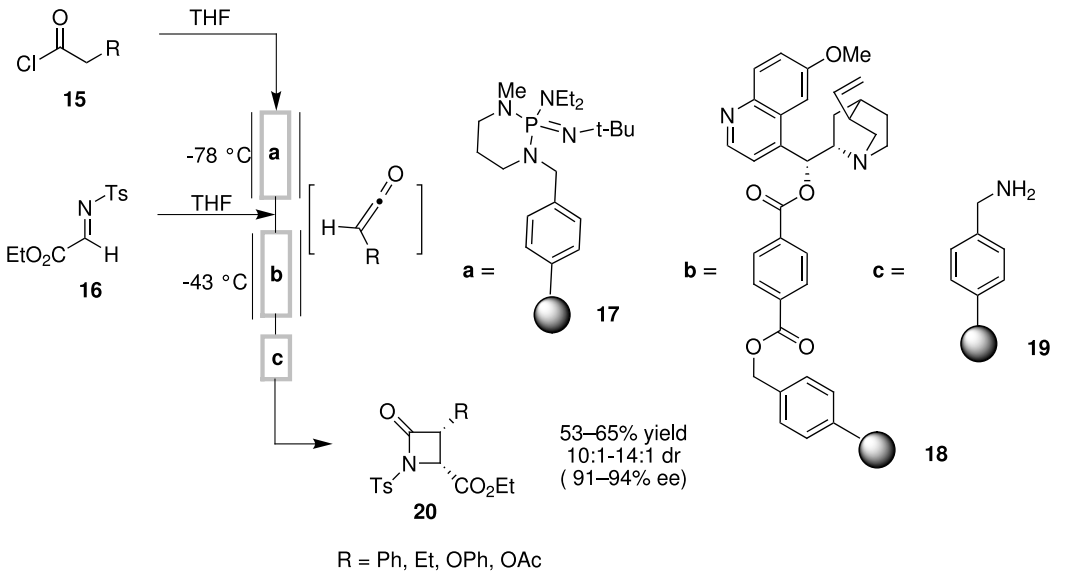

**Scheme 4:** Enantioselective addition of diethylzinc to aryl aldehydes.

An asymmetric reaction that has been examined extensively in continuous flow using supported catalysts is the enantioselective addition of diethylzinc to benzaldehyde [23-28]. A fast, single pass continuous flow process for the addition of diethylzinc to various aldehydes was described recently (Scheme 4) [27]. Reagent solutions were fed by piston-pump driven flow through a fritted column packed with chiral amino-alcohol functionalized Merrifield resin **9**. Under optimal conditions (10 °C, a flow rate of 0.24 mL $min^{-1}$ and a slight excess of $Et_2Zn$) a residence time of only 9.8 min was required for 98% conversion of benzaldehyde to the desired (*S*)-1-phenyl-propanol, with 93% enantioselectivity. In comparison, the reaction time in batch for the analogous reaction was 1.5 h. Gram quantities (2.61 g) of (*S*)-1-phenyl-propanol was produced within 3 h, at a through-put of 4.4 mmol/h per gram of resin. The chiral resin was used for 6 h for three consecutive reactions using different aldehyde substrates; identical conversions and enantioselecitivities as for individual runs were observed.

Another asymmetric C–C bond forming reaction that has been studied in flow is the PyBox-metal complex-catalyzed carbonyl ene reaction [29]. Salvadori and co-workers described the use of a flow reactor comprised of a stainless steel column packed with PyBox ligand functionalized polystyrene **13** for the ene reaction of ethyl glyoxylate with α-methylstyrene (Scheme 5).




**Scheme 5:** Glyoxylate-ene reaction in flow.




**Scheme 6:** Asymmetric synthesis of ß-lactams.

At a flow rate of 0.015–0.025 mL $min^{-1}$, an 83% conversion to the desired product **14** was achieved. After initial loading of the $Cu(OTf)_2$ catalyst, the column was used for up to five runs (over 80 h), with essentially no erosion of enantioselectivity and yield observed between each run and without the need for catalyst regeneration, providing 78% total yield of **14** with 88% ee.

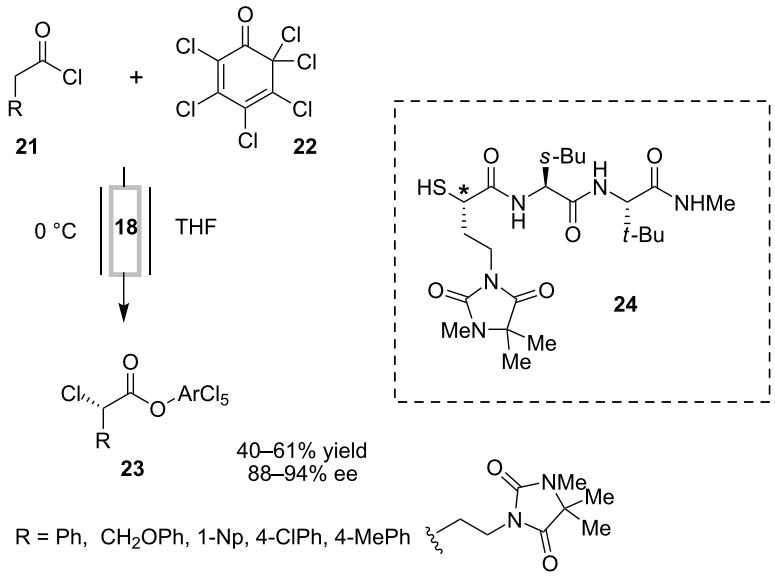
Cinchona alkaloid derivatives have been featured in a number of solid support-based continuous flow asymmetric reactions. For example, a Wang-resin supported quinine derivative was developed for the reaction of imino esters with ketenes, leading to the stereoselective synthesis of ß-lactams [30]. Ketene was generated from the corresponding acid chloride with polymer-supported BEMP **17**, and was reacted with an imino ester in a reaction catalyzed by the resin-supported quinine derivative **18**. In this way, the handling and isolation of reactive ketene intermediates was directly avoided. A long and rigid linker to the resin was found to be ideal for obtaining good selectivities in this reaction. Nucleophilic scavenger **19** was used to remove excess reagents and byproducts. This three-step sequence was carried out in a single process using an assembly of jacketed glass columns with gravity driven flow-through over the course of 2 h (Scheme 6). The catalyst column was reused 60 times without any observed decrease in activity or enantioselectivity.

Resin-immobilized quinine **18** was also employed in a similar flow system for the asymmetric α-chlorination of acid chlorides (Scheme 7) [31,32]. This cinchona alkaloid derivative served the dual purpose of dehydrohalogenation and asymmetric induction, and was found to be reusable at least up to 100 times, after regeneration each time by flushing with a solution of *i*-$PrNEt_2$ in THF. A diastereoselective synthesis of the metalloproteinase inhibitor BMS-275291 **24** was developed using this column-based flow approach, with this α-chlorination reaction as a key step (Scheme 7) [32].

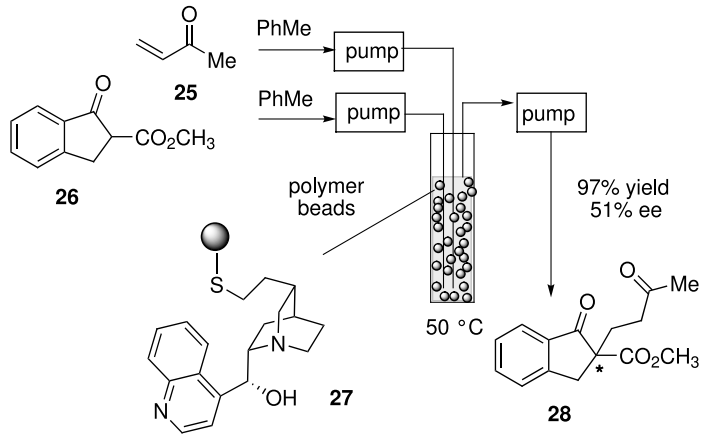
The Michael addition of indanone **26** to methyl vinyl ketone was investigated in flow using polystyrene-supported cinchonine and cinchonidine **27** (Scheme 8) [33]. A fluid bed reactor was devised for this asymmetric reaction, which allowed for the polymer beads to move around freely. Solutions of the reagents were introduced into the bottom of the column bed, and the reactants were removed from the top via peristaltic pumping. At a flow rate of 5.0 mL $h^{-1}$ (residence time of ca. 6 h), a high yield of the Michael addition product **28** was obtained with enantioselectivity comparable to results obtained in batch with free cinchonidine.

Macroporous monolithic materials as solid-supports for catalysts and reagents have been found to be particularly well-suited for flow chemistry [34-36]. These rigid structures have large surface areas, leading to improved mass-transfer between the supported catalyst with the liquid phase and do not suffer from large pressure drops during flow-through that can often be problematic with gel-type resins. The flexibility and ease for adjusting porosity, composition and shape of these materials is an additional advantage [37,38].

The monolith-supported chiral amino alcohol catalyst **29** has been developed for the enantioselective addition of diethylzinc to benzaldehyde [26]. The monolithic catalyst was prepared as a column that was attached to a pump and a reservoir of the

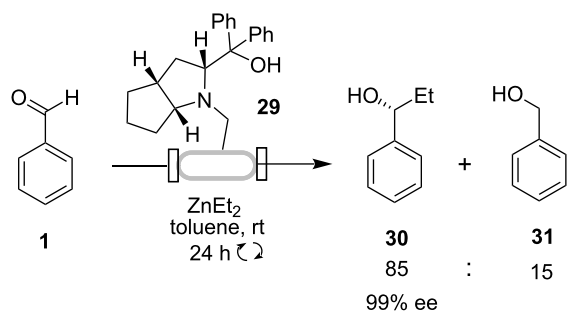



**Scheme 7:** α-Chlorination of acid chlorides in flow.




**Scheme 8:** Asymmetric Michael reaction in continuous flow.

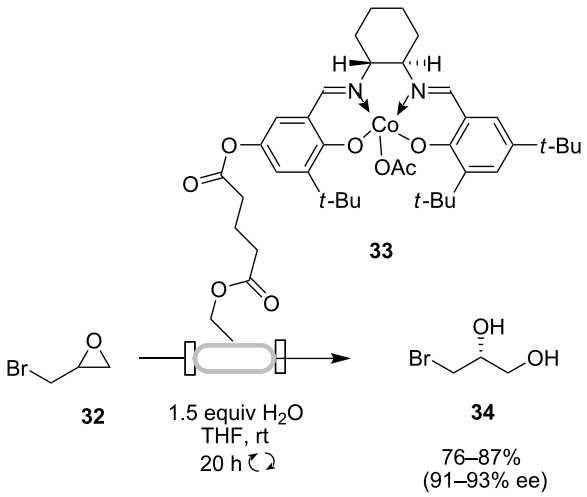
reagents. The reaction mixture of benzaldehyde and an excess of $Et_2Zn$ was then pumped and recirculated through the column over 24 h, resulting in complete conversion of benzaldehyde to the desired (*R*)-alcohol **30** with 85:15 selectivity and 99% ee (Scheme 9). Lower enantioselectivities were observed in batch reactions using a homogeneous analogue (87% ee) and also for a heterogeneous analogue with the catalyst grafted onto Merrifield resin (89% ee). The monolith-supported catalyst **29** also demonstrated potential long-term stability. It was reused four times (each a 24 h cycle) successively, with the fourth cycle being carried out 2 weeks after the first, without any changes in catalytic activity.




**Scheme 9:** Enantioselective addition of $Et_2Zn$ to benzaldehyde using monolithic chiral amino alcohol.

It should be noted that the support medium can have a profound effect on accessibility to the catalytic sites, creating microenvironments which can lead to quite different catalytic behavior compared to that observed in solution phase. Even the use of different polymeric supports can lead to significant perturbations in selectivity, as illustrated by an investigation on the use of Ti-TADDOL-functionalized monolithic columns for Diels-Alder cycloaddition of cyclopentadiene and 3-crotonyl-1,3-oxazolidin-2-one [39]. In this case, a complete reversal of topicity was observed, switching from a monolithic catalyst to the one grafted on a polymer matrix.

Kirschning and co-workers have designed a continuous-flow reactor system, PASSflow [40], based on the use of a functionalizable monolithic rod derived from a glass/polymer composite. This device was used for the dynamic kinetic resolution of epibromohydrin **32**, using a monolith reactor functionalized with a chiral Co(salen) complex **33** (Scheme 10) [41]. Three consecutive 1 mmol scale runs (20 h each), where a solution of epibromohydrin was continuously circulated through the reactor via a pump, were performed without any loss of enantioselectivity and catalyst activity (76–87% yield, 91–93% ee). A fourth, larger scale run (10 mmol) was performed continuously over a 6 day period (until complete consumption of epibromohydrin), providing the desired (*R*)-diol **34** also in similar yield and enantioselectivity. The hydrolytic kinetic resolution of a terminal epoxide in continuous flow has also been investigated using a silica-supported chiral Co(salen) complex [42].

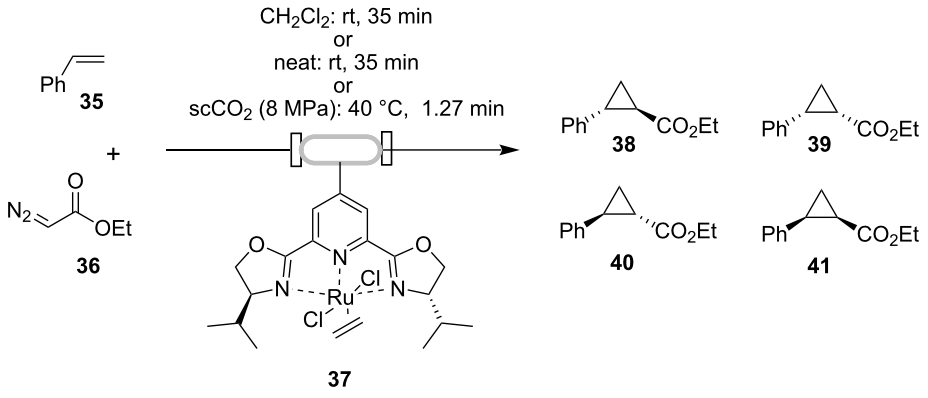



**Scheme 10:** Continuous-flow hydrolytic dynamic kinetic resolution of epibromohydrin (**32**).

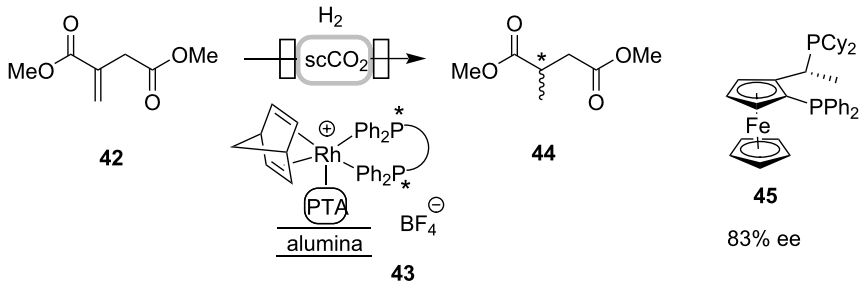
Asymmetric cyclopropanation has also been studied in continuous flow, using monolithic reactors immobilized with chiral PyBox ligands [43,44]. The cyclopropanation of stryrene with ethyldiazoacetate was investigated as a model reaction for this asymmetric process (Scheme 11). The Ru-PyBox complexes were generated by flow-through of a solution of dichlororuthenium(II) (*p*-cymene), followed by washing to remove uncomplexed material [43].

The yields, trans/cis selectivity and enantioselectivities of runs performed in flow with the monolithic reactors were found to be comparable to the analogous reaction carried out in batch under homogeneous conditions. Multiple runs (each lasting 5–8 h) were performed in the reactors with consistent results during as well as between each run. These continuous flow reactions were first conducted in $CH_2Cl_2$ and neat conditions as well as in supercritical carbon dioxide ($scCO_2$), as means of creating a more 'environmentally-friendly' process [45]. Under the solventless or $scCO_2$ flow conditions, the productivity of the catalyst was observed to be much higher.

The use of supercritical fluids, in particular $scCO_2$, as an alternative reaction medium to traditional organic solvents is




**Scheme 11:** Continuous-flow asymmetric cyclopropanation.

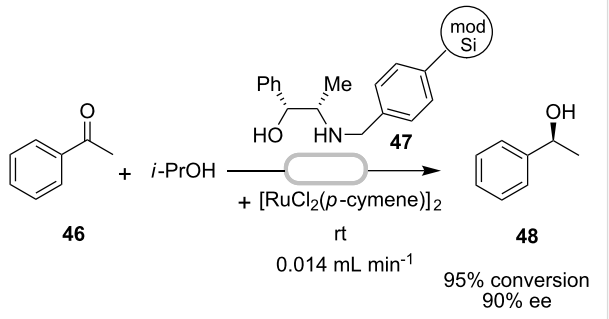



**Scheme 12:** Continuous asymmetric hydrogenation of dimethyl itaconate in $scCO_2$.

attractive not only for environmental reasons, but also because of its high miscibility with gases, and its ease of removal from the product (simply by depressurization) [46]. In an early example of asymmetric hydrogenation in flow, ethyl pyruvate was reduced using a cinchonidine-modified $Pt/Al_2O_3$ catalyst in a fixed bed reactor in both supercritical carbon dioxide and ethane [47]. Poliakoff and co-workers have investigated the continuous asymmetric hydrogenation of dimethyl itaconate in $scCO_2$ [48,49]. By using the catalyst $[Rh(COD)_2(nbd)]^+[BF_4]^-$, immobilized on alumina via a phosphotungstic (PTA) linker $H_3O_{40}PW_{12}$, a variety of chiral bisphosphine ligands were screened for improving enantioselectivity [49]. The best enantioselectivity (83% ee) was obtained using Josiphos ferrocenyl ligand **45** at 55 °C and 16 MPa (Scheme 12).

Silica has also been used as a heterogeneous support medium in continuous flow. A ruthenium catalyst complexed to a norephedrine-derived ligand **47** was immobilized onto modified (alkylsilyl-capped) silica and employed to catalyze a continuous asymmetric transfer hydrogenation [50] (Scheme 13).

The use of unmodified silica lowered the activity of the catalyst system, presumably via adsorption of some of the Ru(II) catalyst. Under optimal flow conditions, the transfer hydrogenation of acetophenone in isopropanol (using a flow-reactor consisting of a column packed with a slurry of the immobilized catalyst) provided a steady state conversion of 95% to alcohol **48** with 90% ee. Less than 1% of ruthenium leaching was observed over 11 h of flow with consistent catalyst activity and selectivity throughout the process. At slower flow rates, enantioselectivities were found to be lower due to the opportunity for equilibration during the longer residence times. Incidentally, this silica supported catalyst system was active up to at least three weeks compared to the homogeneous catalyst that was stable up to 20 h only. This property is perhaps a consequence of favourable active site isolation [50]. Several other examples of asymmetric transfer hydrogenation in flow have also been reported [51,52].

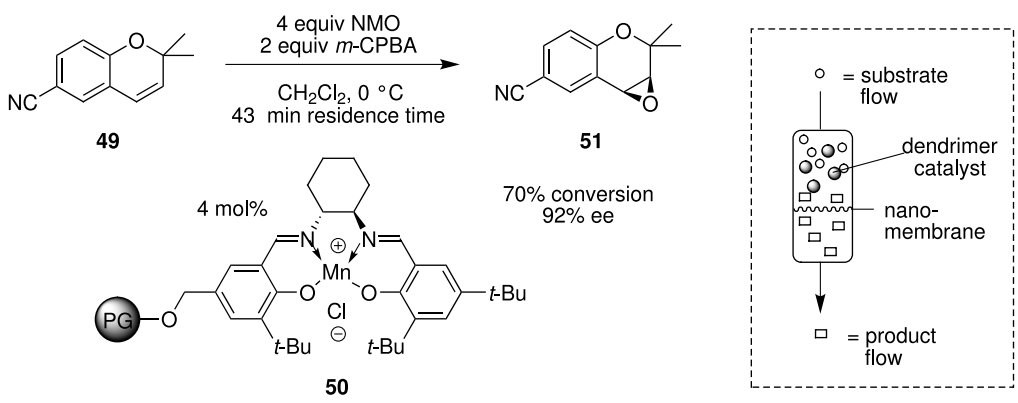



**Scheme 13:** Continuous asymmetric transfer hydrogenation of acetophenone.

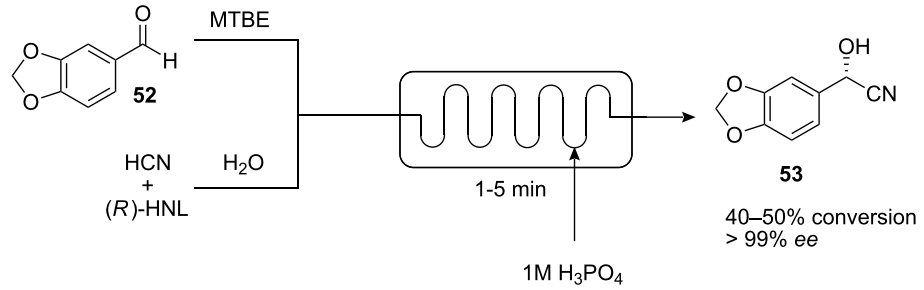
Supported catalysis has been extended to reactions involving the use of continuous flow membrane reactors [19-22]. For example, the asymmetric epoxidation of a chromene derivative **49**, catalyzed by homogeneous dendritic polyglycerol supported Mn-salen catalyst **50**, was recently developed in a continuous membrane flow reactor [53]. This type of flow system involves the continuous removal of the product from the high molecular weight macrostructured catalysts by filtration through a nanomembrane (Scheme 14). In this case, a stainless steel ultrafiltration cell was fitted with a solvent-stable MPF-50 nanomembrane that was able to retain up to 98% of soluble catalyst **50**. Under steady state conditions 70% conversion to the epoxide with up to 92% ee was achieved.

## Biocatalysis

The usefulness of enzyme-driven catalysis as a clean and efficient method for effecting chemical transformations has found applications in a number of industrial processes, some of which rely on continuous flow [54]. Recently, efforts have been made to combine the advantages of micro flow devices with enzymatic transformations. For example, Rutjes and co-workers have developed a method using a borosilicate microreactor chip for the enantioselective formation of cyanohydrins from aldehydes using hydroxynitrile lyase (HNL)-containing crude cell lysates (Scheme 15) [55]. The flow device consisted of three inlets: one for the aqueous phase delivering the cell lysate, KCN



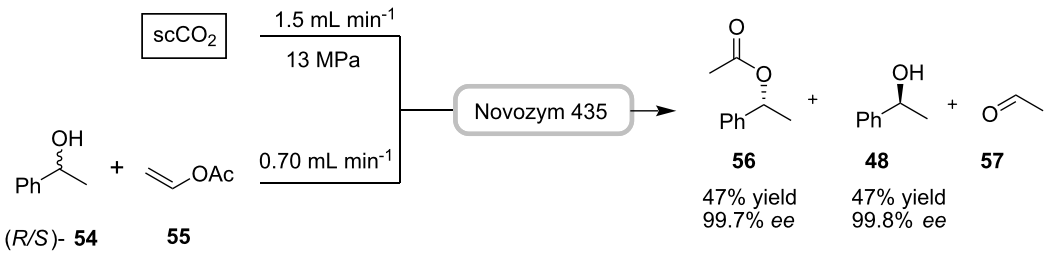

**Scheme 14:** Asymmetric epoxidation using a continuous flow membrane reactor.



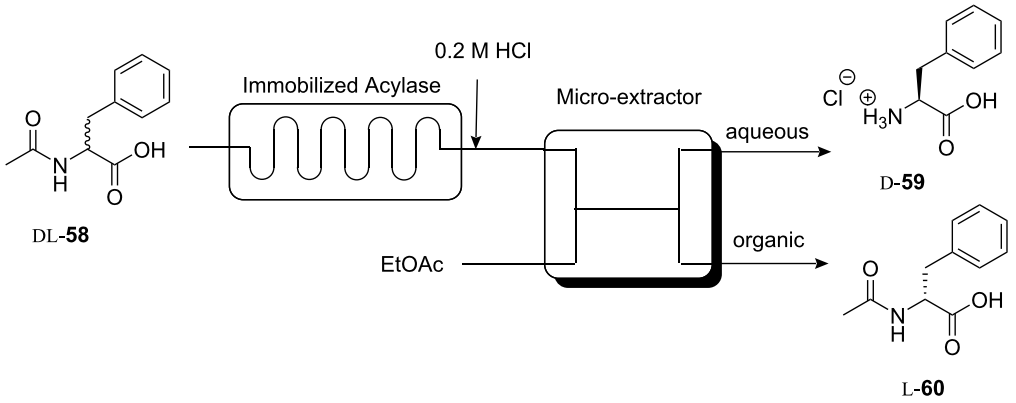

**Scheme 15:** Enzymatic cyanohydrin formation in a microreactor.

and citric acid (*in situ* HCN generation), one for the organic phase containing the aldehyde substrate and a third one at the end of the reactor channel as quenching inlet for deactivation of the enzyme. Under batch conditions, these reactions required vigorous stirring in order to maintain a constant emulsion that was necessary for high yields and enantioselectivities. Pillar-structured channels in the microreactor were designed to facilitate biphasic laminar flow. However, undefined plug flow was observed instead. Various aldehydes were tested using the system; with aromatic substrates, enantioselectivities higher than 95% ee were obtained and with an aliphatic substrate, 85% ee. Screening experiments were performed with piperonal **52** as the substrate, to evaluate the effect the ratio of the two phases and the reaction time have on the enantioselectivity and conversion (Scheme 15). The results were found to be similar to the batch results where steady emulsions were formed. Up to 58 reactions were performed serially within 4 h, requiring a total of only 150 μL of cell lysate.

Numerous applications involving the enzymatic resolution of racemic substrates in flow devices have been developed recently, including processes using alternative solvents such as ionic liquids and/or $scCO_2$ [56-61]. The kinetic resolution of racemic 1-phenylethanol **54** was performed continuously in $scCO_2$, using an immobilized lipase (*Candida antarctica*, Novozym 435) and vinyl acetate (**55**) (Scheme 16) [61]. This




**Scheme 16:** Resolution of (*R/S*)- **54** with immobilized lipase in a continuous $scCO_2$- flow reactor.




**Scheme 17:** Enantioselective separation of Acetyl-D-Phe in a continuous flow reactor.

reaction in continuous flow proceeded to give both (*R*)-acetate **56** and in 99.7% ee, in 47% yield and the (*S*)-alcohol **48** in 99.8% ee, in 47% yield. In comparison to the reaction in a 10-mL batch reactor (0.83 mmol in 7 h), a throughput of 25 mmol $h^{-1}$ was achieved in the 5-mL continuous flow reactor when 221 g of alcohol **48** were processed, providing consistent results over a period of 3 days.

An interesting example of a chiral separation using a cross-linked polymeric acylase aggregate immobilized in a microreactor was reported by Maeda and coworkers [57]. Taking advantage of a continuous flow system, the resolution of a mixture of the racemic acetyl-amino acid (DL-**58**) was carried out in tandem with a microextractor for the selective separation of the resulting chiral products (Scheme 17). The racemic substrate was introduced into the microreactor in a buffered aqueous solution, then acidified with HCl subsequent to reaction completion, and combined with ethyl acetate organic phase for the extraction step. A chemically modified channel with hydrophobic/hydrophilic surfaces was used for the microextractor in order to maintain consistent laminar flow. Laminar flow is important for good interfacial mass transfer and efficient extraction. Under optimal flow rates for both the aqueous and organic phases, almost 100% of L-Phe **60** (99% ee) remained in the aqueous phase, while up to 84–92% of the acetyl D-amino acid **59** was extracted into the organic phase (Scheme 17).

## Conclusion

Asymmetric reactions have been carried out under both homogeneous and heterogeneous conditions in flow. Good control of reaction parameters is particularly important for these transformations, where minor changes in reaction parameters can have an adverse effect on stereoselectivity. Under flow conditions, reliable and consistent stereoselectivities as well as yields can be maintained; scale-up and rapid screening is also facilitated. While many notable examples of asymmetric synthesis using continuous flow technology have been reported, it is certain that many more applications will be developed in the near future.

## Acknowledgments

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# Polyionic polymers – heterogeneous media for metal nanoparticles as catalyst in Suzuki–Miyaura and Heck–Mizoroki reactions under flow conditions

Klaas Mennecke and Andreas Kirschning*

Full Research Paper

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Address:
Institut für Organische Chemie and Zentrum für Biomolekulare Wirkstoffe (BMWZ), Leibniz Universität Hannover, Schneiderberg 1B, D-30167 Hannover, Germany

Email:
Andreas Kirschning* - andreas.kirschning@oci.uni-hannover.de

* Corresponding author

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## Abstract

The preparation of monolithic polyionic supports which serve as efficient heterogeneous supports for palladium(0) nanoparticles is described. These functionalized polymers were incorporated inside a flow reactor and employed in Suzuki–Miyaura and Heck cross couplings under continuous flow conditions.

## Introduction

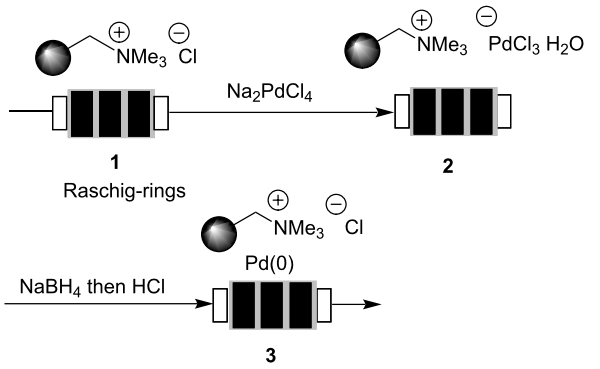
Functionalized solid supports like polymers loaded with homogeneous catalysts are well established in organic synthesis [1-4]. Simple purification of the products and easy recyclability of the catalysts are major advantages of heterogenization of transition metals. A major hurdle for industrial applications of heterogenized homogeneous metal catalyst is associated with keeping metal leaching down to a minimum. Immobilization can be regarded as one enabling technique in organic chemistry [5,6] that in conjunction with continuous flow processes creates an ideal setup for an automated solution-phase synthesis. Furthermore, this combination of enabling techniques has great potential in the production of fine chemicals [7,8].

In continuation of our efforts in developing immobilization concepts for reagents and catalysts including transition metals on solid phases inside monolithic flow reactors [9-18] we describe the preparation of palladium nanoparticles loaded on polyionic polymers and their use under continuous flow conditions in various C-C-cross-coupling reactions [19-22].

## Results and Discussion

### Preparation of the catalyst

Recently, we reported on the preparation of a monolithic polymeric material incorporated inside megaporous glass shaped Raschig-rings [11-18,23,24]. The polymeric phase was created




**Scheme 1:** Preparation of Pd(0) nanoparticles inside flow reactors.

by radical precipitation polymerization of styrene, vinylbenzyl chloride and divinylbenzene as monomers and consists of very small bead-like particles (0.2–2 µm) which are connected through polymeric bridges. As a result an extended monolithic polymeric phase inside a glass monolith is created. Incorporation of the resin inside a porous glass has the advantage that the resin can only swell inside the glass while the glass monolith provides a stable rod-like shape inside the microreactor. The Merrifield-type resin was aminated to yield polyionic support **1**. This polymer serves as an anchor to leave the metal species (sodium tetrachloropalladate; $Na_2PdCl_4$) in close proximity to the ammonium group by means of ion exchange (Scheme 1). In the following, the active Pd particle is generated upon reduction with a solution of sodium borohydride. A particular benefit of the resulting solid support is the stabilization of the generated nanoparticles by the polymer-bound ammonium species [23-29]. These functionalized composite Raschig-rings are incorporated inside the flow microreactor which has a dead volume of about 1–2 mL (Figure 1) [30]. We could show that the palladium clusters are composed of palladium nanoparticles. Particle sizes highly depend on the monomer composition of the polyionic support [4-vinylbenzyl chloride (VBC), divinylbenzene (DVB), styrene]. Depending on the particle diameter a large impact on their catalytic performance (batch vs. flow; conventional vs. microwave heating) was noted [24]. In this context these materials have clear advantages over Pd(0) on

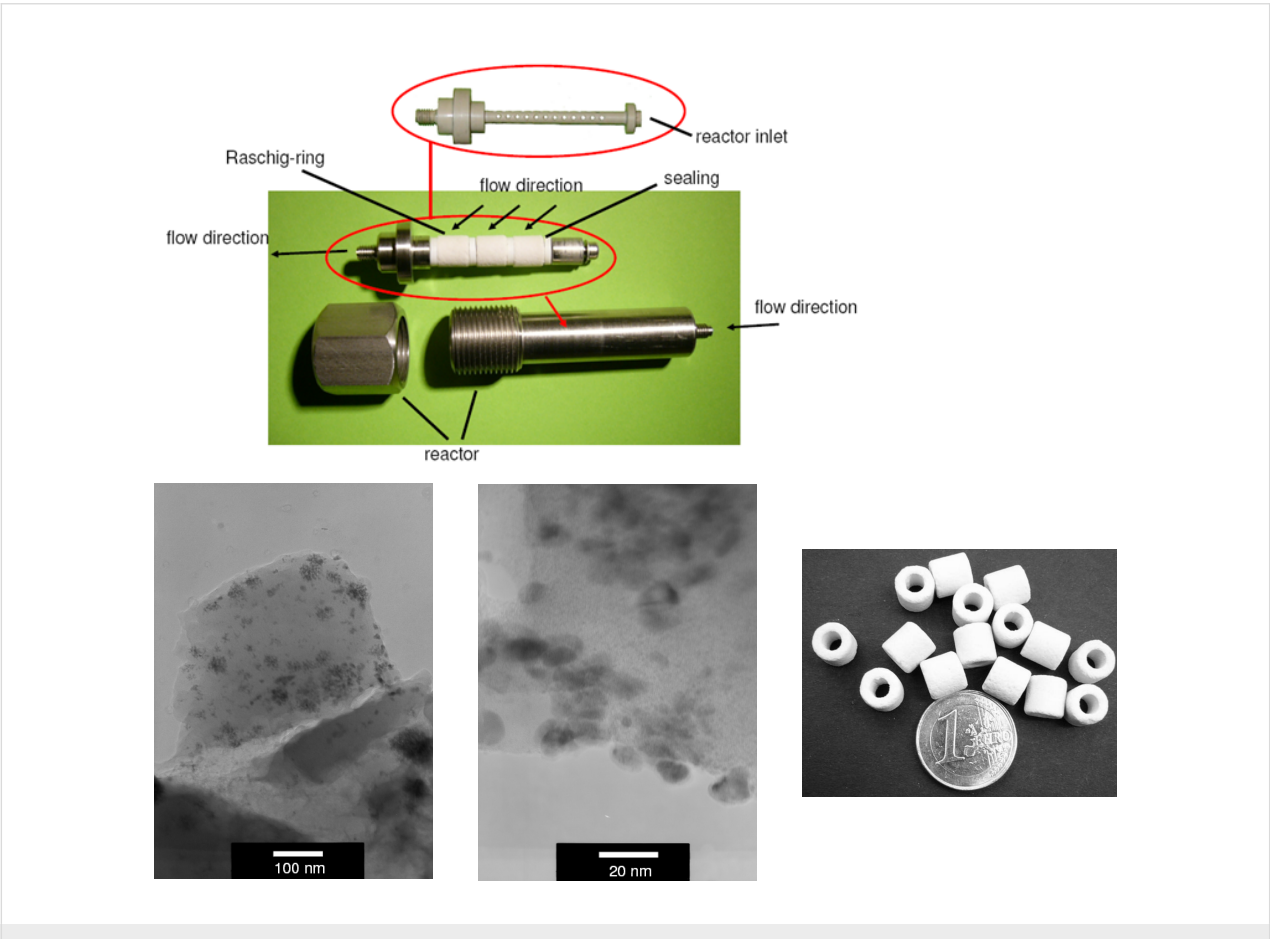



**Figure 1:** Top: Reactor (1–2 mL dead volume) with functionalized Raschig-rings; bottom: TEM-micrographs of Pd(0) nanoparticles on optimized polyionic gel (left and central) and Raschig-rings (right).

charcoal because the latter cannot be further optimized with respect to the mode of application [31-33]. In the present study, our highly optimized composite material was chosen (5.3% DVB crosslinker and a 1:1 mixture of VBC/styrene) doped with nanoparticles (7–10 nm in size and a palladium content of 0.03 weight% Pd on polyionic polymer).

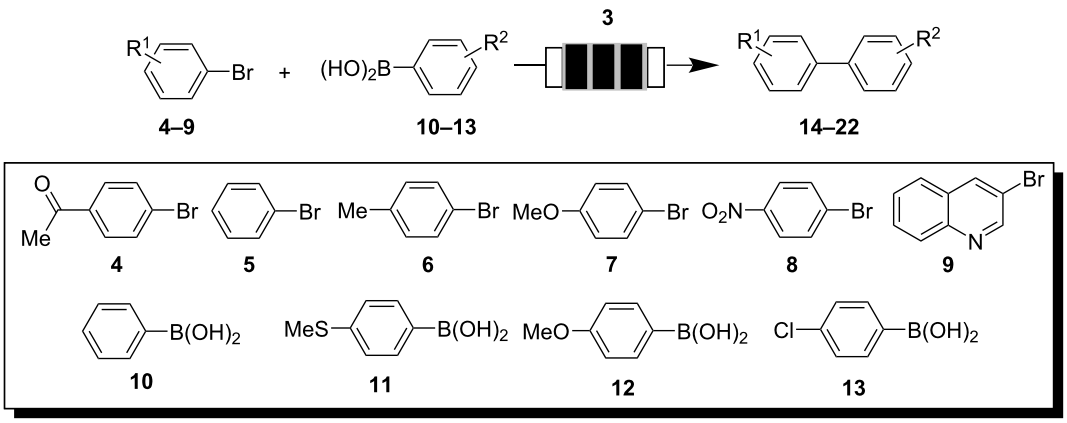
## Suzuki–Miyaura cross coupling reactions

In our earlier work we showed that these materials are well suited for transfer hydrogenations under flow conditions [23, 24]. Recently, the Suzuki–Miyaura reaction and other palladium catalyzed reactions have emerged as industrially very desirable processes and miniflow fixed bed reactors loaded with Pd(0) nanoparticles should be well suited to perform these C-C coupling reactions [34]. A particular challenge for utilizing the Suzuki–Miyaura reaction in flow devices is the quest for truly homogeneous reaction conditions in order to prevent clogging of the irregular microchannels. We chose the coupling of 4′-bromoacetophenone and phenylboronic acid as model reaction for optimizing the process and found that 85% conversion could be achieved within 10 min at 95 °C in DMF/water 10/1 with 2.5 mol% of catalyst **3** using CsF as base. The reaction was performed in a cyclic mode with a flow rate of 2 mL/min. Single pass experiments with flow rates between 0.1 and 1 mL/min did not result in improved results, so that we commonly operated the system as a closed loop reactor in the following.

Under these optimized conditions several examples of successful cross coupling reactions were achieved that are listed in Table 1. We included combinations of electron rich and electron deficient aryl bromides with functionalized boronic acids and yields of coupling products were commonly good to excellent. Aryl chlorides did not react with catalyst **3** under flow conditions.

To fully explore the potential of polyionic gel **3** its reusability was investigated next. The Suzuki reaction of 4-bromotoluene (**6**) with phenylboronic acid (**10**) served as model reaction. After each reaction the continuous flow reactor was regenerated by pumping a solution of DMF/water (10:1, 40 mL) through the reactor before the next run was initiated (Figure 2). The palladium particles inside the flow reactor showed excellent stability without loss of activity after the tenth run. Palladium leaching was determined to be about 0.7 ppm for each run. This very low value for leaching corresponds to the leaching determined for transfer hydrogenations with this catalytic flow system using cyclohexene as hydrogen source and solvent [23,24].

**Table 1:** Suzuki–Miyaura reactions catalyzed by Pd nanoparticles **3** inside flow reactors.




| aryl bromide | boronic acid | product | time [h] | yield [%][a] |
|---|---|---|---|---|
| **4** | **10** | **14** | 1 | 85 |
| **5** | **10** | **15** | 5.5 | 85 |
| **6** | **10** | **16** | 5.5 | 60 |
| **7** | **10** | **17** | 3.5 | 75 |
| **8** | **10** | **18** | 4.5 | 99 |
| **9** | **10** | **19** | 24 | 86 |
| **4** | **11** | **20** | 1 | 81 |
| **4** | **12** | **21** | 2.5 | 89 |
| **4** | **13** | **22** | 2 | 99 |

[a]Isolated yield of pure product.

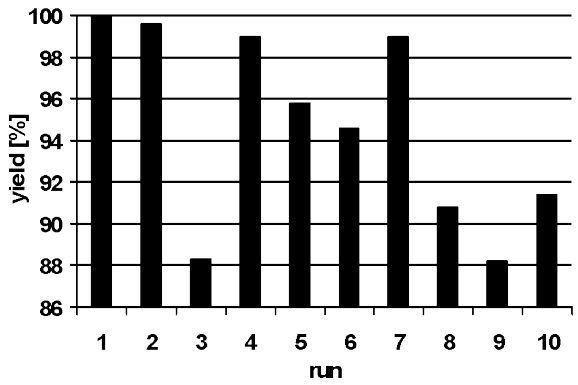



**Figure 2:** Repeated Suzuki reaction of 4-bromotoluene (**6**) with phenylboronic acid (**10**) under flow conditions. Deviations may result from work up as only isolated yields are presented.

## Heck–Mizoroki reactions

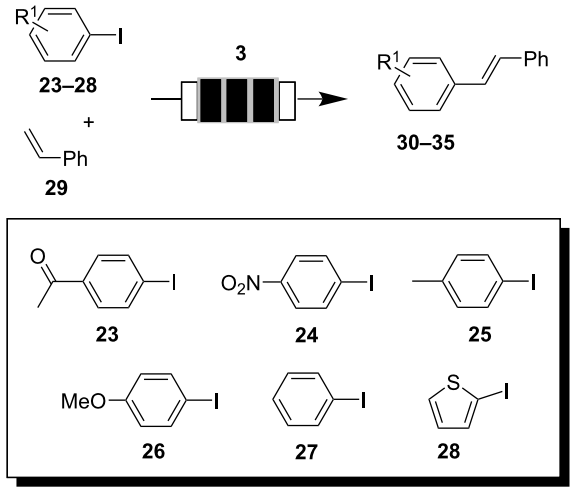
One other very important cross coupling reaction that bears industrial relevance is the Heck–Mizoroki reaction. We were able to perform C-C coupling reaction under flow conditions with aryl iodides **23**–**28** using catalyst **3** (Table 2). Optimization of the conditions for our monolithic flow reactor was conducted with 4′-iodoacetophenone (**23**) and styrene (**29**) as coupling partners. With *n*-butylamine as base and 2.5 mol% catalyst **3** in DMF at 120 °C and a flow rate of 2 mL/min it was possible to achieve full conversion with complete *E*-selectivity within 30 min. Formation of by-products resulting from homocoupling was not observed. When 4′-iodoacetophenone (**23**) was exchanged with 4′-bromoacetophenone coupling with styrene yielded Heck-product **30** in only 35%.

In order to generalize the reaction protocol different aryl iodides were coupled with styrene. In all cases, the C-C coupling products were formed within 0.5 to 24 h in very good yield with excellent stereocontrol (see Table 2). Palladium leaching was determined to be 0.04% for each run based on the catalyst used initially, which is an exceptionally low value in view of the fact that DMF a well coordinating solvent is employed [35].

Even commercially available and widely employed catalysts that are based on encapsulated Pd particles such as PdEnCat [35] show a similarly low degree of leaching in DMF to our Pd nanoparticles [36]. With reference to the fundamental work by Reetz and de Vries the ionic environment on the polymer phase that is located in very close vicinity to the palladium nanoparticles has very likely to be made responsible for the stabilization of the nanoparticles which results in low degree of leaching [25-29].

It has to be noted that like many other heterogenized Pd sources [15,16,36-41] these polyionic gels very likely also serve as reservoirs for Pd nanoclusters that are released into solution at very low concentrations. With respect to transfer hydrogenations using precatalyst **3** we recently conducted a thorough study on the principal question whether **3** serves as a Pd reservoir [23]. As was first demonstrated by Reetz [25-28] and de Vries [29] these clusters exert pronounced catalytic activity in solution at very low concentrations. This view is further supported by the fact that the catalytic species operating in the

**Table 2:** Heck–Mizoroki reactions catalyzed by Pd nanoparticles **3** inside flow reactors.




| aryl iodide | product | time [h] | yield [%][a] |
|---|---|---|---|
| **23** | **30** | 0.5 | 99 |
| **24** | **31** | 24 | 99 |
| **25** | **32** | 19 | 93 |
| **26** | **33** | 3 | 77 |
| **27** | **34** | 24 | 99 |
| **28** | **35** | 4 | 99 |

[a]Isolated yield of pure product.

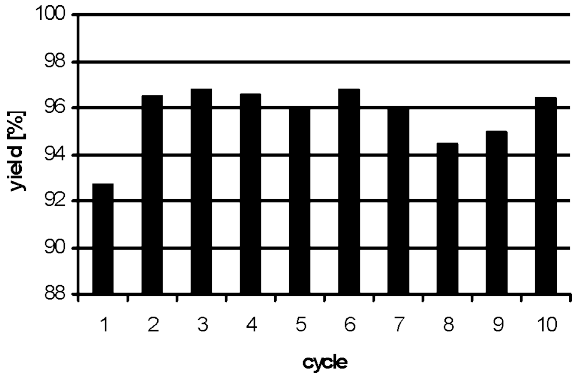



**Figure 3:** Repeated Heck–Mizoroki reaction of 4′-iodoacetophenone (**23**) with styrene (**29**) under flow conditions.

present case is able to promote Suzuki–Miyaura cross coupling reactions with aryl bromides while aryl chlorides are not good substrates under these standard conditions. This observation has been noted in many examples of heterogenized palladium salts or complexes [34]. Likewise, these species are commonly not reactive enough to promote the Heck–Mizoroki reaction with aryl bromides. It should be noted that under supercritical or high pressure/high temperature conditions aryl chlorides (for Suzuki–Miyaura reactions) or aryl bromides (for Heck–Mizoroki reactions) may very well serve as substrates for this kind of palladium species.

## Conclusion

In summary, we demonstrated that polyionic gel **3** is a well suited ion exchange resin for the generation of metal nanoparticles. The ionic nature of the resin has a positive impact on the stabilization of the Pd species which results in extended use for Suzuki–Miyaura cross coupling reactions as well as Heck reactions without substantial reduction of activity even when solvents such as DMF are employed and therefore leads to a minimum degree of leaching. The ease of preparation and the properties of polyionic catalyst **3** make it an attractive catalytic monolith for industrially relevant continuous flow processes particularly when employed in combination with a scavenger column for removing traces of soluble Pd species.

## Supporting Information

### Supporting Information File 1

Experimental
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-5-21-S1.doc]

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## Note added in proof

In a detailed study McQuade and coworker demonstrated that PdEnCat 30 also behaves as heterogeneous sources for soluble, catalytically active species during the course of Heck and Suzuki couplings. They note a solution-phase contribution for catalysis and determined leaching up to 46% in DMF as solvent which is significantly higher compared to our polyionic gels: Broadwater, S. J.; McQuade, D. T. *J. Org. Chem.* **2006**, *71*, 2131–2134.

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# Continuous flow based catch and release protocol for the synthesis of α-ketoesters

Alessandro Palmieri[1], Steven V. Ley[*,1], Anastasios Polyzos[1,2], Mark Ladlow[3] and Ian R. Baxendale[1]

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Address:
[1]Innovative Technology Centre (ACS), Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, United Kingdom, [2]CSIRO Molecular and Health Technologies, Bayview Avenue, Clayton South, Melbourne, Australia, 3169 and [3]Uniqsis, Shepreth, Cambridgeshire, SG8 6GB, United Kingdom

Email:
Steven V. Ley[*] - svl1000@cam.ac.uk

* Corresponding author

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## Abstract

Using a combination of commercially available mesofluidic flow equipment and tubes packed with immobilised reagents and scavengers, a new synthesis of α-ketoesters is reported.

## Introduction

Organic synthesis is changing rapidly owing to the discovery of processes that challenge current dogma and lead to the invention of new chemical reactions [1,2]. Likewise, new synthesis tools are impacting on the way we assemble molecules. Of these, flow chemistry technologies are becoming especially important [3-14]. For many years, our group [15-22] has been focussed on using immobilised systems [23-29] to more effectively and cleanly bring about chemical transformations, especially in multistep mode [17,30-37]. Given the success of these concepts, it is not surprising that we would want to adapt these principles to various flow-chemical synthesis platforms to effectuate automated multistep chemical syntheses [38-54]. In this work we report the use of the Uniqsis FlowSyn™ continuous flow reactor [55] (Figure 1) to effect a flow-based preparation of α-ketoesters. The key feature of this process is the application of a catch and release protocol [56-72], under the flow reaction conditions. Our choice of α-ketoesters as products of the process was governed by their use as starting materials for various synthesis programmes [73-81] and as important products in their own right [82-88]. Common methods for the preparation of α-ketoesters include the modified Dakin-West reaction [89] and the addition of a Grignard reagent to oxalates or oxalyl chlorides [90-92] together with a few alternative syntheses [93-99]. These procedures often suffer

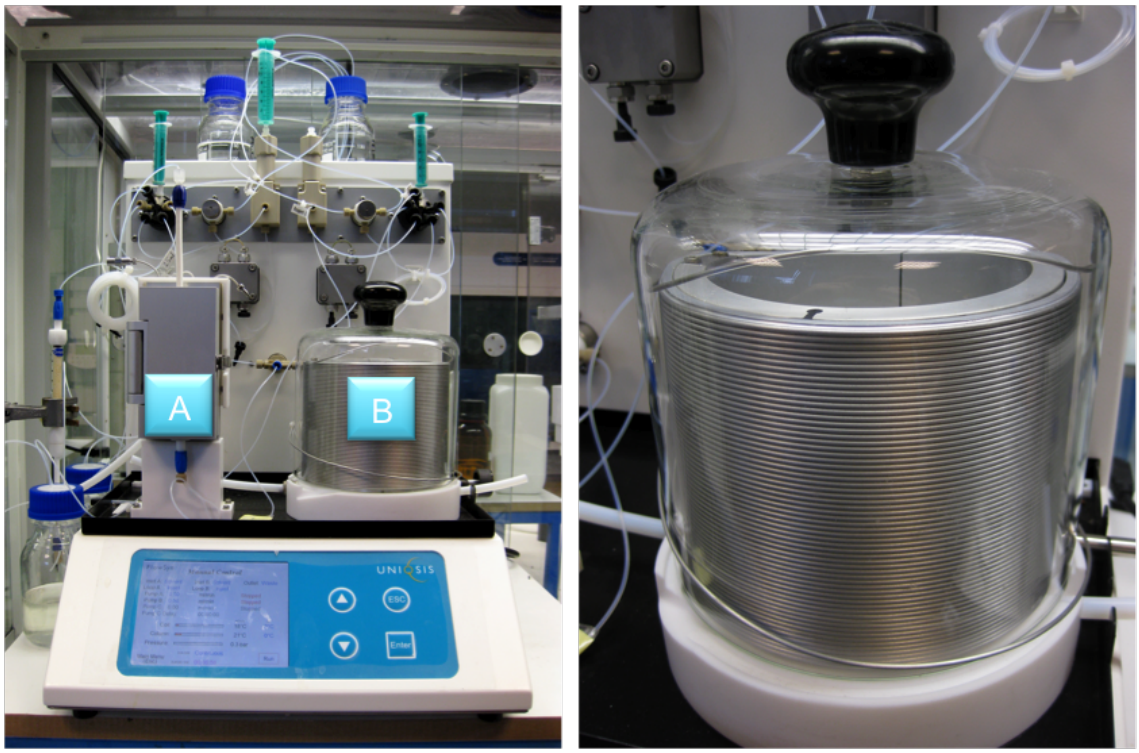


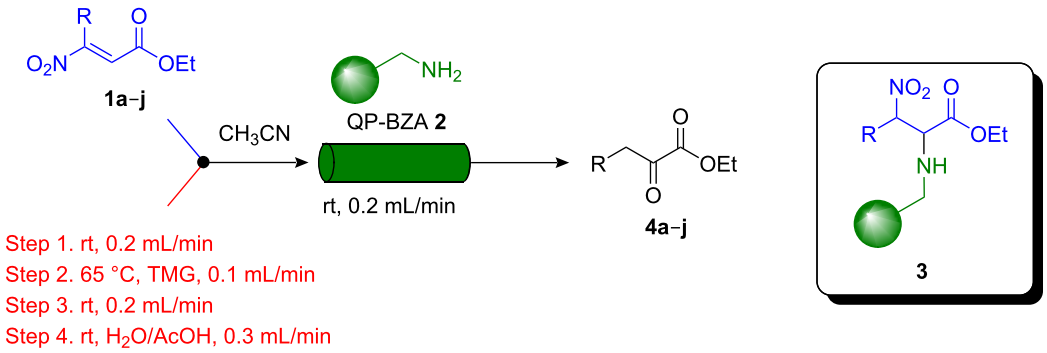

**Figure 1:** The Uniqsis FlowSyn™ continuous flow reactor comprising of a column holder and heating unit (A) and the reactor coil (B). A detailed image of the reactor coil is shown on the right.

from drastic conditions, restricted selectivity and poor yields. Our flow-based approach delivers a new and general method for the preparation of α-ketoesters, which proceeds under mild conditions, with good functional group tolerability and generates products in high purity.

## Results and Discussion

The experimental set up for these transformations involves the use of the Uniqsis FlowSyn™ device [55]. The fully integrated instrument employs a dual channel flow system, with each channel independently driven by a variable high-pressure piston pump. The starting materials and reagents are dispensed from sample loops (0.5–10 mL) and are united in a T-mixing piece and then passed into either a coil or column reactor (Figure 1). The column reactor utilises adjustable glass columns with variable internal diameter (1–1.5 cm) and range in volume from 6–83 mL (unpacked). The coil reactors are made from a selection of materials including PTFE, PEEK, stainless steel or Hastelloy® and accommodate volumes from 2–20 mL. The column reactor (Figure 1, A) can be heated up to 150 °C and the coil heater (Figure 1, B) up to 260 °C, over a range of flow rates between 0.01–20 mL/min, and can be configured for multistep or parallel operation. Exiting products can be collected as aliquots using an automated fraction collector for reaction optimisation or as a bulk sample for scale-up. In addition, product purification can be achieved as part of the overall flow process by in-line solid phase extraction (SPE) or alternatively by diverting the flow stream into an attached HPLC system [100].

A series of preliminary experiments was carried out on the flow equipment to profile the reaction in terms of optimum reaction temperature, concentration, residence time, solvent and stoichiometry. Following rapid screening of conditions, we fixed upon a set of reaction parameters for efficient synthesis of α-ketoesters (Scheme 1). The overall reaction process proceeds in the flow apparatus *via* nitroolefinic esters **1** as substrates which are captured onto a benzylamine polymer **2** (QuadraPure™ QP-BZA polymer, loading 5.5 mmol/g, 4 equiv) to give **3** to effect product clean-up. In this way the immobilised species **3** can be washed and any solution phase impurities (resulting from the formation of the nitroolefinic ester – see later) are directed to waste (step 1). Next the column is treated with a flow stream of tetramethylguanidine (TMG; step 2) to cause elimination of nitrous acid and produce the corresponding enamino acid esters, which remain attached to the polymer support. Finally, after flow-washing (step 3), the solid supported species is hydrolysed, liberating α-ketoester product **4** by flowing aqueous acetic acid (step 4) through the in-line column. The overall route constitutes a new flow chemistry

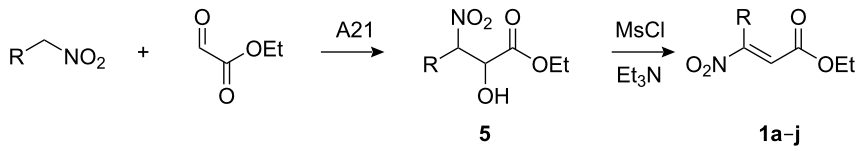



**Scheme 1:** General procedure for the flow synthesis of α-ketoester products **4a–j**.

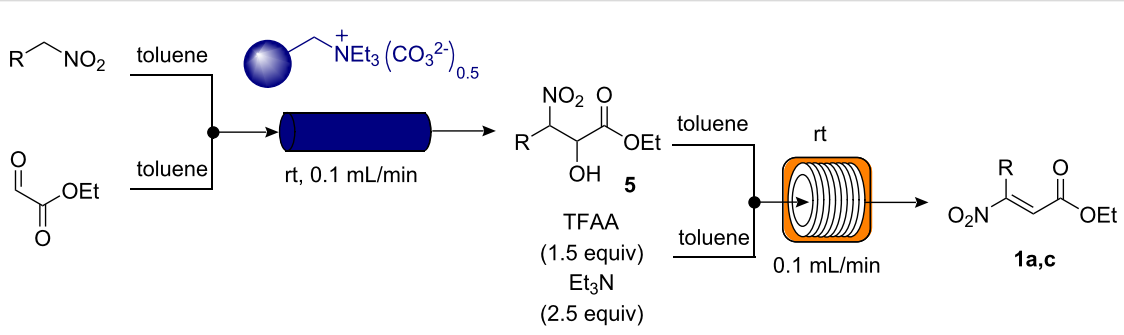
example of the *catch-react-and-release* concept that we have used successfully in other synthesis programmes [101-103].

The nitroolefinic esters **1** were originally formed in a separate batch reaction from a Henry coupling of appropriate nitro compounds with ethyl glyoxalate over Amberlyst™ 21 (A21) resin to give the corresponding nitroalkanol **5** [104]. This was followed by treatment of **5** with methanesulfonyl chloride (MsCl) or trifluoroacetic anhydride (TFAA) to promote the base-catalysed dehydration, affording the nitroolefinic esters **1** (Scheme 2) [105]. As we have deliberately constructed this sequence for implementation in a continuous flow process, the intermediate nitroalkanols **5** were not isolated and the nitroolefinic esters were used without further purification. The average yield for the nitroolefins **1a–j** prepared as described in Scheme 2 was approximately 60% by LCMS. Impurities were readily removed following immobilisation of nitroolefinic esters **1** on the QP-BZA resin.

In addition, the flow synthesis of two representative compounds was undertaken to allow for the complete generation of α-ketoester products in flow from the starting nitroalkanes (Scheme 3). As shown in Table 1, we demonstrate that the synthesis of the nitroolefinic esters was achieved under flow conditions in a clean and effective fashion. Moreover, this synthesis demonstrates the first reported example of Henry reaction conducted in flow and we intend to elaborate on this important transformation in future studies.

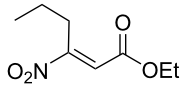
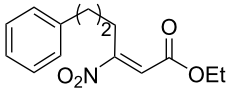



**Scheme 2:** General procedure for the batch synthesis of nitroolefinic esters **1a–j**.




**Scheme 3:** General procedure for the flow synthesis of nitroolefinic esters **1a**,**c**.

**Table 1:** Nitroolefinic esters **1a,c** prepared under flow conditions (as described in Scheme 3).

| Entry | **1** | Compound | Yield (%)[a] |
|---|---|---|---|
| 1 | **1a** |  | 63 |
| 2 | **1c** |  | 55 |

[a]Isolated yields are shown.

Figure 2 illustrates the examples and yields of α-ketoester products afforded by this new approach. While the list is not extensive, we have established that the process is tolerant of both aliphatic and aromatic substituted nitro-derivatives in the first step, and accommodates ester, acetate, acetal, nitrile and olefinic functionality in the final product. The process was reliable over several runs and consistently afforded very clean material (≥ 97% by NMR). The yields while only moderate for the *overall process* still equate to an average step conversion of 68–78% per chemical iteration, given that the sequence is a multistep process (see Supporting Information for full experimental data).

## Conclusion

In conclusion, we have demonstrated the versatility of the Uniqsis FlowSyn™ unit to achieve multi-step organic synthesis under continuous flow-chemistry conditions. This was accomplished by adapting the device to incorporate immobilised reagents packed in flow tubes, enabling clean transformations without recourse to conventional product work-up or purification. The overall process delivers synthetically useful α-ketoester products in high purity from various nitroalkane inputs and paves the way for more extended reaction sequences.

## Supporting Information

### Supporting Information File 1

Supporting Information – Continuous flow based catch and release protocol for the synthesis of α-ketoesters
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-5-23-S1.doc]

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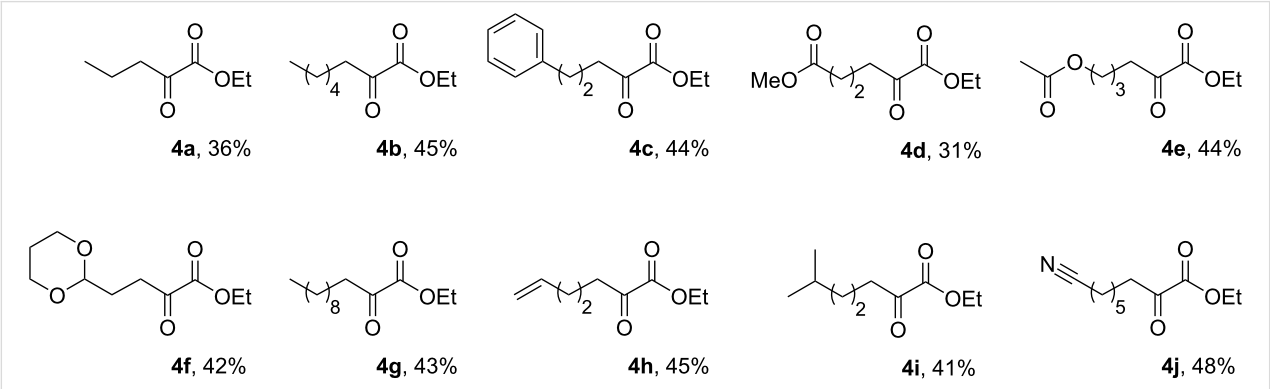



**Figure 2:** α-Ketoesters prepared and isolated yields.

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# The development and evaluation of a continuous flow process for the lipase-mediated oxidation of alkenes

Charlotte Wiles[*,1,2], Marcus J. Hammond[1] and Paul Watts[*,1]

Full Research Paper

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Address:
[1]Department of Chemistry, The University of Hull, Cottingham Road, Hull, HU6 7RX, UK and [2]Chemtrix BV, Burgemeester Lemmensstraat 358, 6163JT, Geleen, The Netherlands

Email:
Charlotte Wiles[*] - c.wiles@chemtrix.com; Paul Watts[*] - p.watts@hull.ac.uk

* Corresponding author

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## Abstract

We report the use of an immobilised form of *Candida antarctica* lipase B, Novozym® 435, in a preliminary investigation into the development of a continuous flow reactor capable of performing the chemo-enzymatic oxidation of alkenes in high yield and purity, utilising the commercially available oxidant hydrogen peroxide (100 volumes). Initial investigations focussed on the lipase-mediated oxidation of 1-methylcyclohexene, with the optimised reaction conditions subsequently employed for the epoxidation of an array of aromatic and aliphatic alkenes in 97.6 to 99.5% yield and quantitative purity.

## Introduction

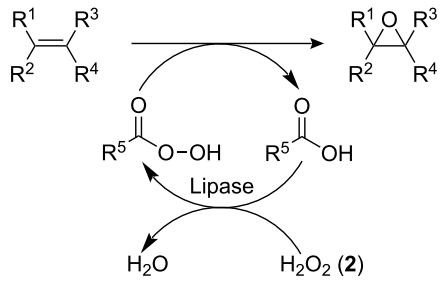
In addition to their synthetic value as intermediates in the preparation of diols, alcohols, hydroxyesters and alkenes, epoxides are a key raw material in many industrial processes, finding application in adhesives, polymers, coatings and paints [1,2], with some epoxides even exhibiting biological activity [3,4]. As such, over the years, convenient and efficient techniques have been sought for their preparation.

Within the research laboratory, epoxidation of alkenes is achieved using organic peroxides and metal catalysts [5] or peracids [6] such as *m*-chloroperbenzoic acid (*m*-CPBA) [7,8]. The hazardous nature of these techniques and the potential to hydrolyse the epoxide [9] however precludes their use on a large scale. Many of the epoxides produced industrially are synthesised using the chlorohydrin method, or *via* in situ generated peracids derived from formic acid or acetic acid (**1**)/ hydrogen peroxide (**2**). As $H_2O_2$ (**2**) is itself not sufficiently electrophilic to epoxidise a non-conjugated double bond directly, its use in the formation of a peracid has afforded a route to the epoxidation of alkenes in the presence of a strong mineral acid [10,11]. Along with the numerous safety issues that these methods present, the generation of large quantities of chlorinated by-products and acidic waste make these approaches undesirable; not only from a disposal stand point, but also with respect to product quality, with reduced chemoselectivity observed in strongly acidic media.

As a means of addressing these problems, the past 20 years has seen a series of authors investigate the use of a chemo-enzymatic process for the oxidation of olefins, based on the enzymatic formation of peracids from carboxylic acids and oxidants such as $H_2O_2$ (**2**) and urea–hydrogen peroxide (UHP, **3**) [12].

For this transformation, the biocatalysts of choice are lipases (E.C. 3.1.1.3), which are a group of water soluble enzymes that catalyse the hydrolysis of lipid substrates, i.e. triglycerides and fats, in biological systems and are a subclass of the esterases [13]. Changes in enzymatic behaviour observed when lipases are employed in organic solvent systems have led to their use in the synthesis of lipids, carbohydrate esters, amines and amides, along with finding industrial application in the synthesis of pharmaceuticals, fine chemicals and cosmetics [14]. In these reactions, the lipases have been shown to exhibit excellent regio- and stereo-selectivity, enabling a facile route to the synthesis of optically active compounds [15-17].

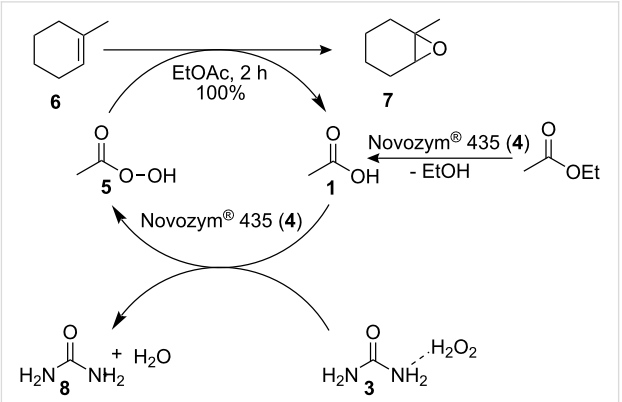
Chemo-enzymatic epoxidation provides an environmentally benign approach to the synthesis of epoxides, with Björkling and co-workers [18,19] initially reporting the generation of epoxides under mild conditions using seven lipases. As Scheme 1 illustrates, the biocatalytic epoxidation involves the lipase catalysed formation of a peroxy acid, from a carboxylic acid and an oxidant, such as $H_2O_2$ (**2**), which donates oxygen to the double bond, affording the respective epoxide or oxirane and regenerating the carboxylic acid.




**Scheme 1:** Illustration of the chemo-enzymatic epoxidation of an alkene; involving the biocatalytic perhydrolysis of a carboxylic acid followed by a peroxy acid epoxidation.

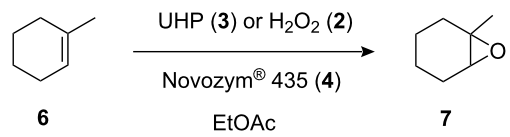
Initial investigations illustrated the highest conversions in solvents such as hexane and toluene, with the lowest in dioxane and acetonitrile, following the lipase trend where the biocatalysts typically perform better in water immiscible solvents. Moderate deactivation of the enzyme was however observed, attributed to the use of high concentrations of $H_2O_2$ (**2**). This was overcome by adding aliquots of the oxidant over an extended period of time (4 h) affording the target epoxides in conversions ranging from 15% to quantitative depending on the alkene employed.

Törnvall et al. [20] subsequently conducted a detailed investigation into the source of enzyme deactivation, concluding that high temperature (60 °C) and high concentrations of $H_2O_2$ (**2**, 6 to 12 M) resulted in rapid loss of enzyme activity, again illustrating that careful dosage of $H_2O_2$ (**2**) increased the operational lifetime of the biocatalyst. The authors also noted that the presence of EtOH and urea resulted in moderate deactivation of the enzyme. In 2006, Olivo and co-workers [21] reported an environmentally benign method for alkene epoxidation *via* the chemo-enzymatic perhydrolysis of ethyl acetate using Novozym® 435 (**4**), immobilised *Candida antarctica* lipase B, and UHP (**3**). They utilised the high specificity of *Candida antarctica* lipase B towards ester hydrolysis to generate acetic acid (**1**) in situ and subsequently synthesise the peracid **5** (Scheme 2). The authors found that compared to the use of aq $H_2O_2$ (**2**), the use of UHP (**3**) enabled controlled release of anhydrous $H_2O_2$ (**2**) and enabled the enzyme to be recycled with no observable effect on conversion over two catalytic cycles. Using this approach, Olivo et al. demonstrated the synthesis of twelve epoxides with yields ranging from 73% for 1-hexene to quantitative for 1-methylcyclohexene (**6**) and reaction times of 166 to 2 h respectively. Along with Björkling and co-workers [18,19], the authors found the use of aq $H_2O_2$ (**2**) resulted in a reduction in conversion after two cycles (60%) affording complete deactivation of the enzyme on the third cycle; yields in the range of 73 to 85% were however obtained upon adding the oxidant in aliquots over a period of 24 h.




**Scheme 2:** Illustration of the chemo-enzymatic epoxidation of 1-methylcyclohexene (**6**) to 1-methylcyclohexene oxide (**7**), using EtOAc as both a reactant and a solvent.

Although the chemo-enzymatic epoxidation of alkenes is an attractive alternative to the hazardous reagents currently employed, finding use in the synthesis of the aroma linalool




**Scheme 3:** Model reaction used to compare the continuous flow epoxidation strategy with the conventional batch technique.

oxide and epoxidised soybean oil [16], the reaction times employed for the transformations (< 166 h) and observed reductions in enzyme activity in the presence of $H_2O_2$ (**2**) do not currently make the technique a practical alternative to traditional techniques. With this in mind, we report herein the development and evaluation of continuous flow technique for the enzyme-mediated synthesis of epoxides, employing the immobilised *Candida antarctica* lipase B, Novozym® 435 (**4**). This was recently found to be the most efficient biocatalyst with respect to peracid formation, facilitating a series of oxidations including alkenes [21] and ketones *via* the Baeyer–Villiger reaction [22] and retaining the broad substrate specificity of *Candida antarctica* lipase B.

In the past decade micro reactors, and more generically continuous flow reactors, have been shown to offer many advantages to the synthetic chemist, such as reduced reactions times, increased catalytic efficiency, increased product purity and atom efficiency [23-26]. More recently, authors have begun to incorporate biocatalysts into flow reactors as a means of increasing productivity, biocatalyst lifetimes and exploring the potential of employing immobilised enzymes in industrial processes. Recent examples include the continuous flow enantioselective acetylation of a series of racemic secondary alcohols [27] and the continuous flow synthesis of alkyl esters [28].

## Results and Discussion

Combining our experience of micro reaction methodology with the observations made by Olivo and co-workers [21,22], it was proposed that by conducting the lipase-mediated epoxidation under continuous flow it would be possible to reduce the reaction times required to oxidise synthetically useful alkenes, whilst increasing the biocatalyst's lifetime. With this in mind, our initial investigation into the development of a continuous process for the synthesis of epoxides focussed on the incorporation of immobilised *Candida antarctica* lipase B, Novozym® 435 (**4**), into a flow reactor and the use of urea–hydrogen peroxide (**3**) as the oxidising agent.

In addition to reports made by Olivo and co-workers, UHP (**3**) [29] was selected as the oxidant as it is a cheap, commercially available, source of anhydrous $H_2O_2$ (**2**) which, in addition to its use in the synthesis of epoxides [30,31], has found widespread application in the conversion of nitriles to amides [32], aldehydes to acids [33], and sulfides to sulfones [34]. To enable comparison of the method developed here with batch investigations previously conducted, the oxidation of 1-methylcyclohexene (**6**) to 1-methylcyclohexene oxide (**7**) was selected as a model reaction (Scheme 3) for investigation within the reaction set-up illustrated in Figure 1.

### Micro reactor set-up

As Figure 1 depicts, the flow reactor consisted of a borosilicate glass capillary (3.0 mm (i.d.) × 3.6 cm (long) packed with 100 mg of Novozym® 435 (**4**), with reactions conducted by pumping a pre-mixed solution of the alkene **6** and UHP (**3**) through the packed-bed using a syringe pump.

The reaction products were collected in a sample vial containing EtOAc (1 ml) over a period of 10 min, and analysed by GC-MS in order to quantify the conversion of 1-methylcyclohexene (**6**) to 1-methylcyclohexene oxide (**7**). Using this approach enabled rapid screening of the reaction conditions to be conducted: if residual alkene **6** was detected the reaction was simply repeated employing an increased reaction time, which was achieved by reducing the flow rate of the reactant stream. Upon changing the reaction conditions, the system was allowed

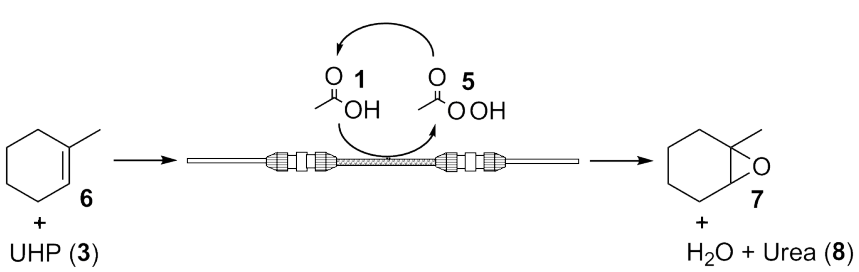



**Figure 1:** Schematic of the reaction set-up used to evaluate the continuous flow chemo-enzymatic epoxidation of 1-methylcyclohexene (**6**) *via* the perhydrolysis of acetic acid (**1**).

to equilibrate for 30 min prior to sampling, thus ensuring equilibration of the reactor. In addition, to ensure that meaningful data was obtained, all reaction conditions were monitored for a minimum of 5 samples (*n*) and the average result reported along with the relative standard deviation (% RSD).

## Evaluation of UHP as an oxidant

When adapting or developing reaction methodology for a continuous flow application, it is imperative to ensure that all reactants, by-products and products remain soluble over the course of the reaction, so as to prevent blockage formation within the fluidic system which can lead to the build-up of pressure followed by leaking from any interconnections. Consequently, due to the limited solubility of UHP (**3**) in those organic solvents found to promote the epoxidation of alkenes (typically ethyl acetate and DCM) the use of conditions analogous to those reported within the literature (~0.3 M) were not feasible within the flow reactor. As such, an ethyl acetate solution of reduced concentration [alkene **6** ($2.5 \times 10^{-2}$ M) and UHP (**3**) ($5.0 \times 10^{-2}$ M)] was employed and initial investigations focussed on evaluating the effect of reaction time on the epoxidation of 1-methylcyclohexene (**6**). Employing a flow rate of 10 µl $min^{-1}$, hence a residence time of 2.6 min, it was gratifying to observe that under continuous flow conditions, enzymatic hydrolysis of ethyl acetate to acetic acid (**1**) followed by formation of peracetic acid (**5**) and finally oxidation of 1-methylcyclohexene (**6**) had occurred, albeit in low conversion (5.1%). Varying the flow rate of the reactant solution through the packed bed between 0.1 and 50 µl $min^{-1}$, at 27 °C, enabled us to identify 0.1 µl $min^{-1}$ (4.3 h residence time) as the optimum flow rate for the synthesis of 1-methylcyclohexene oxide (**7**, 89.0%).

Using such a low flow rate is however impractical as it would only generate $6.0 \times 10^{-3}$ mg $h^{-1}$ of 1-methylcyclohexene oxide (**7**), thus providing no practical advantage over a conventional, stirred batch reaction. Although a facile approach to increasing the throughput of flow reactions is to increase the concentration of the reactant stream, in this case the limited solubility of UHP (**3**) precludes this as a viable option.

## $H_2O_2$ as an alternative oxidant

As a means of increasing the reactor throughput, an alternative oxidant was sought. $H_2O_2$ (**2**) was initially considered as it presented the distinct advantage over UHP (**3**) that it is soluble in the selected reaction solvent, ethyl acetate, enabling it to be employed at a higher concentration if required. Although batch investigations had highlighted problems associated with the use of $H_2O_2$ (**2**) in the chemoenzymatic epoxidation of alkenes, with it found to deactivate *Candida antarctica* lipase B [35] and prevent recycling of the biocatalyst, it was proposed that by conducting the reactions under continuous flow, where at any one time the quantity of oxidant **2** in contact with the enzyme would be low, continued operation and efficient recycling would be feasible.

As the aim of the investigation was to develop a continuous flow process for the synthesis of epoxides in high purity, it was decided at this stage to employ 5 µl $min^{-1}$ as the minimum flow rate and increase the reactant concentrations by a factor of four; the 2:1 oxidant to alkene ratio was however maintained. With these factors in mind, flow reactions were performed by pumping a pre-mixed solution of 1-methylcyclohexene (**6**, 0.1 M) and $H_2O_2$ (**2**, 0.2 M), in ethyl acetate, through the reactor (0.10 g Novozym® 435 (**4**)) at a flow rate of 50 µl $min^{-1}$ (0.52 min residence time). After a short equilibration time, 30 min, the reaction products were once again collected at ten minute intervals and analysed by GC-MS in order to determine the percentage conversion of the alkene **6** to 1-methylcyclohexene oxide (**7**). As Figure 2 illustrates, at room temperature a moderate conversion of 10.1% was obtained, this was however improved upon by systematically reducing the flow rate, which had the effect of increasing the residence time from 0.52 to 5.20 min and afforded an optimal conversion of 46.2% at a flow rate of 5 µl $min^{-1}$ (5.20 min).

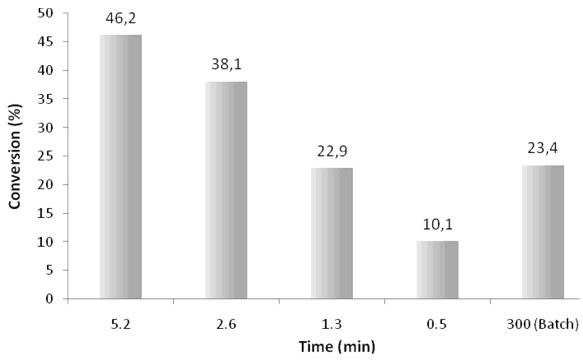



**Figure 2:** Graph illustrating the effect of flow rate (hence residence time) on the conversion of 1-methylcyclohexene (**6**) to 1-methylcyclohexene oxide (**7**) at room temperature (27 °C); employing 2.0 equiv of $H_2O_2$ (**2**).

To ensure that the results obtained were as a result of employing a packed-bed reactor and to exclude the possibility that the reaction was continuing within the collection vial, as only the hydrolysis and perhydrolysis steps were enzyme catalysed, five samples were analysed immediately and then subjected to re-analysis 5 h later. Analogous results were obtained within experimental error (± 0.1%), confirming that the reaction occurred only within the packed bed.

Although up to this point we had failed to oxidise the alkene **6** completely, the use of $H_2O_2$ (**2**) was found to be advantageous compared to UHP (**3**) as it removed the issues associated with reagent insolubility and enabled flow reactions to be conducted at increased alkene concentrations, with product isolation simplified as the only by-product from $H_2O_2$ (**2**) is water. In addition, compared to an analogous batch reaction, it can be seen that equivalent results can be obtained within the flow reactor with reaction time of 1.3 min (22.9%) compared to 5 h (23.4%) in batch and improved conversions attainable with a reaction time of 5.2 min (46.2%). This approach is therefore advantageous as it provides a facile means of continuously adding the oxidant **2**, therefore removing the need for the time consuming practise of adding aliquots of the oxidant **2** in order to maintain the enzymes activity.

## Effect of reaction temperature on the oxidation reaction

Novozym® 435 (**4**) has been shown to retain activity when heated to 60 °C, however in the presence of $H_2O_2$ (**2**) the enzyme has been reported to lose activity, with a half life of 3.9 h at 60 °C [6.0 M $H_2O_2$ (**2**)] [20]. It was therefore proposed that due to the short contact times between the enzyme and oxidant **2** within the flow reactor, denaturation of the enzyme by the oxidant **2** would be avoided; consequently the effect of reactor temperature on the epoxidation of 1-methylcyclohexene (**6**) was investigated.

When heating a flow reactor, it is important to consider the boiling point of the reactants and solvent system as any changes in viscosity, and even boiling, of the components can lead to irreproducible residence times within the reactor; at 5 µl $min^{-1}$ and 60 °C, 64.5 ± 14.5% ($n$ = 5) 1-methylcyclohexene oxide (**7**)

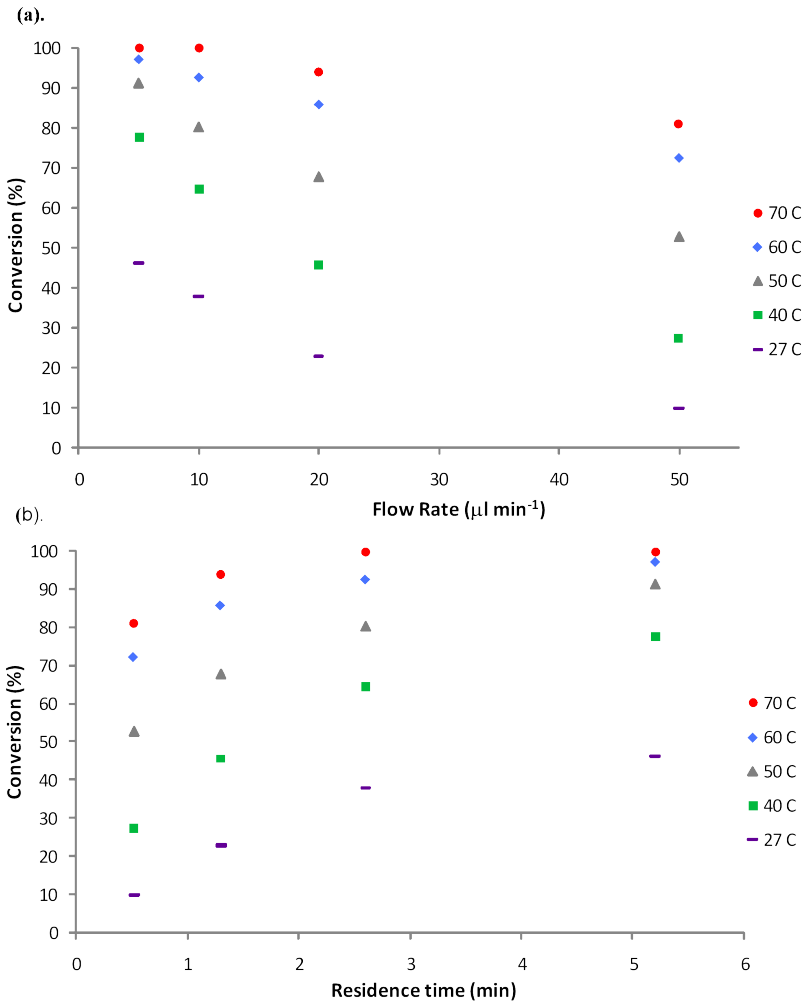



**Figure 3:** Graph illustrating the effect of (a) flow rate and (b) residence time on the conversion of 1-methylcyclohexene (**6**) to 1-methylcyclohexene oxide (**7**) at various reaction temperatures (27 to 70 °C).

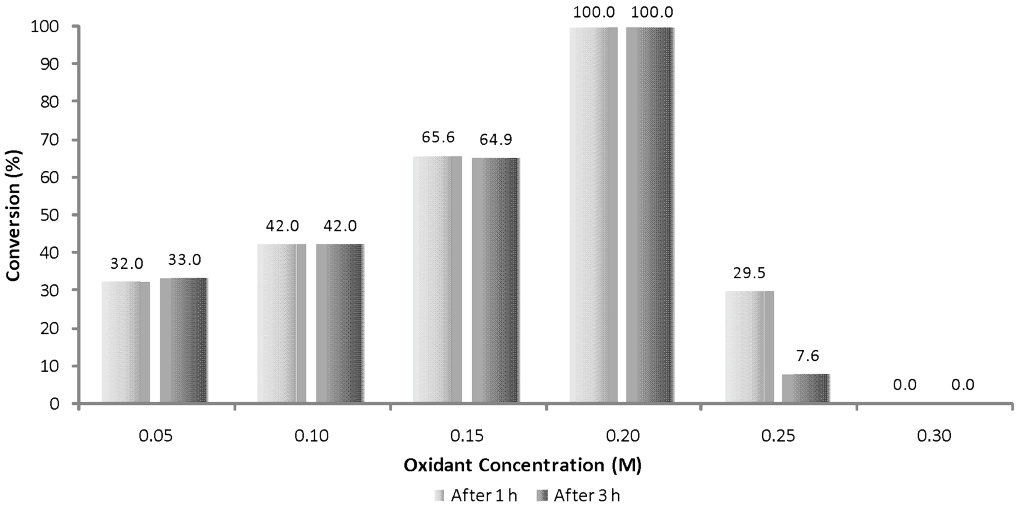



**Figure 4:** Graph illustrating the effect of oxidant stoichiometry on the conversion of 1-methylcyclohexene (**6**) to 1-methylcyclohexene oxide (**7**) at a residence time of 2.6 min (70 °C).

was obtained. To ensure that a uniform residence time was obtained, a back-pressure regulator (100 psi) was inserted into the reaction set-up (between the packed-bed and the collection tube), enabling heating of the reactor above the boiling point of the solvent − in this case 77 °C. To supply heat to the bioreactor, a commercially available HPLC column heater was employed and the effect of reaction temperature on the rate of epoxidation assessed (40 to 70 °C) over a range of flow rates. Incorporation of a BPR into the reaction system reduces the error associated with the process (± 0.1%) and is a facile means of obtaining stable, plug flow at elevated reaction temperatures.

Although the percentage of epoxide **7** synthesised was found to increase with reducing flow rate, when comparing the data obtained at room temperature with that collected at elevated temperatures (40 and 70 °C), it can be seen that the oxidation of 1-methylcyclohexene (**6**) increased most notably with reaction temperature; whereby quantitative conversion was obtained at 70 °C, cf. 38.1% **7** at 27 °C (10 μl $min^{-1}$) (Figure 3). Under the optimised conditions stated, 1-methylcyclohexene oxide (**7**) was synthesised at a throughput of 6.7 mg $h^{-1}$ from a single reactor with post reactor processing consisting simply of an aqueous extraction to remove water and acetic acid (**1**) from the epoxide **7**.

Having subjected the same portion of enzyme **4** to a prolonged thermal regime (21 h), it was imperative to ensure that the enzyme had not lost activity; to evaluate this a flow reaction was performed using the initial reaction conditions of 5 μl $min^{-1}$ at room temperature. Using this approach, 46.3% 1-methylcyclohexene oxide (**7**) was obtained, which compared favourably to the 46.2% **7** obtained prior to heating the bioreactor; confirming enzyme activity was maintained.

## Effect of oxidant concentration on enzyme stability

Although it was pleasing to observe stability of the Novozym® 435 (**4**) at various reaction temperatures, with literature precedent reporting enzyme deactivation at an oxidant concentration of $5.0 \times 10^{-2}$ M the next step of the investigation was aimed at evaluating the enzyme's tolerance to $H_2O_2$ (**2**) in the micro reactor. To achieve this, the concentration of alkene **6** was maintained at 0.1 M and the oxidant **2** concentration varied between $5 \times 10^{-2}$ and 0.3 M (0.5 to 3.0 equiv with respect to alkene **6**) and the reactions conducted at 10 μl $min^{-1}$ (2.6 min) and 70 °C, with samples taken after 1 and 3 h of continuous operation. As Figure 4 illustrates, when employing 0.5 equiv of oxidant **2** an average of 32.5% conversion was obtained. This rose to 42.0% when employing equimolar quantities of $H_2O_2$ (**2**), whereas employing a slight excess afforded 65.3% conversion (1.5 equiv) and 2 equiv again affording quantitative conversion to 1-methylcyclohexene oxide (**7**). Interestingly when a concentration of 2.5 M $H_2O_2$ (**2**) was employed, rapid deactivation of the enzyme was observed, illustrated by a reduction in conversion to 29.5% after 1 h and 7.6% after 3 h. To confirm that the enzyme had undergone irreversible damage, the reactor was purged with ethyl acetate (2.5 ml) and the reaction utilising 2 equiv of $H_2O_2$ (**2**) repeated at 70 °C, whereby baseline formation of the epoxide was observed. Prior to conducting investigations at 0.3 M, the Novozym® 435 (**4**) was removed and a second portion of the biocatalyst packed into the reactor (0.10 g), again however deactivation was observed, this

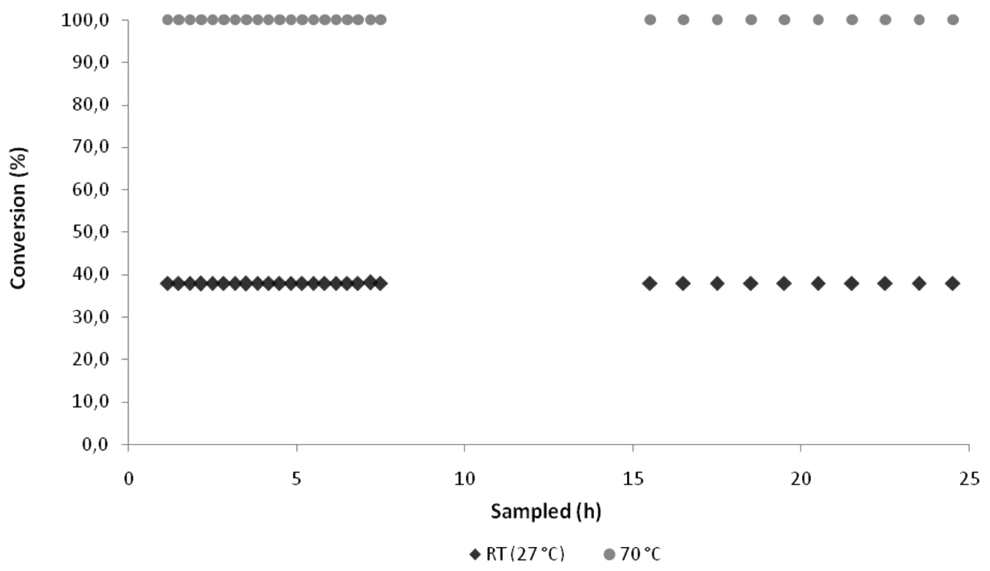



**Figure 5:** Illustration of the enzyme **4** stability to $H_2O_2$ (**2**) for the conversion of 1-methylcyclohexene (**6**) to 1-methylcyclohexene oxide (**7**) (residence time = 2.6 min) at 27 °C and 70 °C over a 24 h period.

time after only 1 h. Although deactivation of the enzyme was observed at 2.5 and 3.0 M $H_2O_2$ (**2**), the biocatalyst **4** was found to be tolerant to four times the oxidant concentration (0.2 M) compared to stirred and shaken batch investigations (0.05 M), illustrating another advantage associated with micro reaction technology.

## Monitoring enzyme stability over an extended period of operation

Having confirmed that the optimum conditions for the synthesis of 1-methylcyclohexene oxide (**7**) were a residence time of 2.6 min, a reactor temperature of 70 °C and an oxidant **2**/alkene **6** ratio of 2:1, the stability of the reaction system was monitored over a period of 24 h using fresh biocatalyst (0.10 g **4**). In order to highlight any fluctuations in the system, along with demonstrating continuous operation of analytically pure **7** under the optimised conditions, the system was also operated at the sub-optimal temperature of 27 °C. Samples were collected every 10 min for 7.5 h, then once an hour for 9 h, after an 8 h break in sampling; for visual clarity, over the initial 7.5 h every other data point is plotted.

As Figure 5 illustrates, in both cases stable operation was observed over the 24 h period, with no fluctuations in the purity of the epoxide **7** synthesised at 70 °C and 0.08% RSD observed for the reaction conducted at room temperature.

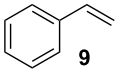
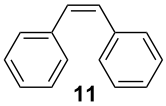
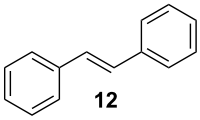
## Effect of substrate

Having demonstrated the ability to rapidly optimise the reaction conditions required for the chemo-enzymatic epoxidation of 1-methylcyclohexane (**6**), attaining quantitative conversion to **7** with a reactor temperature of 70 °C and a reaction time of 2.6 min, the investigation was extended to evaluate the generality of the methodology developed. Employing the aforementioned conditions, the epoxidation of a series of alkenes was conducted and the results obtained are summarised in Table 1.

In the case of styrene (**9**), incomplete conversion was obtained with a residence time of 2.6 min hence the flow rate was reduced to 5 μl $min^{-1}$ (5.2 min) whereby quantitative conversion to styrene oxide was obtained; continuous operation of the reactor, followed by an aqueous extraction, afforded the target compound in 99.2% isolate yield. Cyclohexene (**10**) was readily converted to cyclohexene-1,2-oxide at 70 °C, 2.6 min residence time, and was isolated in 97.6% yield. In addition to evaluation of aromatic and aliphatic alkenes discussed, the epoxidation of *cis*-stilbene (**11**) and *trans*-stilbene (**12**) was investigated (Scheme 4).

Due to the molecule's symmetry, the configuration of the epoxides synthesised could not be characterised by $^1$H NMR spectroscopy; however the compounds did possess significantly different retention times ($t_R$) when analysed by GC-MS; *cis*-1,2-diphenyloxirane (**13**, $t_R$ = 9.81 min) and *trans*-1,2-diphenyloxirane (**14**, $t_R$ = 10.28). Consequently, GC-MS in conjunction with a synthetic standard of *trans*-1,2-diphenyloxirane (**14**) was used to confirm the geometric isomer synthesised. In both cases, the optimal reaction conditions were 70 °C and a residence time of 5.2 min, affording the *cis*-isomer **13** in 99.5% yield as colourless oil and the *trans*-isomer **14** in 99.1% yield as a

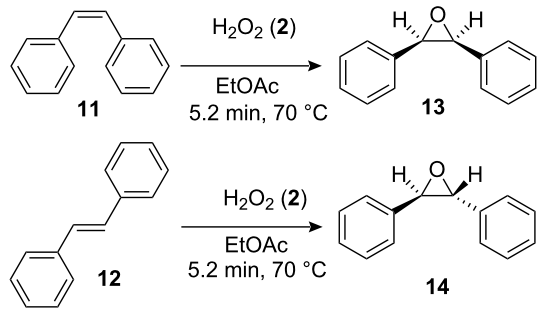
**Table 1:** Summary of the reaction conditions employed for the lipase-mediated epoxidation of an array of alkenes under continuous flow.

| Alkene | Temperature (°C) | Residence Time (min)[b] | Conversion (%) | Yield (%)[b] |
|---|---|---|---|---|
|  **6** | 70 | 2.6 (2) | 100.0 | 99.1 (6.7)[c] |
|  **9** | 70<br>70 | 2.6<br>5.2 (33) | 57.2<br>100.0 | –<br>99.2 (3.6) |
|  **10** | 70 | 2.6 (40) | 100.0 | 97.6 (5.9) |
|  **11** | 70<br>70 | 2.6<br>5.2 | 31.9<br>100.0 | –<br>99.5 (5.9) |
|  **12** | 70<br>70 | 2.6<br>5.2 | 32.1<br>100.0 | –<br>99.1 (5.9) |

The number in parentheses represents [a]the reaction time required under batch conditions (h) [21], [b]the isolated yield obtained after continuous operation of the reactor for 24 h and [c]the throughput (mg $h^{-1}$) using the optimised conditions.

white crystalline solid. In all cases, the epoxides were synthesised in excellent yield and purity with no hydrolysis products observed.

In comparison to the reaction times employed in analogous batch reactions, Table 1, the examples reported herein serve to illustrate the dramatic reductions in reaction time attainable through the use of micro reaction technology; in the case of the epoxidation of styrene (**9**), a 381-fold reduction in reaction time is obtained by employing $H_2O_2$ (**2**) under continuous flow. In addition to the reduced reaction times, the continuous flow methodology also enables larger quantities of oxidant **2** to be used, compared to conventional batch systems where deactivation of *Candida antarctica* lipase B was observed with 25% less oxidant **2**. Consequently, the oxidation of styrene (**9**) can be performed at a throughput of 3.6 mg $h^{-1}$ compared to 0.1 mg $h^{-1}$ in batch. Furthermore, the continuous reactor capacity can be increased by employing additional packed-bed reactors, operated under identical reaction conditions, compared to batch where increases in reactor volume/capacity will result in the need for longer dosing times for the oxidant **2**.




**Scheme 4:** Illustration of the reaction products obtained when conducting the continuous flow epoxidation of *cis*-stilbene (**11**) and trans-stilbene (**12**).

## Conclusion

In conclusion, we have demonstrated the successful transfer of a chemo-enzymatic batch process to a packed-bed flow reactor, enabling a dramatic reduction in reaction time to be obtained. In addition, the use of a flow reactor enabled higher quantities of $H_2O_2$ (**2**) to be employed over prolonged periods of time (> 24 h) without deactivation of the biocatalyst. Using this approach has enabled the development of a robust and operationally simple technique for the chemo-enzymatic epoxidation of olefins.

In the examples reported herein, we focussed on the use of ethyl acetate as it acted as both a solvent and reagent with in situ hydrolysis providing a source of acetic acid (**1**), from which the peracid **5** could be generated. It is however acknowledged that other solvents may be required and future work will therefore focus on the use of alternative solvents systems, employing a catalytic quantity of a carboxylic acid additive to generate the

respective peracid, enabling greater system flexibility, along with evaluating the methodology towards other synthetically useful oxidations.

# Experimental

## Materials

1-Methylcyclohexene (**6**, 99%, Aldrich), styrene (**9**, Reagent-Plus®, ≥ 99%, Aldrich), *cis*-stilbene (**11**, 96%, Aldrich), *trans*-stilbene (**12**, 96%, Aldrich), cyclohexene (**10**, 99%, Aldrich), urea–hydrogen peroxide (**3**, Aldrich), hydrogen peroxide (**2**, 30%, 100 volume, Fisher Scientific), Novozym® 435 (**4**) (Lipase acrylic resin from *Candida antarctica*, ≥ 10 000 U $g^{-1}$, Nordisk), deuterated chloroform (+0.03% TMS, < 0.01% $H_2O$, Euriso-top) and ethyl acetate (Reagent grade, Fisher Scientific). In all cases, materials were used as received.

## Instrumentation

Unless otherwise stated, nuclear magnetic resonance (NMR) spectra were obtained at room temperature as solutions in deuterated chloroform ($CDCl_3$) using a Jeol GX400 spectrometer; in the case of known compounds, all spectra obtained were consistent with the literature. The following abbreviations are used to report NMR spectroscopic data; s = singlet, d = doublet, t = triplet, br s = broad singlet, q = quartet, dd = double doublet, dt = doublet of triplets, m = multiplet and $C_0$ = quaternary carbon. Analysis of samples by Gas Chromatography-Mass Spectrometry (GC-MS) were performed using a Varian GC (CP-3800) coupled to a Varian MS (2100T) with a CP-Sil 8 (30 m) column (Phenomenex, UK) and ultra high purity helium (99.9999%, Energas, UK) as the carrier gas. Reactions employing 1-methylcyclohexene (**6**), cyclohexene (**10**), styrene (**9**), *cis*-stilbene (**11**) and *trans*-stilbene (**12**) were analysed using the following method; injector temperature 200 °C, carrier gas flow rate 1.00 ml $min^{-1}$, oven temperature 50 °C for 4 min then ramped to 150 °C at 30 °C $min^{-1}$ and held at 150 °C for 6.17 min, with a 2.5 min filament delay. Mass spectrometry data was obtained using a Shimadzu QP5050A instrument with an EI ionisation source. Batch reactions were conducted using a carousel reactor/rotator (SB2, Stuart) to reduce mechanical degradation of the immobilised enzyme. Flow reactions were conducted using a displacement pump (MD-1001, Bioanalytical Systems Inc.), capable of delivering three solutions at flow rates between 0.1 and 100 µl $min^{-1}$ (calibrated for a 1 ml gas-tight syringe) and solutions delivered to the flow reactor using a 2.5, 10 or 20 ml gas-tight syringe (Hamilton, UK). The packed-bed consisted of a borosilicate glass column (3.0 mm (i.d.) × 3.6 cm (long)) (Omnifit), the immobilised enzyme was held in place using 25 µm polyethylene frits and fluidic connections made using commercially available PEEK and PTFE connectors (Supelco). The flow reactor was heated using a HPLC programmable column heater, containing stainless steel blocks (Jones Chromatography) and the reactor temperature monitored using a thermocouple (206-3750, RS). When heating the reactor in excess of 50 °C, reactions were conducted under pressure, using a back-pressure regulator cartridge (100 psi) housed within a stainless steel holder (Upchurch Scientific, IDEX Corporation), to prevent boiling of the reactants and solvent system.

## General procedure for the epoxidation of olefins in batch

To a solution of Novozym® 435 (**4**, 0.10 g) and UHP (**3**, 1.0 mmol) in ethyl acetate (5 ml), was added the alkene (0.5 mmol) and the reaction mixture shaken on a carousel reactor at room temperature. Upon completion of the reaction, as indicated by TLC, the reaction mixture was filtered through a plug of cotton wool and the organic solvent evaporated prior to dissolution of the residue in DCM (20 ml). The organic layer was then washed with an aq solution of saturated $NaHCO_3$ (2 × 20 ml) to remove any acetic acid (**1**) and residual urea (**8**). The organic layer was then dried using $MgSO_4$, filtered and concentrated *in vacuo* to afford the target epoxide. The reaction products were then analysed by GC-MS, $^1H$ and $^{13}C$ NMR spectroscopy and the spectroscopic data compared with those reported within the literature.

## General procedure for the epoxidation of olefins in batch using $H_2O_2$ (**2**)

To a stirred solution of Novozym® 435 (**4**, 0.10 g) and alkene (0.5 mmol) in ethyl acetate (5 ml) was added $H_2O_2$ (**2**, 1.0 mmol) in aliquots of 0.1 mmol 15 $min^{-1}$, dispensed from an autopipettor. Upon completion of the reaction, as indicated by TLC, the reaction mixture was filtered through a plug of cotton wool and the organic solvent evaporated prior to dissolution of the residue in DCM (20 ml). The organic layer was then dried using $MgSO_4$, filtered and concentrated *in vacuo* to afford the target epoxide. The reaction products were then analysed by GC-MS, $^1H$ and $^{13}C$ NMR spectroscopy and the spectroscopic data compared with those reported within the literature.

## General procedure for the optimisation of olefin epoxidation under continuous flow

To optimise a continuous flow epoxidation, a gas-tight syringe (2.5 ml) was filled with a solution containing the alkene under investigation (0.1 M), oxidant (0.2 M) in ethyl acetate and connected to the Omnifit reactor cartridge using PTFE tubing [150 µm (i.d.) × 10 cm (long)] and a PEEK luer connector coupled to a 1/16″ HPLC connector. To the pre-weighed reactor was added Novozym® 435 (**4**, 0.10 g, 26 µl total volume) and the reactor outlet formed from a length of PTFE tubing [150 µm (i.d.) × 5 cm (long)] to enable efficient sampling. The reaction mixture was then pumped through the packed bed (5 to 50 µl

$min^{-1}$) for a period of 30 min, in order to equilibrate, prior to collection of the reaction products every 10 min for a minimum of 50 min. The resulting reaction products were analysed by GC-MS in order to determine the conversion of alkene to epoxide. If residual alkene was detected, the reaction was repeated at a slower flow rate to increase the reaction time (0.52 to 5.2 min).

To increase the rate of epoxidation, reactions were also conducted at elevated reaction temperatures (27 to 70 °C), with heating achieved using a stainless steel column heater and the reaction temperature monitored using a thermocouple. When employing reaction temperatures > 50 °C, a back-pressure regulator (100 psi) was incorporated into the system at the reactor outlet in order to prevent boiling of the reactants, products and solvent. Samples were again taken at intervals of 10 min and analysed off-line by GC-MS to determine the percentage of epoxide synthesised.

## General protocol used to synthesise epoxides under continuous flow

In order to deliver a constant stream of reactants through the packed-bed, a 20 ml gas-tight syringe (10 ml) was filled with a pre-mixed solution containing the alkene under investigation (0.1 M) and 30% hydrogen peroxide (**2**, 0.2 M) in ethyl acetate. The reaction mixture was then pumped through the packed-bed, containing Novozym® 435 (**4**, 0.10 g, 26 μl total volume), under the previously optimised reaction conditions for 12 h. The reaction mixture was then concentrated in vacuo to remove the reaction solvent, prior to dissolution of the residue in DCM (20 ml). The organic layer was then washed with an aq solution of saturated $NaHCO_3$ (2 × 20 ml) to remove any acetic acid and residual peracetic acid (**5**). The organic layer was then dried using $MgSO_4$, filtered under suction and the filtrate concentrated *in vacuo* to afford the target epoxide. The reaction product was then analysed by GC-MS, $^1H$ and $^{13}C$ NMR spectroscopy in order to characterise the epoxide and determine product purity.

## Enzyme stability

To confirm the Novozym® 435 (**4**) was sufficiently stable to be used for the continuous flow synthesis of epoxides over extended periods of operation, two experiments were conducted over a period of 24 h. In both cases a 20 ml solution of 1-methylcyclohexene (**6**, 0.1 M) and hydrogen peroxide (**2**, 0.2 M) in ethyl acetate was pumped through the reactor at a flow rate of 10 μl $min^{-1}$, with one reaction performed at 27 °C and the other at 70 °C. Samples were taken every 10 min for 7.5 h and then every 1 h for 9 h after a break in sampling of 8 h; operation was maintained for these 8 h but no samples taken. At 27 °C, an average conversion to 1-methylcyclohexene oxide (**7**) of 37.9% (% RSD = 0.08) was obtained and at 70 °C, quantitative conversion was obtained over the 24 h period.

## 1-Methylcyclohexene oxide (**7**)

A pre-mixed solution of 1-methylcyclohexene (**6** ,0.1 M) and 30% $H_2O_2$ (**2**, 0.2 M) was pumped through the enzyme filled reactor, at a flow rate of 10 μl $min^{-1}$ and a reaction temperature of 70 °C, for a period of 24 h to afford 1-methylcyclohexene oxide (**7**) as a colourless oil (0.160 g, 99.1% yield) after an aqueous extraction; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.49–1.68 (m, 4H), 1.65 (s, 3H), 1.89–2.20 (m, 4H) and 2.91 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 17.6 ($CH_3$), 19.9 ($CH_2$), 20.1 ($CH_2$), 25.2 ($CH_2$), 26.1 ($CH_2$), 52.1 (CH) and 62.2 ($C_0$); *m/z* (EI) 113 ($M^+$+1, 20%), 112 (10), 97 (77), 85 (15), 95 (100), 83 (15), 69 (15) and 55 (25); GC-MS $t_R$ = 5.26 min. The spectroscopic data obtained for 1-methylcyclohexene oxide (**7**) was consistent with that reported within the literature [36].

## 1,2-Epoxy-1-phenylethane (styrene oxide)

A pre-mixed solution containing styrene (**9**, 0.1 M) and 30% $H_2O_2$ (**2**, 0.2 M) in ethyl acetate was pumped through the enzyme filled reactor at a flow rate of 5 μl $min^{-1}$ and a reaction temperature of 70 °C for a period of 24 h. The resulting reaction products were concentrated *in vacuo* and the residue subjected to an aqueous extraction, affording 1,2-epoxy-1-phenylethane as a colourless oil (0.086 g, 99.2% yield); $^1H$ NMR (400 MHz, $CDCl_3$) δ 2.75 (dd, *J* = 2.8, 5.6, 1H), 3.08 (dd, *J* = 4.1, 5.6, 1H), 3.80 (dd, *J* = 2.8, 4.1, 1H) and 7.24–7.33 (m, 5H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 51.0 ($CH_2$), 51.1 (CH), 125.3 (2 × CH), 128.0 (CH), 128.2 (2 × CH) and 137.5 (C); *m/z* (EI) 121 ($M^+$+1, 5%), 120 (20), 119 (50), 92 (25), 91 (100), 89 (40) and 77 (20); GC-MS $t_R$ = 5.37 min. The spectroscopic data obtained for 1,2-epoxy-1-phenylethane was consistent with that reported within the literature [37].

## *cis*-1,2-Diphenyloxirane (*cis*-stilbene oxide, **13**)

A solution containing *cis*-stilbene (**11**, 0.1 M) and 30% $H_2O_2$ (**2**, 0.2 M) in ethyl acetate was pumped through the packed-bed reactor (70 °C) at a flow rate of 5 μl $min^{-1}$ and the reactor effluent collected over a period of 24 h. The reaction products were concentrated *in vacuo* and subjected to an aqueous extraction to afford *cis*-stilbene oxide (**13**) as a colourless oil (0.140 g, 99.5% yield); $^1H$ NMR (400 MHz, $CDCl_3$) δ 4.31 (s, 2H), 7.09–7.21 (m, 10H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 59.9 (2 × CH), 125.9 (4 × CH), 127.2 (2 × CH), 127.5 (4 × CH) and 135.6 (2 × C); *m/z* (EI) 197 ($M^+$+1, 100%), 196 (75), 195 (76), 167 (75), 152 (10), 105 (50), 89 (25) and 77 (10); GC-MS $t_R$ = 9.81 min. The spectroscopic data obtained for *cis*-1,2-diphenyloxirane (**13**) was consistent with that reported within the literature [38].

### *trans*-1,2-Diphenyloxirane (*trans*-stilbene oxide, **14**)

A pre-mixed solution of *trans*-stilbene (**12**, 0.1 M) and 30% $H_2O_2$ (**2**, 0.2 M) was pumped through the enzyme filled reactor, at a flow rate of 5 μl $min^{-1}$ and a reaction temperature of 70 °C, for a period of 24 h to afford *trans*-stilbene oxide (**14**) as a white crystalline solid (0.140 g, 99.5% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 2H) and 7.25–7.59 (m, 10H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 62.8 (CH), 125.5 (4 × CH), 128.3 (2 × CH), 128.5 (4 × CH) and 137.1 (2 × C); *m/z* (EI) 197 ($M^+$+1, 70%), 196 (75), 195 (73), 180 (65), 167 (100), 165 (50), 105 (25), 89 (20) and 77 (10); GC-MS $t_R$ = 10.28 min. The spectroscopic data obtained for *trans*-1,2-diphenyloxirane (**14**) was consistent with that reported within the literature [39].

### 1,2-Epoxycyclohexane (cyclohexene oxide)

A pre-mixed solution of cyclohexene (**10**, 0.1 M) and 30% $H_2O_2$ (**2**, 0.2 M) was pumped through the packed-bed reactor at a flow rate of 5 μl $min^{-1}$ and a reaction temperature of 70 °C for a period of 24 h. The reaction products were concentrated *in vacuo* and the residue subjected to an aqueous work up, affording 1,2-epoxycyclohexane as a colourless oil (0.138 g, 97.6% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.15–1.27 (m, 2H), 1.31–1.49 (m, 2H), 1.65–1.99 (m, 4H) and 3.11 (s, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 19.9 (2 × $CH_2$), 25.1 (2 × $CH_2$) and 52.2 (2 × CH); *m/z* (EI) 99 ($M^+$+1, 5%), 98 (7), 97 (20), 83 (100), 81 (80), 69 (20) and 55 (25); GC-MS $t_R$ = 4.876 min. The spectroscopic data obtained for 1,2-epoxycyclohexane was consistent with that reported within the literature [40].

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# From discovery to production: Scale-out of continuous flow meso reactors

Peter Styring* and Ana I. R. Parracho

Full Research Paper

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Address:
Department of Chemical & Process Engineering, The University of Sheffield, Mappin Street, Sheffield S1 3JD, United Kingdom

Email:
Peter Styring* - p.styring@sheffield.ac.uk

* Corresponding author

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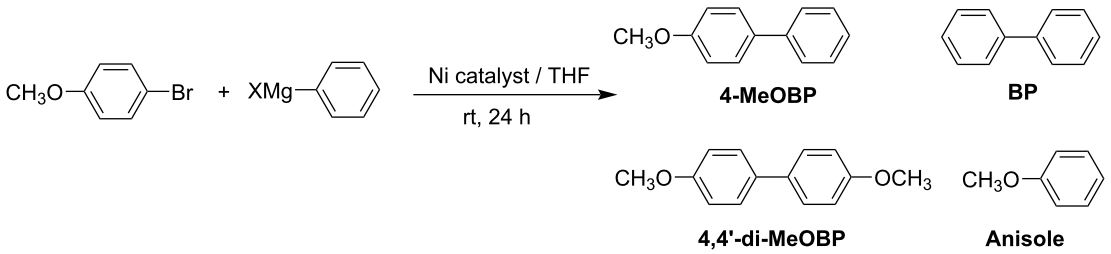
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## Abstract

A continuous flow parallel reactor system has been developed to provide a rapid and seamless transition from the discovery phase and production phase of chemical synthesis, particularly in low volume-high value pharmaceuticals production. Using a single fixed bed catalytic meso reactor, reactions can be screened on a small discovery scale over short time scales. The intensified process produces sufficient material for a full analysis. By replication of the single reactor in parallel, the same chemistry can be achieved on a larger scale, on a small footprint and without the mass and heat transport limitations of reactor scale-out in batch.

## Introduction

Cross-coupling reactions are an essential tool in organic synthesis, from pharmaceuticals through to functional materials. In the majority of cases on the laboratory scale, coupling reactions are performed in stirred batch reactors such as round-bottom flasks using homogeneous catalysts and often activating agents such as substituted phosphines, or else catalysts possessing ligands with complex and expensive motifs [1]. Often, the scale at which such reactions are performed is far greater than that required for initial characterisation and property screening [2,3]. Once a compound is identified for further study and even commercialisation it is then required to be produced on a larger scale. The problem is that to move from small discovery to larger pilot or commercial scale production is not simply a case of scaling up the quantities of reagents and solvents [4]. There are also supply issues when dealing with large scale syntheses and at times it may be economically sensible to move a reactor to the supply source rather than vice versa, particularly where hazardous chemical feedstocks are involved [5]. Furthermore, small footprint processes would be advantageous for safety reasons, particularly containment in the case of a failure [2,3]. Scaling up in volume of a reactor has implications on the mass and heat transfer within the system so the reaction must be re-optimised for the prevailing conditions. This is a time-consuming process and often results in the abandoning of the bench scale process in favour of conditions more favourable in bulk. In particular, the use of homogeneous catalysts in scaled-up processes is problematic. Homogeneous catalysts often decompose or dissociate under reaction conditions so that the true active catalyst is not in fact the compound added at the onset of the reaction. This makes catalyst recovery and re-cycling problematic if not impossible. It also leads to the possibility of metal contamination at trace levels in the final




**Scheme 1:** Synthesis of 4-methoxybiphenyl (4-MeOBP) and by-products in the Kumada reaction.

product. Furthermore, added phosphines and other activating agents tend to be expensive and also difficult to recover, adding both an environmental and economic burden on the process.

Previously, we have described a series of catalysts based on nickel(II) and palladium(II) that have functionalised salen-acac (salenac) ligands that were functionalised such that they could be covalently bound to organic or inorganic polymer supports [6-10]. Such materials show the beneficial properties of homogeneous catalysts (activity and selectivity) as well as those of a heterogeneous catalyst (robust and re-usable). These materials have been termed 'androgynous' due to these dichotomous properties [8]. The palladium catalysts are active in the Suzuki and Heck coupling reactions at elevated temperatures while the nickel catalyst is active in the Kumada coupling [11,12] reaction at room temperature in batch (Scheme 1) and continuous flow reactors. In the latter, the catalyst is packed into a 3 mm diameter glass reactor tube of length 25 mm and the reagent solution flowed using a syringe pump [8,9,13]. This is termed as meso reactor as it shows many of the benefits of a micro reactor but at a slightly larger volume. Using a mesoporous version of the catalyst the rate of reaction was enhanced over 3000 times which meant that useful quantities of material could be produced within minutes rather than overnight [13].

In this paper, we report on the fabrication and testing of a new parallel reactor capable of scaling out chemistries using the same chemistries developed on the discovery scale, while retaining a small area footprint that sits on a standard stirrer hotplate and is capable of being employed in a standard laboratory fume cupboard. Despite a number of publications describing the theory and practicalities of scaled-out micro and meso reactors [14,15], no practical examples of large-scale production have been described.

# Results and Discussion

## Batch Reactor

Batch reactions were performed using a Radley's Carousel Parallel Synthesiser fitted with a fuzzy logic controller unit giving temperature control of ±0.1 °C. The systems consists of 12 tubes (45 ml) which are fitted with screw-on Teflon caps that are equipped with valves for the introduction of inert or reactive gases and a septa for the introduction of reagents. The 12 reaction tubes sit in two stacked aluminium blocks; the lower fits on a hotplate-stirrer and can be maintained at a constant temperature, while the upper block has circulating water which cools the top of tubes allowing reactions to be performed under reflux conditions if required.

## Single Channel Mini Reactor

A stainless steel reactor was constructed using Swagelok components as shown in Figure 1. This has a bed size of 30 mm × 3 mm. The stainless steel column is packed with the catalyst particles; these are held in place by 40 μm woven stainless steel wire mesh with a 25 μm wire integrated in to the reduction unions so that it connects the column to the fluidic delivery system at the reactor entrance and exit in order to prevent loss of the resin catalyst. The reduction unions allowed one end of the reactor to be connected to a disposable solvent-resistant syringe, while the other end was attached to a syringe needle leading to a vessel containing quenching solution. The design of the reactor system makes catalyst filling and removal an extremely easy and quick process. This channel was packed with nickel immobilised onto Merrifield resin (mean average particles size of 45 μm when dry and 72 μm when wet in THF), with approximately 3% nickel loading. A syringe pump (RAZAL A-99) was used to pump a pre-determined volume of the solution of known concentrations at different flow rates.




**Figure 1:** Stainless steel single column flow reactor for discovery scale synthesis.

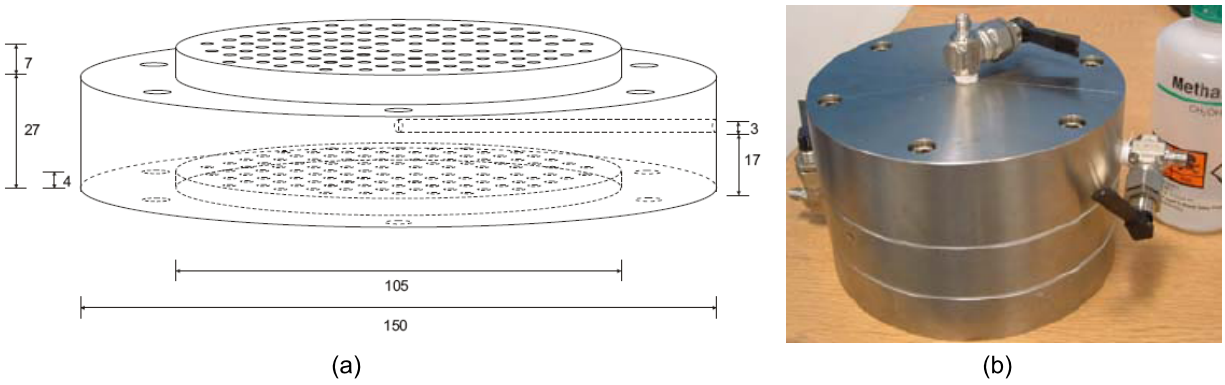



**Figure 2: (a)**: Schematic diagram of the parallel reactor housing (dimensions in mm); **(b)** the stainless steel parallel flow reactor with the reactor housing sat between the flow inlet manifold (bottom) and headspace with gas and liquid outlets (top).

## Parallel Capillary Reactor

The parallel capillary reactor consisted of a capillary block, head space, bottom space inlet manifold, spacer plate, PTFE seal and a packing spacer. Figure 2a shows the schematic of the reactor while Figure 2b is an external photograph of the actual reactor giving an indication of scale. Uniform packing was achieved using an array of stainless steel spacer pins that were inserted into the base of the reactor body while the catalyst was added from the top. The stainless steel mesh was used to hold the catalyst in place at top and bottom of the reactor. Reagents flowed against gravity along the capillary tubes to ensure uniform distribution. The bottom space helps uniform distribution of the reactant solution to be achieved and the reaction products are collected from the head space through a side mounted outlet valve. A gas release valve was included at the top of the headspace unit in order to relieve any pressure build up. The capillary block is the body of the reactor, which contains 120 capillary tubes of 3 mm diameter and 30 mm length. An access point was also drilled in the middle of the reactor, between the reactor tubes, in order to monitor reactor temperature. The inserted temperature probe can be used to control the temperature through feedback with a stirrer hot plate using an IKA Fuzzy Logic controller. Reagents of known concentrations were pumped into the reactor using a pneumatically driven calibrated system with nitrogen as the carrier gas. The pre-mixed reagents were stored in a glass bottle (vessel 1) as shown in Figure 3. In order to maintain a constant flow from the vessel it was necessary to maintain a constant pressure and this was achieved using a second vessel filled with water, which was filled at the same rate as reagents were exiting vessel 1.

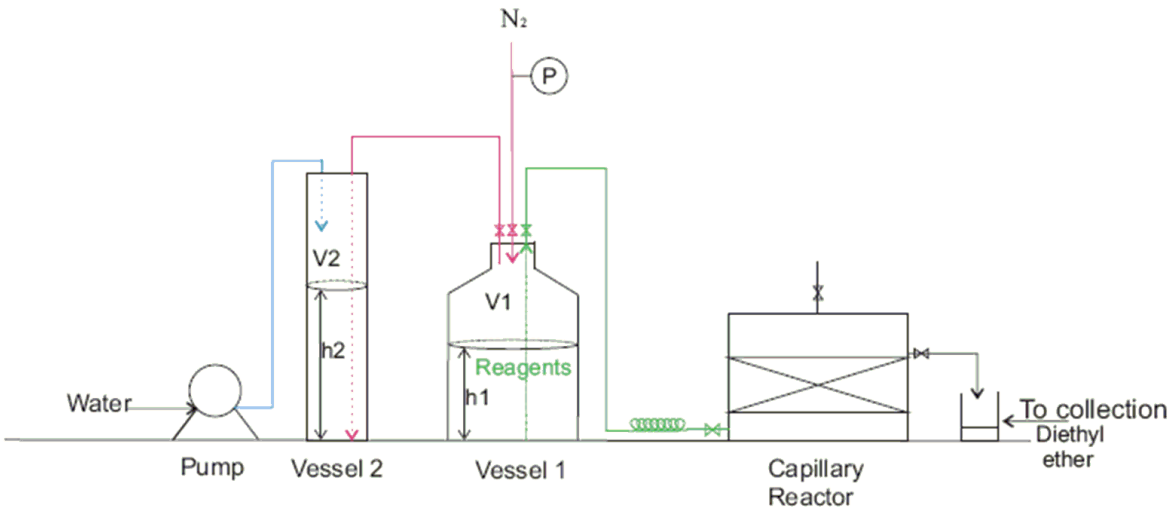
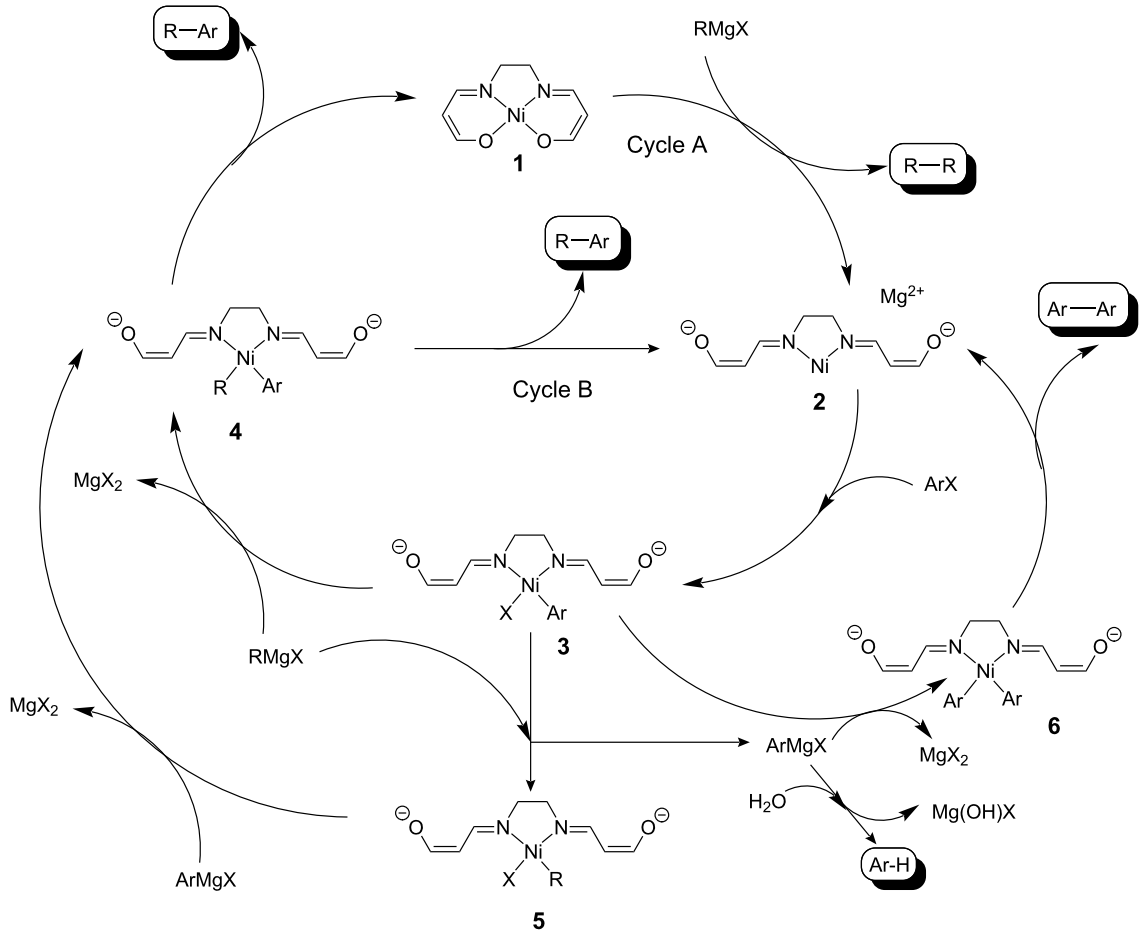



**Figure 3:** Schematic diagram of the pneumatic pumping system.

The reaction studied was the Kumada reaction [11,12] which involves the coupling of an aryl halide and a Grignard reagent, in this case 4-bromoanisole and phenylmagnesium chloride, to produce 4-methoxybiphenyl (4-MeOBP, R-Ar). It was also observed that anisole, 4′,4-dimethoxybyphenyl (4,4′-di-MeOBP, Ar-Ar) and biphenyl (BP, R-R) were obtained as reaction by-products. The catalytic cycle that we originally proposed [6] neglects the formation of the other by-products so we investigated the whole scheme in detail. The chloro rather than the bromo Grignard reagent was used, even though it was less reactive, as the waste magnesium chloride or mixed halide was more soluble in THF under the reaction conditions than magnesium bromide and this prevented significant build up of the salt in the reactor while in use, which would otherwise lead to blockage. Batch reactions were performed in order to probe the mechanism for the reaction further. If the activation of the catalyst was important then a pre-wash with the Grignard reagent should improve the yield of the desired cross-coupled product. This was indeed found to be the case. Without any pre-wash or with a 4-bromoanisole pre-wash there was no difference in conversion with a maximum yield of 44% being observed by GC. However, with a pre-wash using phenylmagnesium chloride, the yield increased to 52%. The revised scheme is shown (Scheme 2) and includes the original cycle, shown as cycles A and B. Two mechanisms were originally thought to be important: (a) the activation of the catalyst through sacrificial loss of the Grignard reagent to form the homo-coupled product biphenyl then subsequent cross-coupling to give the desired product (Cycle A); (b) continued production of the cross-coupled product without the need to reactivate the catalyst (Cycle B).

The complex in the free and immobilised form possesses a hard central $Ni^{2+}$ ion chelated by both hard (anionic oxygen) and soft (neutral nitrogen) donor atoms from the ligand [6,7]. Cycle A involves pre-activation of the catalyst by reduction to Ni(0),




**Scheme 2:** Proposed catalytic cycles for the transformation of 4-haloanisole (Ar-X) and Grignard reagent (RMgX) into 4-methoxybiphenyl (Ar-R) with by-products anisole (Ar-H), biphenyl (R-R) and 4,4′-dimethoxy-biphenyl (Ar-Ar) using the polymer supported nickel catalyst. Ligands are simplified for clarity.

chelated by soft nitrogen donors, with the production of the homo-coupled organic product through sacrifice of some of the Grignard reagent. This is an essential step as $Ni^{2+}$ is inactive towards the oxidative addition of the organobromide. In general the yield of this homo-coupled product is not proportional to the principal cross-coupled product so the possibility arises that the catalyst takes an alternative pathway (route B) once the catalyst initiation has occurred. As the cross-coupled product is observed as the highest yielding product, it was proposed that the rate constant for route A is smaller than for route B.

The proposed catalytic cycle therefore serves as a working hypothesis for the formation of the principal cross-coupling product, 4-methoxybiphenyl. A study of bromo-Grignard reagent to organo bromide ratio necessary to optimise the yield of cross-coupling product by Phan *et al.* [7,8] showed that the reaction was best performed using a 1:1 substrate ratio with 67% conversion to the desired 4-methoxybiphenyl. The production of biphenyl as a homo-coupling product was also observed in a significant amount of approximately 20% of the final mixture. Indeed, the problem of homo-coupling was encountered in earlier publications involving the coupling reaction under discussion. This by-product can be formed by sacrificial loss of the Grignard reagent in the reduction of Ni(II) to the real catalytically active Ni(0) form as the first step in the proposed catalytic cycle mentioned above. However, the composition of the final reaction mixture also included anisole and 4,4′-dimethoxybiphenyl and the level of biphenyl itself indicates that it is also forming by an alternative pathway. Therefore, the catalytic cycle is more complex than originally proposed. However, using the results from this study together with previously obtained data we have been able to construct a viable alternative route that explains the observed by-products.

Product scrambling occurs through trans-metallation between the intermediate nickel complex **3** formed by oxidative addition of the aryl bromide (Ar-Br), and the Grignard reagent. This results in the formation of the homo-coupled 4,4′-dimethoxybiphenyl by-product. Anisole (Ar-H) is formed by hydrodebromination of the aryl bromide *via* the same oxidative addition intermediate complex **3** due to the presence of traces of water in the system. This occurs both in the batch system, where there is only residual water in the solvent, and in the flow system. Even though water is used to equalise the pressure in the flow system, the reactor is protected from the pumping system using a self-indicating silica gel drying tube that is regularly recharged.

## Mini-Continuous Flow Reactor

Previous work carried out by Styring *et al.* [13] has described the use of a salenac nickel complex immobilised on a polymer support for the Kumada reaction in pressure driven mini flow reactor. In further studies [6-8], a similar nickel resin catalyst [6] and a silica supported nickel catalyst were used [7,8]. The Kumada reaction was carried out in a glass mini flow reactor (Omnifit) and good yields were achieved in a matter of minutes, compared to the conversion obtained in batch over a period of 24 h, albeit on a much smaller scale. The optimum conversion and selectivity was achieved using a flow rate of 13 µl $min^{-1}$, with a 67% yield of 4-methoxybiphenyl being achieved using phenylmagnesium bromide.

As the residence time has an important effect on the product yield, and with the aim of scaling out the same reaction in the parallel capillary reactor, the reaction was carried out in the continuous flow reactor at different flow rates. The motivation was to investigate the effect of the residence time of the reagents within the catalyst bed on the coupling process. The mean residence time in a continuous flow reactor is also assumed to be the reaction time. Therefore the reaction was performed at different flow rates in a Swagelok stainless steel column, of the same size of a single channel in the capillary reactor. The reaction was carried out using an equimolar solution of 0.5 M of 4-bromoanisole and phenylmagnesium chloride. The results obtained are shown in Figure 4.

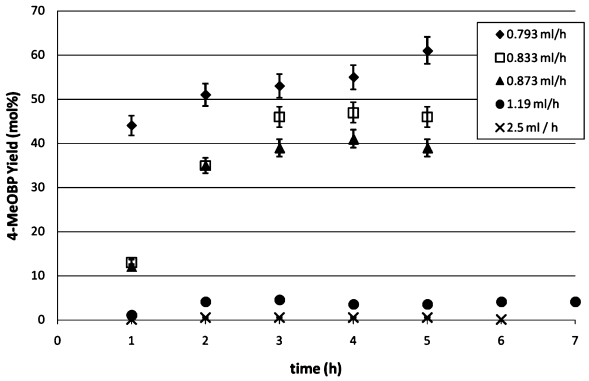



**Figure 4:** Comparative study of flow rates in a single channel meso flow reactor. The output was sampled hourly and analysed by GC during the period of extended flow.

It was observed that as the flow rate increases the yield of 4-methoxybiphenyl decreases, as expected. At higher flow rates of 1.2 and 2.5 ml $h^{-1}$, the yields of 4-methoxybiphenyl were between 0 and 2%. Therefore, it was decided to carry out the Kumada reaction in the capillary parallel reactor at a flow rate of 0.79 ml $h^{-1}$ (13 µl $min^{-1}$) as in previous studies. All conditions were kept the same as in the study of Phan *et al.* [8], however, it was observed that a lower product yield was obtained. This is due to the lower reactivity of the chloro Grignard reagent compared to the bromo derivative used in

previous studies. No deterioration of the catalyst was detected over the course of the cycles and ICP-ES studies showed the nickel content in the resin was the same as when the catalyst was initially prepared.

An important point of concern when using heterogeneous catalyst is its lifetime, particularly for industrial and pharmaceutical applications. In an ideal case [16] the catalyst can be recovered and reused several times before it eventually deactivates. At the same time, catalyst recovery can also reduce the environmental pollution caused by heavy metals used in the catalyst systems. When using a supported metal catalyst, another critical issue is the possibility that some active metal migrates from the solid to the liquid phase and this leached metal would become responsible for a significant part of the catalytic activity which would then occur homogeneously. When the solid catalyst was removed from a batch reactor no reaction occurred until the catalyst was replaced, showing leaching is not a problem. The polymer supported catalyst was then tested for its reusability. The catalyst was packed in the Swagelok column and the Kumada reaction was carried out three times without unpacking and without any catalyst regeneration. The conditions were assumed to be the same as in the parallel capillary reactor. In between the reactions the column was flushed with dried THF to remove any excess reagents and salts deposited on the surface of the catalyst. Results showed that the nickel resin catalyst can indeed be re-used in further reactions without a significant degradation in activity. Although there was a slight decrease in activity over subsequent runs, the average yield of 4-methoxybiphenyl still remained greater than 40%.

One of the by products of the Kumada reaction is biphenyl, which is the result of the self-coupling of the phenylmagnesium chloride, as explained in Scheme 2. As the yield of product obtained in the Kumada reaction in this work was comparatively low compared to that of Phan *et al.* [8], the stoichiometry of the reagents was varied accordingly. Two different studies were carried out, in a continuous reaction and the other in a batch process. In the continuous reaction studies, the column was packed with catalyst and pre-washed with a solution of phenylmagnesium chloride in THF (0.5 M) and then rinsed with THF and the experiment was carried out as described previously. Two different stoichiometric ratios (1:1 and 1:1.5 of 4-bromoanisole and phenylmagnesium chloride respectively) were used. There an increase in the 4-methoxybiphenyl yield from 28 to 45% at the higher ratio when a pre-wash was carried out. At the same time the amount of biphenyl produced almost doubled compared to the smaller increase in 4-methoxybiphenyl yield. A comparative study of 1:1 and 1:2 of 4-bromoanisole to phenylmagnesium chloride was then undertaken in a batch process and the production of biphenyl as well as 4,4′-dimethoxybiphenyl was monitored. The nickel complex catalyst instigates the homo-coupling of the Grignard reagent, in this case to produce biphenyl. The yield of 4-methoxybiphenyl was increased by over 20% as seen in Table 1. However, while the yield of 4,4′-dimethoxybiphenyl almost doubled, the yield of biphenyl increased three-fold. If there was simple transmetallation occurring then there should be equity in the yields. However, the elevated value for biphenyl production together with the effectiveness of the Grignard pre-wash supports our theory that the activation of the catalyst through Cycle A is essential for the reaction to proceed effectively. While the comparisons indicates that a stoichiometry of 1:2 yielded better results than a 1:1 stoichiometry, it should be noted that this is both an economic and environmental burden as the excess Grignard reagent is quenched at the end of the process. This could be overcome by building a recycle into the process. In fact, when a mass balance was carried out over the reaction it was found that less Grignard reagent was actually consumed when the higher stoichiometry was used. It should also be noted that the increased stoichiometric ratio has little effect on the turnover frequency (TOF). Although a slight increase was observed, this is within 5% experimental error.

**Table 1:** Comparative study of aryl bromide to Grignard reagent ratio on product and by-product yields.

| | Ratio of 4-BA to PhMgCl | |
|---|---|---|
| | 1:1 | 1:2 |
| 4-Methoxybiphenyl (mol%) | 57 | 80 |
| 4-Bromoanisole (mol%) | 23 | 1 |
| Anisole (mol%) | 7 | 9 |
| 4,4′-Dimethoxybiphenyl (mol%) | 13 | 23 |
| 4-Methoxybiphenyl (mmol) | 0.57 | 0.8 |
| Biphenyl (mmol) | 0.03 | 0.09 |
| TOF ($h^{-1}$) | 683 | 719 |

## Parallel Flow Reactor

Having established the reaction protocol from the mini-continuous flow reactor runs, and having checked for the reusability of the catalyst, the Kumada reaction was performed in the scaled-out system using the parallel capillary reactor. The stoichiometry used remained constant in all studies, with 1 equivalent of 4-bromoanisole to 1.5 equivalent of phenylmagnesium chloride. This would enhance the yield of product while minimising the Grignard reagent waste in the absence of a recycle stream. Equimolar (0.5 M) solutions were used in all cases.

In the first study, the reaction was carried out for 6 h at a flow rate of 95 ml $h^{-1}$, which equates to 0.79 ml $h^{-1}$ per channel, as

used in the single channel studies. The graph of conversion against time is shown in Figure 5. Samples were taken at hourly intervals by diverting the flow away from the quenching vessel to a separate small volume of quenching solution. The ether layer was decanted off, dried and then analysed by GC. It was observed that the yield increased steadily for the first 3 h and reached a peak of 74% where it remained constant within experimental error. The yield was consistent for a 1:1.5 stoichiometry and higher than the yields originally reported for single channel meso flow reactors. It is proposed that during the first hours of the reaction there is period of induction that conditions the reactor and activates the catalyst. Steady state is then achieved after this induction period, which occurs irrespective of whether or not a pre-wash is used. The induction is therefore most likely to be limited by adsorption of the aryl bromide onto the catalyst surface once catalyst activation is achieved. This is consistent with the Langmuir–Hinshelwood mechanism [17] for surface kinetics which depends on adsorption of both species on to the catalyst surface before reaction can proceed.

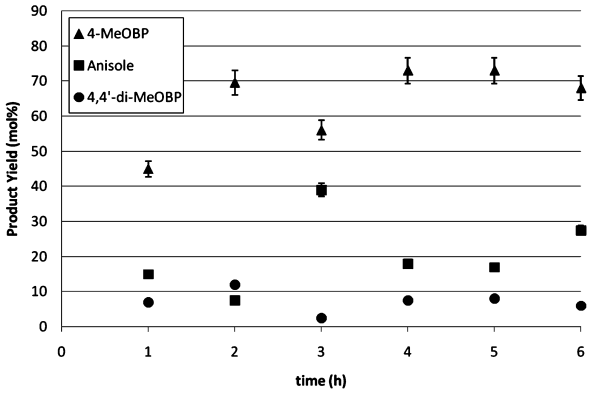



**Figure 5:** Kumada reaction carried out in a parallel channel meso reactor at a flow rate of 95 ml $h^{-1}$.

The reaction was then carried out for a period of 31 h using the same flow rate as above, giving a residence time on each of the capillary reactors of 11 min. A linear relationship in the 4-methoxybiphenyl yield with respect to time in the initial hours of the reaction is seen from Figure 6. This induction period is longer than in the six-hour study, however the average yield of 4-methoxybiphenyl after this period was found to be 66% which is consistent with previous studies. As the catalyst used was that used in the six-hour study the possibility of catalyst deactivation was considered. However, the fact that steady state production of around 66% over the study up to 31 h would dispel this theory. Indeed ICP-AES studies showed no significant loss of nickel from the catalyst. The likely scenario is that magnesium salts had become deposited on the catalyst beads on standing between studies and that the initial linear increase in yield was a consequence of the salts being washed off in the continuous flow and adsorption of the organobromide on to the newly freed reactive sites.

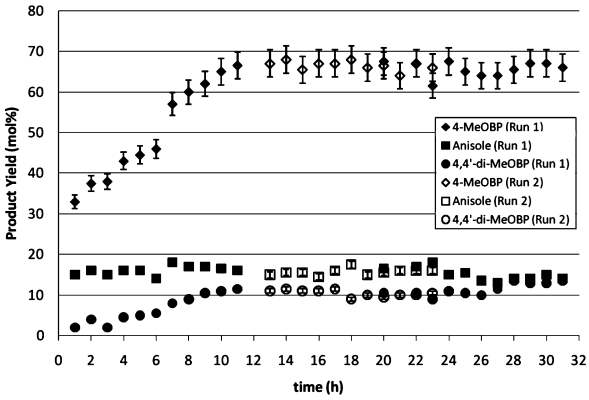



**Figure 6:** Kumada reaction carried out in a parallel channel meso reactor over a 31-hour period at a flow rate of 95 ml $h^{-1}$ to show catalyst stability and lifetime.

It is seen from Figure 6 hat the production of the by-product anisole remains constant throughout the reaction while production of 4-4′-dimethoxybiphenyl increased in a similar way to the main product. The production of 4-methoxybiphenyl during this 31-hour period was found to give an average yield of 58%. This gives a production rate using the parallel capillary reactor of 5.07 g $h^{-1}$ which gives 122 g of 4-methoxybiphenyl per day. If the average at steady state (65%) is taken however, this equates to 5.70 g $h^{-1}$ or 137 g $day^{-1}$. In order to increase production there are two options. One is to replicate further channels in parallel, relying on the fact that the chemistry in each reactor will be identical. The dimensions of the parallel reactor used were such that the design would fit easily onto a standard hotplate-stirrer. However, by making the reactor blocks rectangular they could be readily stacked in three dimensions. The second approach is to increase the flow rate into the reactor, however as this will reduce the residence time it will therefore reduce the effective reaction time with the consequence that the conversion may fall. Therefore, a study in which the flow rate was doubled was undertaken.

A flow rate of 190 ml $h^{-1}$ (1.6 ml $h^{-1}$ per single channel) was used, giving a residence time of 5 min 30 s. The reactor was run for a period of 9.5 h. A decrease in the production yield (%) of 4-methoxybiphenyl with time was observed (Figure 7). The maximum yield was observed after 4 h, however this was only 21%. Yield gradually decreased after this, averaging around 12% although production did not cease. Production of anisole and 4,4′-dimethoxybiphenyl was unaffected however, averaging 6 and 1% respectively, so selectivity decreases with

increased flow. Likewise, there was very little change in the turnover frequency (0.35 $h^{-1}$) based on 4-bromoanisole. However, the TOF was significantly reduced from the reaction carried out at half the flow rate (1.5 $h^{-1}$). It should be noted that the TOFs in flow reactors are lower than in batch as we are dealing with small flows through a packed bed reactor and hence the catalyst concentration is necessarily high.

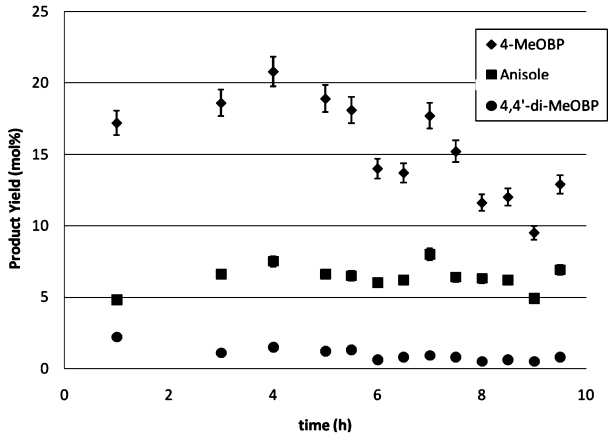



**Figure 7:** Kumada reaction carried out in a parallel channel meso reactor at a flow rate of 190 ml $h^{-1}$.

If the rate limiting step in the reaction is the adsorption of the organobromide onto the surface of the catalyst, as we have proposed according to the Langmuir–Hinchelwood mechanism [17], then increasing the flow rate does not give sufficient time for adsorption of the aryl bromide and reaction with the Grignard reagent to occur and hence the conversion will decrease, as was observed. It appears from the data that while adsorption of the aryl bromide can occur there is low availability of the Grignard reagent at high flow rates and hence the homo-coupled product and anisole have the opportunity to form. The product formation decreases as at the start of the reaction there is an induced high concentration of the Grignard reagent on the beads as a result of the pre-wash to activate the catalyst. As the flow proceeds, the concentration is reduced and if it is difficult for more reagent to access the surface then the production slows. This is an interesting observation and we are undertaking detailed mechanistic studies in an attempt to clarify the situation.

Another approach to increasing yield would be to increase the length of the reactor tubes. We standardised on 30 mm channel lengths as we were targeting a generic reactor system that could be used for many different reactions without the need to change components. All our discovery studies were performed in 25 mm glass and 30 mm stainless steel tubes, hence the choice of 30 mm for the parallel reactor. We have not looked at longer discovery reactors because for the Kumada reaction the selectivity is decreased. At equivalent flow rates on longer tubes there is a large increase in the production of biphenyl with increased residence time on the reactor.

## Conclusions

The Kumada reaction was carried out at room temperature, using a nickel catalyst supported on Merrifield resin beads in a Swagelok meso reactor column, which is of the same dimensions as a single channel in a scaled-out parallel capillary reactor. The objective of this research was to demonstrate that it is possible practically to scale-out a reaction carried out on a single channel reactor on a pilot scale/small production reactor by simple replication of the original channel geometry in parallel. This was clearly demonstrated. Reactions optimised in a single channel are simply replicated in a 120-channel reactor. In the case of the Kumada reaction, the yield is up to 137 g over a 24-hour period on a reactor that sits on a standard hot-plate stirrer. Increased yields can be achieved simply by replicating further in two- or even three-dimensions through more sophisticated manifolding.

The catalytic mechanism was studied using batch reactions, and different pre-washes with the starting reagents were carried out. From the results obtained it is proposed that for the nickel salenac complex, the reaction followed a Langmuir–Hinshelwood mechanism, and that a pre-wash with Grignard reagent activates the many reactive sites present on the catalyst. However there can be a probability of other mechanisms occurring and hence further studies are being undertaken.

In the continuous meso flow column, recycling studies of the catalyst were carried out in order to simulate the re-use of the catalyst bed within the capillary parallel reactor. Due to the volume of catalyst needed to pack the reactor and the down-time requirements for repacking it is essential that the catalyst is stable over prolonged periods of operation. This has been shown to be the case and the reactor ran continuously over a 31-hour period with steady state product synthesis without loss of performance.

## Experimental

### Reagents

Chemicals were obtained from Sigma–Aldrich and Fisher. Diethyl ether (99.8%, Fisher), anisole (99%, Aldrich), biphenyl (97%, Aldrich), 4-bromoanisole (99%, Aldrich), phenylmagnesium chloride (2M in THF, Aldrich), mesitylene (98%, Aldrich), 4-methoxybiphenyl (97%, Aldrich), 4,4′-dimethoxybiphenyl (99%, Aldrich), were used as received. THF (99%, Aldrich) was dried over 4 Å molecular sieves.

## Batch Reaction Procedure

Unless otherwise stated, a solution of 4-bromoanisole (0.187 g, 1 mmol) in dry THF (1 ml) was added to a Radley's Carousel reaction tube containing the required amount of the nickel catalyst. The Grignard reagent, phenylmagnesium chloride (1 M, 1 ml, 1 mmol) in THF was transferred via syringe under a nitrogen atmosphere and added directly into the solution of the organobromide. The mixture was stirred at room temperature for 24 h under a nitrogen atmosphere. To work-up the reaction, saturated aqueous NaCl solution (2 ml) was added to quench excess Grignard reagent. The organic components were extracted into diethyl ether (2 × 3 ml) which was then dried over anhydrous $MgSO_4$ and the resulting solution analysed by GC and GC-MS with reference to standard solutions of 4-methoxybiphenyl, anisole and 4,4′-dimethoxybiphenyl.

## Single Channel Mini Reactor Procedure

The reaction of 4-bromoanisole with phenylmagnesium chloride in THF was carried out in the pressure driven mini flow stainless steel reactor. The reactor was filled with the resin beads containing the immobilised nickel catalyst (72 mg). A syringe pump (RAZAL A-99) was used to drive a pre-determined volume of a solution containing equimolar amounts (0.5 M) of the reagents in THF through the reactor at the different flow rates for at least 5 h. No reaction was observed in the mixed solution in the absence of the catalyst. The organic components were extracted into diethyl ether and analysed by GC with reference to standard solutions of 4-bromoanisole.

## Parallel Capillary Reactor Packing Procedure

Each channel of the parallel reactor was filled simultaneously with resin to a preset volume. Uniformity was achieved using a jig constructed of a series of pillars with spacings identical to the layout of the channel positions, each pillar having the same diameter as the internal diameter of the channel. A series of jigs were constructed with different pillar heights to allow different packing volumes to be achieved. The reactor body was placed over the jig and resin beads added to the top of the reactor and spread so that they evenly occupied the channels. The stainless steel mesh was then located on top of the channel assembly and the reactor lid bolted in place. The reactor was then inverted and the jig carefully removed. The second stainless steel mesh was placed over the reactor assembly and the reactor base bolted in place. The reactor was then ready for connection to the pumping and collection pipe work. An average packing of 75.3 g per channel was calculated. It is not possible to isolate individual channels to inspect their contents due to the large number of capillaries present. However, in order to ensure that the packing procedure was consistent we ran tests on a reactor packed with Merrifield resin beads without catalyst attached by pumping a solution of guaiazulene dye in THF (0.5 M) at a flow rate of 95 ml $h^{-1}$ and the reactor top removed. The reactor was inspected visually for the emergence of the blue solution. This was found to occur simultaneously over all 120 channel within a 1 s time range, confirming equal packing over all channels. When all the beads were removed from the reactor, homogeneous staining was observed.

## Parallel Capillary Reactor Procedure

The Kumada reaction between 4-bromoanisole and phenylmagnesium chloride in THF was scaled out in the parallel capillary reactor. The reactor was packed with approximately 8.7 g of nickel complex immobilised on Merrifield resin. This gives an average of 75.3 mg of resin per channel. A mixture of 4-bromoanisole and PhMgCl was placed in a sealed glass bottle in THF under an atmosphere of nitrogen. In each case 4-bromoanisole was the limiting reagent. The mixture was pumped continuously through the nickel resin bed packed in the reactor, using the pressure driven pumping system described previously, at room temperature. The flow rates used were of 95 ml $h^{-1}$ and 190 ml $h^{-1}$, with samples collected at 1-hour intervals during a period of 7 h or more. The organic components were extracted into diethyl ether and analysed by GC with reference to standard solutions of 4-bromoanisole and mesitylene as an internal standard.

## Analysis Methods

A Varian-GC 3900 gas chromatograph fitted with a 15 m column of 0.25 millimetre diameter and 0.25 μm thickness CP-SIL5CB coating. The temperature program was an initial hold at 50 °C for 30 seconds followed by a ramp from 40–110 °C at 40 °C $min^{-1}$ followed by a ramp of 110–250 °C at 20 °C $min^{-1}$. GC-MS analyses were performed using a Perkin Elmer GC-MS with a 30 m × 0.25 mm × 0.25 μm Phenomenex-2B5 column. The temperature program was 60–260 °C at 10 °C $min^{-1}$ with a final temperature isothermal hold for 10 min. The MS limit was set between 50 and 450 Da.

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Beilstein Journal of Organic Chemistry

# Controlling hazardous chemicals in microreactors: Synthesis with iodine azide

Johan C. Brandt and Thomas Wirth*

Full Research Paper

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Address:
Cardiff University, School of Chemistry, Park Place, Cardiff CF10 3AT, UK.

Email:
Thomas Wirth* - wirth@cf.ac.uk

* Corresponding author

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## Abstract

Aromatic aldehydes have been converted into the corresponding carbamoyl azides using iodine azide. These reactions have been performed safely under continuous flow reaction conditions in microreactors.

## Introduction

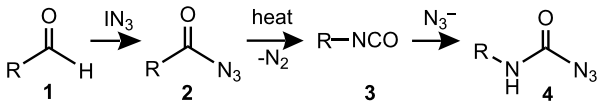
Microstructured devices have already found their way into organic synthesis, because they offer various advantages over traditional large-scale chemistry performed in flasks or vessels [1,2]. The high surface-to-volume ratio as their main characteristic can result in rapid mixing of compounds, uniform reaction conditions due to precise temperature control as well as rate enhancements because of short diffusion distances. In addition, the synthesis and use of potentially hazardous compounds is another advantage of microreactors as only very small amounts of compounds/reagents are handled. Large inventories of dangerous reagents and intermediates are not necessary.

Azides are among the most versatile reagents in modern organic chemistry however they are not often used to their full potential due to safety concerns. Especially azides with low molecular weights are difficult to handle because of their high disposition to detonate [3-5]. However, azides are extremely useful moieties in organic synthesis as they can be transformed easily into a large variety of other functional groups [5].

Iodine azide is a very hazardous but valuable reagent that is easier and much more safely handled under microreactor conditions. Iodine azide is a solid compound, highly explosive and toxic. It is known to add stereospecifically to carbon–carbon double bonds with high regioselectivity following an ionic mechanism. This azido-iodination reaction is by far the most common synthetic application of iodine azide [6-14]. Due to the weakness of the iodine–nitrogen bond iodine azide also reacts in a radical manner upon heating, where this weak bond can be homolytically cleaved and introduce azide moieties efficiently into molecules with weak carbon–hydrogen bonds such as benzyl ethers [15,16] or aldehydes [17,18]. Recently some other research groups have investigated the use of azides in chemistries performed in microreactors [19-22].

## Results and Discussion

The radical addition of azide to aldehydes **1** initially forms acyl azides **2** which directly rearrange in a Curtius rearrangement to the corresponding isocyanates **3**. Isocyanates are very reactive themselves and offer a wide range of possible conversions. An excess of azide leads to the formation of stable carbamoyl azides **4** as shown in Scheme 1.




**Scheme 1:** Azide addition to aldehydes and formation of carbamoyl azides.

As sodium azide is poorly soluble in organic solvents, we decided to use tetrabutylammonium azide for the *in situ* generation of iodine azide. The reaction with iodine monochloride is rapid and after several minutes (depending on the flow rate) the aldehyde **1** was added to the reagent in the microreactor as shown in Figure 1.

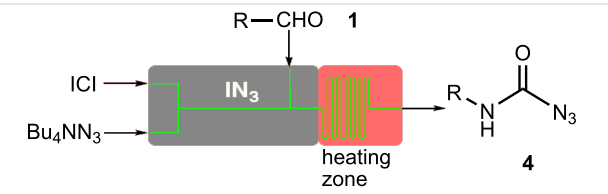
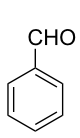
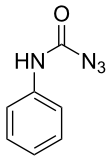
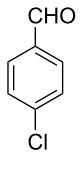
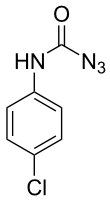
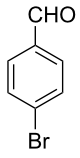
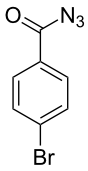
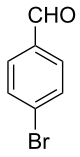
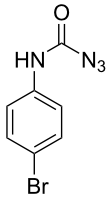
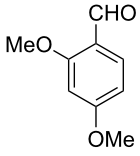
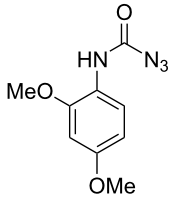



**Figure 1:** Microreactor setup for the *in situ* generation and use of iodine azide ($IN_3$).

All reagents and the aldehyde **1** were used as solutions in acetonitrile. After mixing the aldehyde with the iodine azide reagent the solution is passed through a capillary (volume: 196 µL) in a heating zone to allow the Curtius rearrangement to occur. Flow rates of 20 µL/min or higher led to very low or no conversion. At slower flow rates the yields were enhanced but seemed to stop growing at one point. Optimal yields were constant within a range of 15 to 1.5 µl/min corresponding to residence times in the heating zone of 13–130 minutes. For optimization experiments benzaldehyde **1a** was used. Slower flow rates are technically possible but not very attractive from a synthetic point of view. The reaction would work best at 80 °C, just below the boiling point of acetonitrile. Lower temperatures gave lower conversions. A reaction at 65 °C produced the product **4a** in only 25% yield, whereas a reaction at room temperature did not yield any product. An exchange of the solvent for propionitrile allowed a temperature increase to 110 °C, but conversions were found to be similar to reactions using acetonitrile. In the original publication the solvent had already been optimized and acetonitrile seemed to be the best solvent for this reaction [17].

When using non-distilled *p*-bromobenzaldehyde **1c** the reaction stopped with the formation of the acyl azide **5** contrary to the corresponding chloride derivative (Table 1). However when we modified the protocol to only using freshly distilled aldehydes, we also observed reaction and rearrangement of **1c** via **5** to **4c** and increased yields for the other reactions.

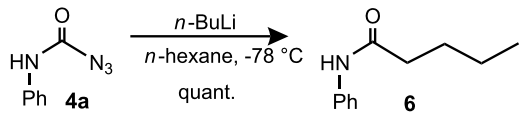
**Table 1:** Products and yields in the addition of iodine azide to aldehydes performed in a tubing microreactor at a flow rate of 7.5 µL/min (26 min residence time) at 80 °C.

| Entry | Aldehyde **1** | Product | Yield [%] |
|---|---|---|---|
| 1 |  **1a** |  **4a** | 44 |
| 2 |  **1b** |  **4b** | 32 |
| 3 |  **1c** not distilled |  **5** | 24[a] |
| 4 |  **1c** distilled |  **4c** | 27 |
| 5 |  **1d** |  **4d** | 21 |

[a]No carbamoyl azide is obtained when crude (non-distilled) aldehyde **1c** is used.

We could show that the quality of the tetrabutylammonium azide is important for the success of the reaction. Its preparation from tetrabutylammonium hydroxide and sodium azide in water and dichloromethane did not lead to dry, crystalline material [23]. Unfortunately also the procedure using tetrabutylammonium chloride and sodium azide produced a product highly contaminated with DMF, which was not removable without decomposition of the product [24,25]. Highest yields were obtained with commercially available tetrabutylammonium azide (Aldrich), although great care has to be taken as this compound is very hygroscopic. Calculations indicate that the synthesis of iodine azide from trimethylsilyl azide and iodine monochloride is slightly endothermic ($\Delta H \approx +15$ kJ/mol) [26-29]. Geometry optimisations and frequency analyses on $Me_3SiN_3$, ICl, $IN_3$ and $Me_3SiCl$ were performed using Gaussian 98 at the B3LYP/6-311+G(d,p) level using the LANL2DZ basis set for iodine augmented with one p function and one d function. NMR experiments showed a ratio of about 1:3 of trimethylsilyl azide and trimethylsilyl chloride upon reaction with iodine monochloride. This mixture was not efficient in the reaction with aldehydes, only an unidentifiable mixture of products was obtained.

The reactivity of carbamoyl azides is analogous to isocyanates, compound **4a** reacted with *n*-butyllithium to give amide **6** in quantitative yields as shown in Scheme 2.




**Scheme 2:** Reaction of carbamoyl azide **4a** with *n*-butyllithium.

Another way to form a stable iodine–azide bonds are hypervalent iodine compounds [30,31]. This source of reagent has indeed been used for radical azidonations in flask reactions [18] and resulted in an interesting approach using solid support [32], but these compounds are usually unsuitable for applications in microreactors because of their poor solubility or they would require a different microreactor set-up that would allow solid supported reagents [33].

For better comparison with literature procedures the reaction was then also investigated as a batch process. The reaction with commercial tetrabutylammonium azide and non-distilled aldehyde precursors would stop after the formation of the acyl azide with *p*-chlorobenzaldehyde and with *p*-bromobenzaldehyde. Rearrangement took place when sodium azide was used, but lower yields (34% yield of **4b**) were observed than those given in literature (53–97%) [17]. Maybe the sodium ion acts like a Lewis acid and accelerates the rearrangement. It is known that Lewis acid catalysts such as zinc triflate can accelerate Curtius rearrangements and the sodium cation might serve a similar role [34]. We obtained 67% yield of **4b** when zinc triflate was used as catalyst in a flask reaction. Even the reaction of non-distilled *p*-bromobenzaldehyde **1c** under these acidic conditions showed traces of the corresponding carbamoyl azide according to $^1$H NMR. But electron rich substrates such as 2,4-dimethoxybenzaldehyde **1d** showed decomposition and unidentifyable product mixtures with this catalyst. Generally, the batch reactions all proceeded less cleanly compared to the microreactor processes.

## Conclusion

After initially promising results we were challenged with a complex optimization task, that included many more parameters than usual in organic synthesis, due to the technical implications of our approach. There are phenomena in this reaction that prevent complete conversion to complete by a long way, probably azide-consuming side reactions or lack of activity of the substrate, lack of acid catalysis, or a combination of these reasons. Additionally, the substitution pattern of the substrates led to an unexpected outcome of the reaction.

## Experimental

### Synthesis of tetrabutylammonium azide:

**Procedure I** [23]: Sodium azide (200 mmol, 13 g) was dissolved in water (30 mL). Then tetrabutylammonium hydroxide (100 mmol, 26 g) was added and the mixture was stirred at room temperature for 90 min. Dichloromethane (50 mL) was added and stirring was continued for 10 min. The organic layer was separated and dried over magnesium sulfate. Finally the solvent was removed under reduced pressure and the product was dried for 24 h under vacuum.

**Procedure II** [24,25]: Sodium azide (79 mmol, 5.13 g) and tetrabutylammonium chloride (85 mmol, 22 g) were mixed in DMF (35 mL) and stirred overnight under argon at 50 °C. Dry THF (70 mL) was added and stirring continued for 15 min. The reaction mixture was filtered and the solvent in the filtrate was removed under reduced pressure. The product was heated under vacuum for 2 h to remove some DMF.

Yields for these reactions cannot be given as the solvents could not be removed completely from the product. IR (Nujol, $cm^{-1}$): $\nu$ = 3418, 2145 (azide), 1643.

### General procedure for the synthesis of carbamoyl azides **4**:

A twin syringe pump (KDS-200-CE) was charged with two 5 ml Hamilton syringes, one containing tetrabutylammonium azide (3 mmol, 853 mg) in dry acetonitrile (3.5 mL) and the

other iodine monochloride (2 mmol, 102 µL) in dry acetonitrile (4.8 mL). The outlets were connected by standard HPLC tubing to a T-junction, after 30 cm tubing a second T-junction was connected to the third syringe containing the substrate aldehyde (1 mmol) in dry acetonitrile (2.4 mL). All HPLC equipment was purchased from CHM GmbH, Fridolfing, Germany. The HPLC tubing used as flow reactor was made of PTFE with the measurements 1/16 × Ø 0.25 mm. The syringes containing the reagents were connected to the flow system with PEEK adapters (1/4- 28f – Luer, female) and 1/4 PEEK fittings. The T-mixers used were PEEK (1/4-28 with 1/16 fittings and Ø 0.5 mm) for low pressure applications. The third syringe was loaded on a separate syringe pump. The flow rate was adjusted to an overall flow rate of 7.5 µL/min. The source of heating for the reaction was a PEG 600 oil bath. After passing the heating zone (80 °C) behind the second T-junction (4 m) the reaction was terminated at the outlet with 5 mol% aq thiosulfate solution. For work-up, the mixture was extracted with dichloromethane (3 × 10 mL). The combined organic phases were separated, dried over magnesium sulfate and the solvent removed under reduced pressure.

### Phenylcarbamoyl azide (**4a**)

The crude product was purified with a silica gel column using hexane/$CH_2Cl_2$ 15:1 as eluent. Yield: 71 mg (44%), colourless solid, mp: 106–107 °C (lit: 107.1 °C) [18].

$^1$H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, $^3J_{HH}$ = 7.9 Hz, 1H, H-2), 7.33 (t, $^3J_{HH}$ = 7.9 Hz, 2H, H-1/H-3), 7.13 (t, $^3J_{HH}$ = 7.4 Hz, 2H, H-4/H-6), 6.97 (s, 1H, N*H*) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): δ 154.0 (C-8), 136.8 (C-5), 129.2 (C-1/C-3), 124.6 (C-2), 119.2 (C-4/C-6) ppm; EI-MS *m/z* (%): 162 ([M]$^+$, 7), 119 (100), 93 (64), 91 (56), 64 (32).

### 4-Chlorophenylcarbamoyl azide (**4b**)

The crude product was purified with a silica gel column using hexane/$CH_2Cl_2$ 1:1 as eluent. Yield: 63 mg (32%), colourless solid, mp: 103–105 °C.

$^1$H NMR (500 MHz, $CDCl_3$): δ 7.39 (d, $^3J_{HH}$ = 8.8 Hz, 2H, H-4/H-6), 7.29 (d, $^3J_{HH}$ = 8.8 Hz, 6.86 (s, 1H, N*H*) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): δ 154.0 (C-9), 135.4 (C-5), 129.8 (C-2), 129.2 (C-1/C-3), 120.4 (C-4/C-6) ppm; EI-MS *m/z* (%): 198 ([M]$^+$, 2), 196 ([M]$^+$, 4), 187 (2), 185 (5), 155 (12), 153 (100), 127 (23), 125 (21); HRMS (EI): calc. for $C_7H_5{}^{35}ClN_4O$: 196.0146, found: 196.0145.

### 4-Bromophenylcarbamoyl azide (**4c**)

The crude product was purified with a silica gel column using hexane/$CH_2Cl_2$ 1:1 as eluent. Yield: 65 mg (27%), colourless crystals, mp: 77–78 °C.

$^1$H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, $^3J_{HH}$ = 8.7 Hz, 2H, H-3/H-5), 7.34 (d, $^3J_{HH}$ = 8.7 Hz, 2H, H-2/H-6) 6.84 (s, 1H, N*H*) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): δ 154.1 (C-7), 136.0 (C-4), 132.2 (C-1), 120.9 (C-2/C-6), 117.4 (C-3/C-5) ppm; EI-MS *m/z* (%): 242 ([M]$^+$, 100), 240 ([M]$^+$, 96), 231 (25), 229 (27), 214 (10), 212 (19). HRMS (EI): calc. for $C_7H_5BrN_4O$: 239.9641, found: 239.9639.

### 2,4-Dimethoxyphenylcarbamoyl azide (**4d**)

The crude product was purified with a silica gel column using hexane/$CH_2Cl_2$ 1:4 as eluent. Yield: 47 mg (21%), colourless solid, mp: 65–67 °C.

$^1$H NMR (500 MHz, $CDCl_3$): δ 8.02 (d, $^3J_{HH}$ = 8.6 Hz, 1H, H-4), 7.22 (s, 1H, N*H*), 6.50–6.47 (m, 2H, H-1/H-3), 3.84 (s, 3H, H-13 or H-14), 3.80 (s, 3H, H-13 or H-14); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 156.7 (C-10), 153.4 (C-2), 149.3 (C-6), 119.9 (C-4), 109.9 (C-3), 103.9 (C-5), 98.7 (C-1), 55.7 (C-13 or C-14), 55.5 (C-13 or C-14) ppm; EI-MS *m/z* (%): 222 ([M]$^+$, 10), 179 (100), 164 (31), 153 (18), 136 (52), 122 (10), 110 (11), 95 (12); HRMS (EI): calc. for $C_9H_{10}N_4O_3$: 222.0753, found: 222.0755; IR (neat): 1531, 1711, 2144, 3415 cm$^{-1}$.

### Azido(4-bromophenyl)methanone (**5**)[35]

The crude product was purified with a silica gel column using hexane/$CH_2Cl_2$ 1:1 as eluent. Yield: 54 mg (24%), light yellow solid.

$^1$H NMR (500 MHz, $CDCl_3$): δ 7.87 (d, $^3J_{HH}$ = 8.8 Hz, 2H, H-4/H-6), 7.59 (d, $^3J_{HH}$ = 8.8 Hz, 2H, H-1/H-3) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): δ 171.7 (C-8), 132.0 (C-5), 130.8 (C-1/C-3), 129.7 (C-2), 129.5 (C-4/C-6) ppm.

### *N*-Phenylpentanamide (**6**)

Phenylcarbamoyl azide **4a** (0.12 mmol, 20 mg) was dissolved in dry THF (35 mL) and cooled to −78 °C under argon. Then *n*-BuLi (0.37 mmol, 0.15 mL, 2.5 M in hexane) was added carefully dropwise into the solution via a syringe. After the addition the cooling bath was removed and the flask was allowed to warm to r.t. The mixture was then diluted with AcOH/THF (20 mL/20 mL) and aq sodium carbonate (20 mL). Then ethylacetate (60 mL) was added, the organic layer separated and dried over magnesium sulfate. The crude product was purified with a silica gel column using hexane/$CH_2Cl_2$ 15:1 as eluent. Yield: 14 mg (quant.) colourless solid, mp: 60–61 °C (lit: 60–61.5 °C) [36].

$^1$H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, $^3J_{HH}$ = 7.9 Hz, 2H, H-4/H-6), 7.32 (t, $^3J_{HH}$ = 7.9 Hz, 2H, H-1/H-3), 7.13 (s, 1H, N*H*), 7.10 (t, $^3J_{HH}$ = 7.4 Hz, 1H, H-2), 2.36 (t, $^3J_{HH}$ = 7.6 Hz, 2H, H-10), 1.72 (qn, $^3J_{HH}$ = 7.6 Hz, 2H, H-11), 1.41 (*sext*, $^3J_{HH}$

= 7.5 Hz, 2H, H-12), 0.95 (t, $^3J_{HH}$ = 7.4 Hz, 3H, H-13) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): δ 171.3 (C-8), 137.9 (C-5), 129.0 (C1/C-3), 124.2 (C-2), 119.7 (C-4/C-6), 37.6 (C-10), 27.7 (C-11), 22.4 (C-12), 13.8 (C-13) ppm.

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# Radical carbonylations using a continuous microflow system

Takahide Fukuyama, Md. Taifur Rahman, Naoya Kamata and Ilhyong Ryu*

Preliminary Communication

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Address:
Department of Chemistry, Graduate School of Science, Osaka Prefecture University, Sakai, Osaka 599-8531, Japan

Email:
Ilhyong Ryu* - ryu@c.s.osakafu-u.ac.jp

* Corresponding author

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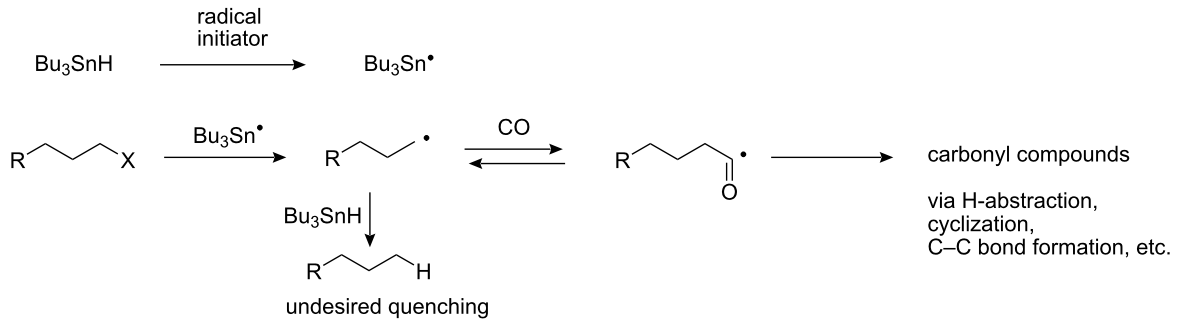
## Abstract

Radical-based carbonylation reactions of alkyl halides were conducted in a microflow reactor under pressurized carbon monoxide gas. Good to excellent yields of carbonylated products were obtained via radical formylation, carbonylative cyclization and three-component coupling reactions, using tributyltin hydride or TTMSS as a radical mediator.

## Introduction

Placing a reaction mixture fluid inside a microstructured channel network helps gain a high surface area to volume ratio that in turn ensures rapid heat and mass transfer [1-3]. Precise control of reaction temperature and residence time, excellent mixing properties for reactants/reagents as well as a flow nature of the microreaction system, often result in higher conversion, greater yields, superior product selectivity and safety. In recent years, the potential of this new technology for organic synthesis have been recognized and many applications have been demonstrated by our group [4-6] as well as others [7-11].

In our recent report, we demonstrated that excellent thermal efficiency of the microflow system would lead to effective execution of tin hydride and TTMSS (tris(trimethylsilyl)silane)-mediated radical reduction and cyclization reactions [12]. The Seeberger group reported reduction and hydrosilylation using TTMSS in a microflow system [13]. In our study, we found that the combination of a rapidly decomposing radical initiator with a microreaction device allowed the reactions to be completed in a very short period of time giving good yields of the desired products. Carbon monoxide is an important feedstock and our group has actively pursued carbonylation reactions [14-17]. Thermally induced radical carbonylations using tin hydride usually require pressurized CO conditions to ensure that the concentration of CO around the radical centers is high enough to compete with the premature quenching by tin hydride (Scheme 1). Encouraged by our previous successes with both radical reactions [12] and metal-catalyzed carbonylation reactions using microflow devices [18-20], we decided to examine a continuous microreaction system for radical carbonylation reac-




**Scheme 1:** Tin-mediated radical carbonylation and the competing reduction.

tions, for which we typically used stainless-steel autoclaves as the reactor in batch systems.

## Results and Discussion

The microflow system we employed was simple, yet robust enough to withstand high CO pressures (ca. 80 atm) (Figure 1). A metered stream of CO gas was fed in a controlled manner into the system and was mixed with the toluene solution containing a radical mediator, a radical initiator and a substrate in a T-shaped micromixer (stainless steel, internal diameter: 1000 μm). This biphasic (gas-liquid) mixture was then guided through a stainless steel tubular reactor (internal diameter: 1000 μm), acting as the residence time unit (RTU), under heated conditions using an oil bath. A back pressure control valve was connected at the end of the RTU to regulate and maintain the pressure of the reactor system. Reaction time was adjusted via the flow rates of CO and the liquid.

Using the microflow system depicted by Figure 1, we carried out the radical formylation of 1-bromododecane (**1**) with CO in the presence of tributyltin hydride (bath temp. 80 °C) [21]. However, we encountered incomplete conversion of the starting bromide when we used AIBN (2,2′-azobisisobutyronitrile) as a radical initiator. This was attributed to the rather slow decomposition rate of the AIBN (half-life time: 90 min at 85 °C) in light of the time frame employed for the microflow reaction (residence time, 12 min). When we switched AIBN to a more rapidly decomposing V-65 (2,2′-azobis(2,4-dimethylvaleronitrile), half-life time: 12 min at 80 °C), 100% conversion was attained to give tridecanal (**2**) in a 77% yield (Table 1, entry 1). Microflow carbonylation of bromocyclohexane (**3**) and 1-bromoadamantane (**5**) also worked well to furnish the corresponding aldehydes **4** and **6** in good yields (entries 2 and 3). The judicious choice of a radical initiator is important for high conversion in a short reaction time for carbonylation reactions, which is in accordance with our previous experience with microflow radical reduction and cyclization of organic halides using tributyltin hydride [12].

Tin-mediated radical carbonylation has a wide range of applications including carbonylative cyclization and multi-component coupling reactions. In this regard, we again chose stannylcarbonylation using 1,6-azaenyne **7** as a model for cyclization [22, 23]. Using a similar microflow system but with an extended reaction time, we were able to obtain the desired six-membered ring lactam **8** in good yield (entry 4). Using a similar micro-

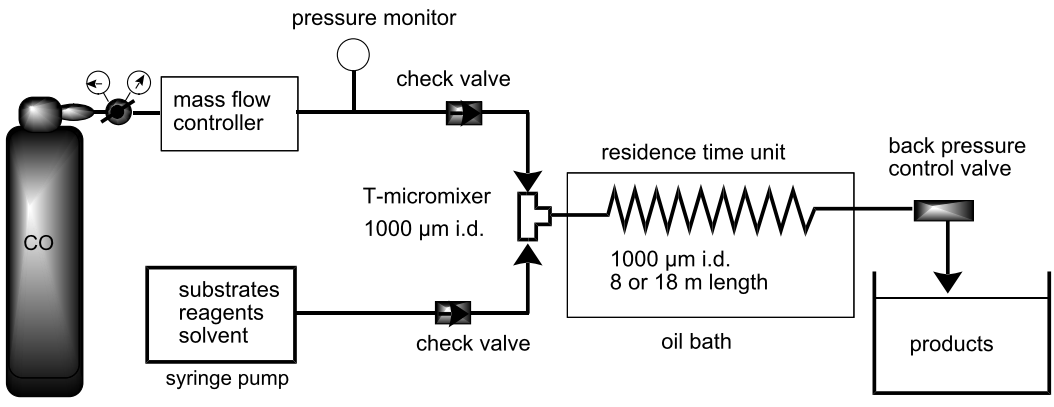
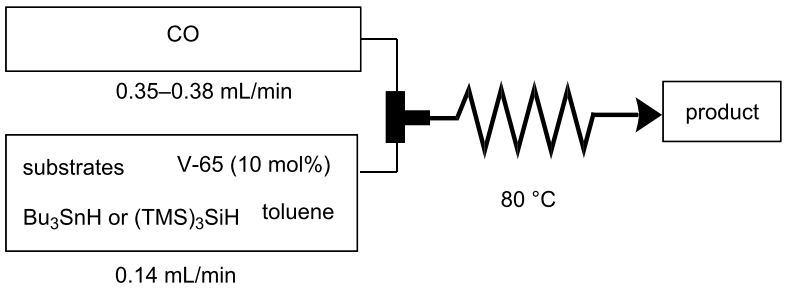
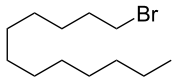
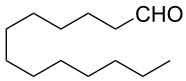
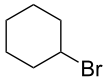
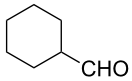
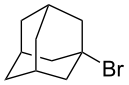
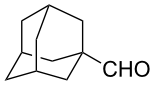
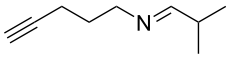
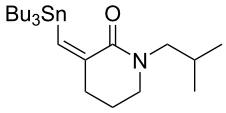
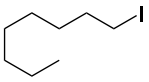
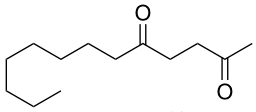
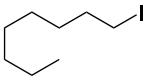
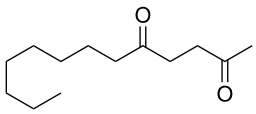
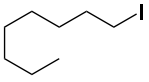
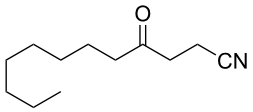



**Figure 1:** Microflow system available for radical carbonylation using pressurized CO.

**Table 1:** Radical carbonylation in a microflow system.[a]




| entry | substrate | conditions | product/yield[b] |
|---|---|---|---|
| 1 |  **1** | 0.02 M in toluene, $Bu_3SnH$ (1.2 equiv), V-65 (10 mol%), CO 83 atm, 12 min |  **2** 77% |
| 2 |  **3** | 0.02 M in toluene, $Bu_3SnH$ (1.2 equiv), V-65 (10 mol%), CO 85 atm, 12 min |  **4** 68% |
| 3 |  **5** | 0.02 M in toluene, $Bu_3SnH$ (1.2 equiv), V-65 (10 mol%), CO 85 atm, 12 min |  **6** 86% |
| 4 |  **7** | 0.05 M in toluene, $Bu_3SnH$ (1.1 equiv), V-65 (10 mol%), CO 79 atm, 27 min |  **8** 85% (E/Z = 0/100) |
| 5 |  **9** | 0.017 M in toluene, $Bu_3SnH$ (1.5 equiv), $H_2C$=CH-$COCH_3$ (4 equiv) V-65 (10 mol%), CO 85 atm, 29 min |  **10** 78% |
| 6 |  **9** | 0.025 M in toluene, $(TMS)_3SiH$ (1.5 equiv), $H_2C$=CH-$COCH_3$ (1.2 equiv) V-65 (30 mol%), CO 20 atm, 30 min |  **10** 92% |
| 7 |  **9** | 0.025 M in toluene, $(TMS)_3SiH$ (1.5 equiv), $H_2C$=CH-CN (1.2 equiv) V-65 (30 mol%), CO 20 atm, 30 min |  **11** 83% |

[a]Conditions: substrate (1 mmol, 0.017–0.05 M in toluene), $Bu_3SnH$ or TTMSS (1.1–1.5 equiv), V-65 (10–30 mol%), CO (20–85 atm), T-shaped micromixer (1000 μm i.d.), residence time unit (1000 μm i.d. length: 8 m for entries 1–3, 18 m for entries 4–7). [b]Yields were determined by GC analysis using decane as an internal standard.

flow system, we then carried out a three-component coupling reaction comprised of 1-iodooctane (**9**), CO, and methyl vinyl ketone in the presence of tributyltin hydride [24], which also worked well to give 2,5-tridecandione (**10**) in 78% yield (entry 5).

Since tris(trimethylsilyl)silane (TTMSS) delivers a hydrogen atom to a carbon-centered radical at a slower rate than tributyltin hydride [25], carbonylation reactions with TTMSS can be carried out at lower CO pressure without being plagued by the premature reduction of the key radical. Hence, we anti-

cipated that the combination of low pressure CO/V-65 could be successfully applied to the TTMSS-mediated three component carbonylative-coupling reaction of 1-iodooctane (**9**) [26,27] in a microflow system using methyl vinyl ketone and acrylonitrile as acyl radical traps (entries 6 and 7 ). Gratifyingly, in both cases, good yields of the three-component coupling products were formed by using reduced CO pressure.

## Conclusion

We have developed a facile platform to conduct radical carbonylation under CO pressure in a flow system comprised of a T-shaped mixer and a tabular residence time unit. Using V-65 as a radical initiator, we were able to carry out typical tin- or silicon-based radical carbonylation reactions leading to aldehydes, unsymmetrical ketones, and a lactam, in a continuous microflow system.

## Experimental

**Typical procedure for radical carbonylation in a microflow system. The radical formylation of 1-bromododecane (1).** 1-Bromododecane (**1**, 1 mmol, 249.5 mg), V-65 (0.1 mmol, 24.8 mg), $Bu_3SnH$ (1.2 mmol, 352.9 mg), and decane (59 mg) as an internal standard were dissolved in toluene (50 mL). The toluene solution was placed in a syringe (17 mL), which was then attached to a syringe pump. The system was pressurized with CO (83 atm) by means of the pressure control valve. The flow rate of CO was controlled at 0.14 mL/min by the mass flow controller. The toluene solution was introduced at a flow rate of 0.37 mL/min, then was mixed with CO in the T-shaped micromixer (i.d. = 1000 μm). The reaction was then fed into the residence time unit, which was immersed in an oil bath and heated at 80 °C. The time needed for the reaction mixture to travel through the residence time unit was expressed as the residence time (12 min). The mixture of products was collected at the outlet. The initial effluent exiting the microflow reactor was discarded (ca. 20 min) until a stable gas-liquid mixing was achieved, and the following portion was collected for a 10 min period. The yield was determined by GC analysis, and the product was identified by comparison of $^1$H NMR spectrum and a retention time for GC analysis with those of authentic sample.

## Acknowledgments

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Beilstein Journal of Organic Chemistry

# Gold film-catalysed benzannulation by Microwave-Assisted, Continuous Flow Organic Synthesis (MACOS)

Gjergji Shore, Michael Tsimerman and Michael G. Organ*

Full Research Paper

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Address:
Department of Chemistry, York University, 4700 Keele Street, Toronto, ON, Canada M3J 1P3

Email:
Michael G. Organ* - organ@yorku.ca

* Corresponding author

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## Abstract

Methodology has been developed for laying down a thin gold-on-silver film on the inner surface of glass capillaries for the purpose of catalysing benzannulation reactions. The cycloaddition precursors are flowed through these capillaries while the metal film is being heated to high temperatures using microwave irradiation. The transformation can be optimized rapidly, tolerates a wide number of functional groups, is highly regioselective, and proceeds in good to excellent conversion.

## Introduction

Microwave-assisted organic synthesis (MAOS) has had a significant impact on organic and medicinal chemistry by dramatically shortening reaction times, producing cleaner product mixtures, and making high-energy transformations routine that might otherwise be avoided [1,2]. Within the last five years, microwave technology has also been applied to reactions performed in a flowed format [3,4]. Flowed chemical synthesis offers numerous advantages over traditional batch-reactor technology [5-24]. Independent inlet streams allow reactive intermediates to be kept separate until brought together in miniscule amounts to react immediately; this rapidly depletes the starting materials and continuously physically moves the product away from the infusing stream. In batch reactors, product molecules form in the presence of a vast excess of starting materials that can lead to significant byproduct formation. Further, a moving synthesis platform allows for in-line analysis and instantaneous changes to reaction conditions for process optimization that can be automated readily. To gain the full advantage of working in flow, reactions should proceed very rapidly and ideally reach completion during the time in which the reactants reside in the flow tube. Microwave heating has been used to drive a wide variety of reactions to high levels of completion in a flowed format [5-24].

We have demonstrated that thin-metal films on the walls of narrow tubes can impart tremendous rate accelerations on

flowed reactions that are being simultaneously microwaved [25-28]. These accelerations can be a result of direct catalysis by the film itself, the tremendous temperatures attainable by microwaved metal films, or a combination of the two. In cross coupling processes, the film has been demonstrated itself to be capable of catalyzing Suzuki–Miyaura and Heck reactions, i.e., Pd-thin films promote these transformations without any additional catalyst being added to the reactant stream(s) that enter the flow tube [28]. Without microwave irradiation, the above-described cross-coupling reactions did not proceed indicating that there is not only a catalytic effect, but also a pivotal heating effect supplied by the film. More recently we have shown that a gold film in the same flow reactor is highly effective for hydrosilylation reactions [25] and we were interested both to expand the use of gold films in synthesis using MACOS and in exploring complex, multi-step catalytic processes in flow.

The benzannulation reaction between aromatic carbonyls and alkynes has received increasing attention since 2002 [29,30]. This transformation has been shown to be promoted by Lewis acids, copper complexes [31] and various gold species, including Au(I)X, Au(III)$X_3$, [32-34] and Au nanoparticles dispersed on different supports. For Au(III) catalysts, the reaction has been proposed to proceed via the formation of no less than four organogold intermediates and/or complexes (Figure 1).

Further, it has been shown computationally by Straub that Au(I) and Au(III) can perform both this and related catalytic cycles with similar energy profiles [35]. This blurs the distinction of the two pathways and raises the possibility that the actual active species in these transformations could be either species, providing that the possibility exists for the starting Au complex to be oxidized or reduced under a specific set of reaction conditions. Given the complexity of this process, we thought that benzannulation would be an ideal transformation to investigate the use of gold films for MACOS.

## Results and Discussion

Our investigation started with an assessment of different types of metal films for their utility in benzannulation. The morphology of Cu, Pd, Ag, and Au films can be compared in the scanning electron microscopy (SEM) images in Figure 2. The films are generally prepared in a reducing environment (see Experimental), thus they are expected to be largely M(0), which has been confirmed by energy-dispersive X-ray (EDX) analysis of the films (e.g., see panel f in Figure 2).

However, film preparation was not conducted under a strictly inert environment, thus oxygen and/or water in the air could play a role in the film's composition leading to the formation metal oxides, for example, on the surface. Palladium films had the greatest porosity (panel b) while silver films (panel c) were the most dense and uniform. Gold films showed poor adhesion to the glass and poor performance when subjected to the rigors of MACOS. However, these properties were dramatically improved when the same gold film was laid down on a transparently-thin silver layer that coated the capillary wall. With these metal-film-coated capillaries in hand, benzannulation was investigated using the substrates shown in Table 1.

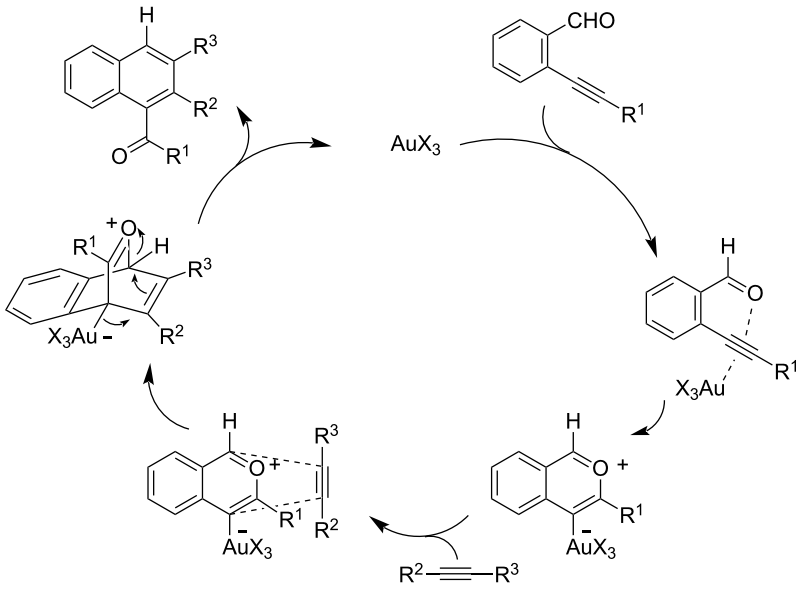



**Figure 1:** Mechanism of Au(III)-catalyzed benzannulation between aromatic carbonyls and alkynes.

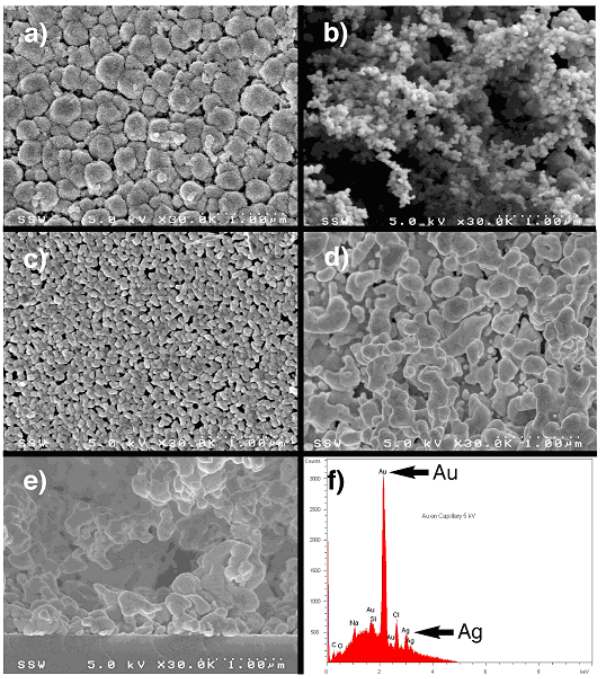
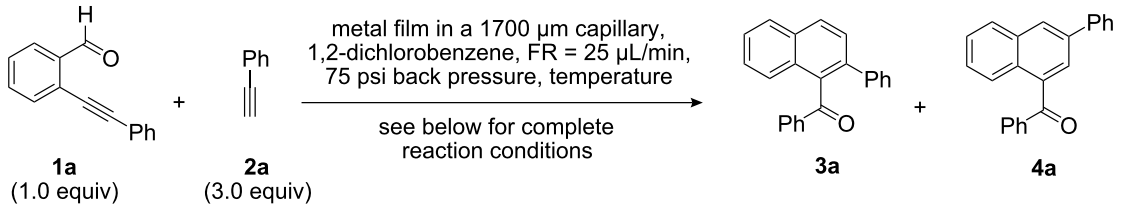



**Figure 2:** X-ray analysis of the metal films used in this benzannulation study. Panels a–e are scanning-electron micrographs (SEM) of all films taken at 30,000 × magnification: a) Cu, b) Pd, c) Ag, d) Au layered on a base film of Ag. Panel e shows the side view of the Au film attached to the glass capillary wall (bottom of image), between which is sandwiched a barely-visible thin Ag coating. Panel f is the energy-dispersive X-ray (EDX) spectrum of the Au film from panel d; note the small level of Ag that is present that helps to anchor the Au to the surface of the glass.

This reaction is reported most widely using homogeneous and heterogeneous gold catalysts, and indeed we found that a pure Au film provided good conversion for a short period (Table 1, entry 4), although the film had a short lifespan. Films of palladium (entry 2) and silver (entry 3) showed no conversion of starting materials at all. Surprisingly, copper, which is reported to be a suitable catalyst for benzannulation, could not be optimized beyond the formation of only trace amounts of product (entry 1). We experimented with the use of bimetallic films and found that optimal film performance was achieved by laying down a porous gold film on top of a thin silver mirror. When run at a high temperature (240 °C, entry 5), as read by the IR sensor in the Biotage Initiator microwave, excellent conversion was achieved that diminished as the temperature was reduced (e.g., 190 °C, entry 6). It is noteworthy that under batch conditions, these reactions are reported to require up to 6 h to obtain similar conversion levels [7] to those obtained in less than 60 s using MACOS, which is the residence time of any reactant plug in the flow reactor.

To probe any special effect brought about by the microwave in this transformation, the identical transformation in entry 6 was performed using an oil bath to achieve the same temperature (i.e., 190 °C, entry 7) and the conversion was dramatically reduced from 68 to 14 percent. It is possible that superior microwave conversion is the result of localized 'hot spots' in the film that are potentially well above the bulk temperature recorded by the IR sensor when microwave irradiation is used.

**Table 1:** Optimization Studies for Benzannulation Reaction using MACOS.




**1a** (1.0 equiv) **2a** (3.0 equiv) **3a** **4a**

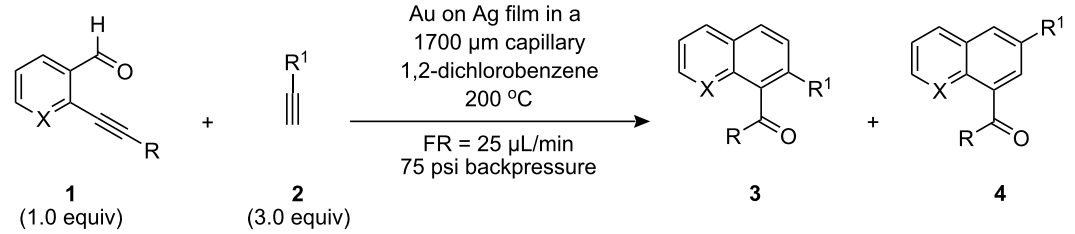
| Entry | Film | Heat Source | Temp. (°C) | Percent Conversion[a] | Percent Yield[b] | **3a** : **4a** |
|---|---|---|---|---|---|---|
| 1 | Cu | microwave | 240 | 5 | 4 | ND |
| 2 | Pd | microwave | 240 | 0 | 0 | – |
| 3 | Ag | microwave | 240 | 0 | 0 | – |
| 4 | Au on Au | microwave | 220 | 75 | ND | |
| 5 | Au on Ag | microwave | 240 | 90 | 78 | 3 : 1 |
| 6 | Au on Ag | microwave | 190 | 68 | ND | ND |
| 7 | Au on Ag | oil bath[c] | 190 | 14 | ND | ND |

[a]Percent conversion was determined by $^1$H NMR spectroscopy by comparing the ratio of product peaks (**3** and/or **4**) to the starting aldehyde (**1**) from aliquots taken directly from the eluent stream. [b]Percent yield was determined by collecting a specific volume of eluent that contained a known amount of starting materials, and purifying the material by silica gel flash chromatography. [c]The metal-film-coated capillary was left in the bath for 20 min to ensure that the film was at temperature prior to flowing the reaction mixture through it.

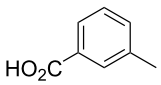
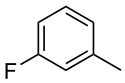
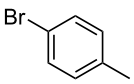
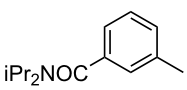
It has been proposed that steps or angles in the surface of the metal film can serve as an antenna resulting in higher levels of microwave absorption in those areas causing higher than normal temperatures. In an oil bath (or oven), only the bulk temperature of the external heating source can be achieved in the film. If this is the case, and localized areas of potentially extreme temperature are required for optimal reaction performance, this would be preferable to heating the entire film to these higher temperatures, which would lead to faster film and product decomposition.

With optimized conditions in hand, we set out to examine the substrate scope of this reaction using capillaries lined with the gold-on-silver films (Table 2).

**Table 2:** Benzannulation reactions with Au on Ag-coated capillaries using MACOS.




**1** (1.0 equiv) + **2** (3.0 equiv) → **3** + **4**

| Entry | R– | –X– | $R^1$– | Percent Conversion[a] | Percent Yield[b] | **3** : **4** |
|---|---|---|---|---|---|---|
| **a** |  | –CH– |  | 90 | 78 | 75 : 25 |
| **b** |  | –CH– | $(CH_3)_3Si$– | 75 | 62 | **4** only |
| **c** |  | –CH– |  | 62 | 52 | 58 : 42 |
| **d** |  | –CH– |  | 76 | 62 | **3** only |
| **e** |  | –CH– |  | 72 | 60 | **4** only |
| **f** |  | –N– |  | 78 | 64 | 70 : 30 |
| **g** |  | –N– |  | 68 | 54 | **4** only |
| **h** |  | –N– | $(CH_3)_3Si$– | 65 | 58 | **4** only |
| **i** |  | –N– |  | 65 | 52 | **4** only |
| **j** |  | –N– |  | 50 | 40 | **4** only |

[a]Percent conversion was determined by $^1$H NMR spectroscopy by comparing the ratio of product peaks (**3** and/or **4**) to the starting aldehyde (**1**) from aliquots taken directly from the eluent stream. [b]Percent yield was determined by collecting a specific volume of eluent that contains a known amount of starting materials, and purifying the material by silica gel flash chromatography.

The reaction was applicable to the hydrocarbon starting materials tried (e.g., entries **a**, **b**, **c**) and was also useful for the preparation of heterocycle-containing molecules such as pyridines and thiophenes (e.g., entries **e**–**j**). A survey of different functional groups revealed a broad tolerance including silyl groups (entries **b** and **h**), halides (entries **g** and **i**), ethers, (entry **c**), amides (entry **j**), and even free carboxylic acids (entry **e**). In all cases where reactions did not fully complete, benzaldehyde (**1**) accounted for the mass balance; crude $^1$H NMR spectra were very clean showing only residual **1**, product and trace by products. In most cases, the reactions displayed a high level of regioselectivity.

All of the above runs were conducted on approximately 700 μL of an infusing starting material solution (35 min per run), which, after purification, generated ~70–80 mg of final product. Such quantities are ample for evaluation in biological screens. However, larger quantities of a compound can be required, so using the substrates in Table 2, entry **a**, a larger-scale benzannulation was performed. To improve efficiency and to reduce solvent consumption (and hence waste production) the concentration of both starting materials was tripled. After running the reactor for 90 min, three quarters of a gram of product (**3a** and **4a**, 3:1) were collected. Under these conditions the concentration of alkyne **2a** was 4.5 M, demonstrating that MACOS can easily handle concentrations that are far above the typical levels (0.1–0.5 M) commonly used in conventionally-heated batch reactors.

The lifetime and durability of the film under the optimized reaction conditions was examined. The transformation in Table 2, entry **a** was followed over the course of 2 h; reaction performance is optimal at the beginning and slowly, but steadily erodes. Visibly, the film darkens over time, which we attribute to small amounts of starting materials and/or products that char over time on the surface of the hot film; this may lead to the blockage of reaction sites. Additionally, the thin-walled capillary glass softened and in some cases failed after 90 min of exposure to the hot film. While bulk manufacturing of very large quantities is not yet attainable with the current reactor design, the device is very suitable for preparing library collections of 50–750 mg of product for evaluation in medicinal chemistry or materials science applications.

## Conclusion

Glass capillaries internally-lined with thin-metal films of gold, copper, silver, and gold-on-silver were prepared and evaluated for their catalytic activity in the microwave-assisted, continuous flow benzannulation of aryl, alkyl and silylalkynes with alkynylbenzaldehydes. Only the gold-on-silver films possessed both the high level of catalytic activity and suitable physical robustness to prepare quantities of product suitable, for example, for biological or material science evaluation purposes (up to ~700 mg). The reaction showed wide functional group tolerance and good to excellent regioselectivity in the cycloaddition. We are now evaluating new materials to replace the glass tube with the plan of making the process more sustainable.

## Experimental

### Microwave irradiation experiments

All MACOS experiments were performed in 1700 μm (ID) borosilicate capillaries, using a single mode Biotage Smith Creator Synthesizer, operating at a frequency of 2.45 GHz with irradiation power from 0 to 300 W. The capillary was fed reactants from Hamilton gastight syringes attached to a Harvard 22 syringe pump pre-set to the desired flow rate. The system was connected to a sealed collection vial, where a pressurized air line (75 psi) was attached to create backpressure. The temperatures reported were measured off the surface of the capillaries by the IR sensor built into the microwave chamber. All reagents and solvents were purchased from commercial sources and used without additional purification. Column chromatography purifications were carried out using the flash technique on silica gel 60 (200–400 mesh). $^1$H NMR spectroscopy was run using a Bruker Advance 400 MHz instrument and all spectra were calibrated to the signal from the residual proton of the deuterated chloroform solvent (7.26 ppm); $^{13}$C NMR spectra were calibrated to the middle carbon signal of the triplet for deuterated chloroform (77.00 ppm).

### General procedure for the benzannulation reactions by MACOS

A stock solution containing the acetylenic aldehyde (0.5 mmol, 1.0 equiv.) and alkyne (1.5 mmol, 3.0 equiv) in 0.7–0.8 mL 1,2-dichloro benzene (total mixture volume is 1.0 mL) was prepared and loaded into a Hamilton gastight syringe. The tubing was primed with 1,2-dichloro benzene and the syringe was connected to the reactor system with the aid of Microtight fittings after which it was placed in a Harvard 22 syringe pump that was set to deliver 20 μL/min. The single mode microwave was programmed to heat constantly; the power level was controled manually so as to keep the temperature constant at the specified levels. The effluent from the reactor was fed into a sealed vial and analyzed directly by $^1$H NMR spectroscopy immediately after the reaction. Typically, 0.7–0.8 mL of the crude reaction mixture was collected and the product was purified by silica gel column chromatography.

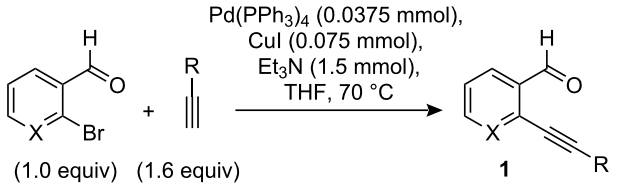
## General procedure for creating the gold-on-silver film coating inside of 1700 micron (ID) capillaries

Tollens' reagent (0.5 mL) was mixed with 0.5 mL of a 5% D-glucose solution into a 2 mL vial. The 1700 μm capillaries (ID) were filled with this mixture, capped at both ends and left to develop at rt. After the Ag coating was fully developed (15 min), the capillaries were rinsed with acetone and placed inside a muffle furnace for calcination at 500 °C (3 × 1 min).

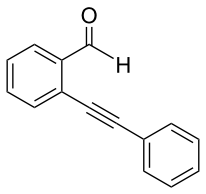
The gold-coating solution was prepared by mixing a 0.4 mmol/mL aqueous solution of $AuCl_3$ (0.5 mL) with a 2% aqueous solution of sodium citrate (0.5 mL). The Ag-lined capillaries were filled with the mixture, capped at both ends, and left to develop at rt for an additional 30 min. After emptying the capillaries and rinsing them with acetone, they were calcinated at 500°C (3 × 1min) before use in MACOS.

Tollen's reagent was prepared as follows: 2.0 mL of 4M NaOH was added drop-wise to 20 mL of a 3% $AgNO_3$ solution, forming a gray precipitate that was titrated with a 4M solution of $NH_4OH$ until the solution became clear.

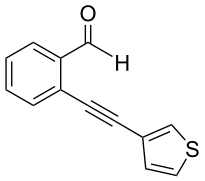
## General procedure for synthesis of benzaldehydes [36]



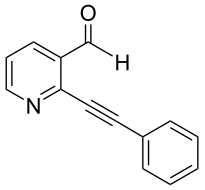

A 10 mL round-bottom flask was charged with $Pd(PPh_3)_4$ (0.0375 mmol), CuI (0.075 mmol), and purged with argon. To it were added consecutively: THF (6 mL), $Et_3N$ (1.5 mmol), the aryl bromide (0.75 mmol), and the alkyne (0.9 mmol). The solution was then heated to 70 °C and stirred for 6–13 h (until the reaction was judged complete by tlc analysis). At the end of the reaction, the mixture was diluted with $H_2O$ (10 mL) and extracted with ethyl acetate (3×). The combined organic layers were dried over anhydrous $Na_2SO_4$, concentrated, the residue dry loaded onto silica gel and purified by column chromatography.



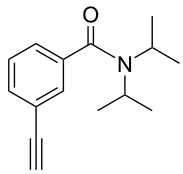

**2-(2-Phenylethynyl)benzaldehyde** (**1a**). Following the general procedure for the synthesis of benzaldehydes, column chromatography (10% diethyl ether in pentane) provided 141 mg of product as a pale-brown oil (91%, yield). $^1$H NMR (300 MHz, $CDCl_3$): δ 10.67 (s, 1H), 7.96 (d, *J* = 7.8 Hz, 1H), 7.63 (t, *J* = 4.5 Hz, 1H), 7.57 (m, 3H), 7.44 (t, *J* = 7.2 Hz, 1H), 7.41–7.37 (m, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 191.6, 135.8, 133.8, 133.2, 131.7, 129.1, 128.6, 128.5, 127.3, 126.9, 122.4, 96.4, 85.0. Spectra matched that found in the literature [37].



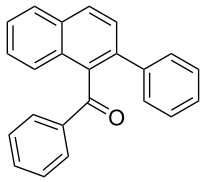

**2-[2-(Thiophen-3-yl)ethynyl]benzaldehyde** (**1d**). Following the general procedure for the synthesis of benzaldehydes, column chromatography (10% diethyl ether in pentane) provided 142 mg of the product as a pale-yellow oil (89%, yield). $^1$H NMR (300 MHz, $CDCl_3$): δ 10.63 (s, 1H), 7.95 (d, *J* = 8.1 Hz, 1H), 7.66–7.51 (m, 3H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.34 (dd, *J* = 5.1, 3.0 Hz, 1H), 7.23 (dd, *J* = 5.1, 1.2 Hz, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 191.7, 135.8, 133.8, 133.1, 129.7 (two carbons overlap), 128.5, 127.3, 126.9, 125.8, 121.4, 91.5, 84.6. HRMS Calcd. for $C_{13}H_8OS$: 212.0296; found: 212.0302: Anal. Calcd. for $C_{13}H_8OS$: C, 73.56; H, 3.80; found C, 73.82; H, 3.57.



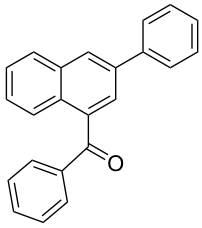

**2-(2-Phenylethynyl)nicotinaldehyde** (**1f**). Following the general procedure for the synthesis of benzaldehydes, column chromatography (30% diethyl ether in pentane) provided 145 mg of product as a dark-yellow solid (93%, yield). Mp = 91–92 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 10.70 (s, 1H), 8.85 (d, *J* = 3.6 Hz, 1H), 8.24 (d, *J* = 7.6 Hz, 1H), 7.67 (d, *J* = 6.8 Hz, 2H), 7.55–7.30 (m, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 190.8, 154.5, 146.1, 134.9, 132.2, 131.8, 129.9, 128.6, 123.2, 121.2, 96.1, 84.6. HRMS Calcd. for $C_{14}H_9NO$ 207.0684; found 207.0685. Anal. Calcd. for $C_{14}H_9NO$: C, 81.14; H, 4.38; found C, 81.43; H, 4.60. Spectra matched that found in the literature [38].



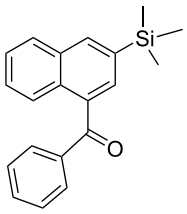
**3-Ethynyl-*N*,*N*-diisopropylbenzamide** (**2j**). A 25 mL round-bottom flask was purged with argon, cooled to 0 °C, and 2.4 mL of dry THF and 157 μL (1.8 mmol) of oxalyl chloride were added. After 20 min., a cooled (0 °C) solution of 3-ethynyl-benzoic acid (1.71 mmol, 250 mg) in 6 mL of dry THF was added over 10 min. When the addition of acid was complete, 3 drops of DMF were added to the mixture and bubbling was observed. After stirring for 30 min. at 0 °C, the solution was stirred an additional 30 min. at rt, and then cooled back to 0 °C. Into a separate 25 mL round-bottom flask at 0 °C were added: $(iPr)_2NH$ (1.8 mmol, 260 μL), $Et_3N$ (1.8 mmol, 250 μL), and 2 mL of dry THF. The contents of the original flask were then added to this flask where upon fuming was observed and a yellow precipitate began to form. The reaction was warmed to rt, stirred for 16 h, and quenched by the addition of 10 mL of water. After stirring for 10 min., the contents were then transferred to a separatory funnel and ethyl acetate was added. The separated organic layer was washed with sat $NaHCO_3$ and the aqueous layer was back-extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, and filtered. Following solvent removal *in vacuo*, the yellow solid residue was dry-loaded onto silica gel and purified by column chromatography using a gradient elution (5% ethyl acetate in pentane to 15% ethyl acetate in pentane, $R_f = 0.5$) to give 390 mg product as a white solid (99% yield). Mp = 107–108 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J* = 7.6 Hz, 1H), 7.43 (s, 1H), 7.36 (t, *J* = 8.4 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 1H), 7.32 (d, 2H), 3,09 (s, 1H), 1.33 (d, 12H). $^{13}$C NMR (150 MHz, $CDCl_3$, 10 °C): δ 169.8, 139.0, 132.2, 129.1, 128.6, 125.9, 122.4, 82.9, 77.9, 51.0, 45.9, 20.7, 20.6. HRMS Calcd. for $C_{15}H_{19}NO$: 229.1467; found: 229.1466. Anal. Calcd. for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; found C, 78.61; H, 8.71.



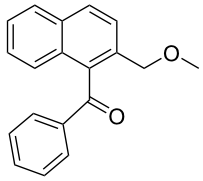
**Phenyl-(2-phenylnaphthalen-1-yl)-methanone** (**3a**). Following the general MACOS benzannulation protocol, 2-(2-phenylethynyl)-benzaldehyde (**1a**) and phenylacetylene were reacted and 700 μL of the crude reaction mixture were collected. Purification by flash chromatography (15% ethyl acetate in hexane) afforded 62 mg of **3a** and 20 mg of **4a** as yellow oils (78% combined yield, minor isomer reported below). $^1$H NMR (400 MHz, $CDCl_3$): δ 8.2 (d, *J* = 8.2 Hz, 1H), 7.95 (d, *J* = 8.3 Hz, 1H), 7.78 (d, *J* = 8.1 Hz, 1H), 7.65 (m, 2H), 7.58 (d, *J* = 8.3 Hz, 1H), 7.35–7.52 (m, 5H), 7.15–7.30 (m, 5H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 199.8, 140.4, 137.9, 137.6, 137.2, 133.4, 132.5, 130.5, 129.5, 129.4, 129.3, 128.3, 128.1, 128.0, 127.6, 127.2, 127.0, 126.4, 125.5. Spectra matched that found in the literature [39].



**Phenyl-(3-phenylnaphthalen-1-yl)-methanone** (**4a**). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 1.1 Hz, 1H), 7.98 (d, *J* = 8.2 Hz, 1H), 7. 90 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 1.1 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.50 (tt, *J* = 7.4, 1.0 Hz, 1H), 7.37–7.47 (m, 6H), 7.30 (tt, *J* = 7.4, 1.0 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 197.7, 139.9, 138.2, 137.2, 137.0, 134.2, 133.4, 130.5, 130.1, 129.0, 128.8, 128.6, 128.3, 127.8, 127.2, 127.0, 126.9, 126.7, 125.7. Spectra matched that found in the literature [40].

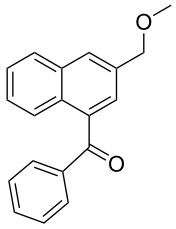


**Phenyl-(3-trimethylsilanyl-naphthalen-1-yl)-methanone** (**4b**). Following the general MACOS benzannulation protocol, 2-(2-phenylethynyl)-benzaldehyde (**1a**) and TMS-acetylene were reacted and 740 μL of the crude reaction mixture were collected. Purification by flash chromatography (15% ethyl acetate in hexane) afforded 68.9 mg of **4b** as a white solid (62% yield). Mp = 86–87 °C (lit. [34]: 88 °C). $^1$H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, *J* = 1.1 Hz, 1H), 8.05 (d, *J* = 8.2 Hz, 1H), 7.85–7.95 (m, 3H), 7.68 (d, *J* = 1.1Hz, 1H), 7.45–7.60 (m, 5H), 0.35 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 198.5, 138.3, 136.8, 136.5, 135.5, 133.3, 133.0, 131.6, 131.1, 130.5, 128.5, 128.3, 127.4, 126.4, 125.6, −1.20. Spectra matched that found in the literature [34].

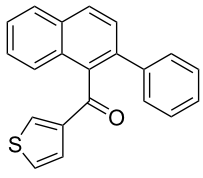


**[2-(Methoxymethyl)naphthalen-1-yl]-phenylmethanone** (**3c**). Following the general MACOS benzannulation protocol, 2-(2-phenylethynyl)-benzaldehyde (**1a**) and methyl propargyl ether were reacted and 815 μL of the crude reaction mixture were collected. Purification by flash chromatography (15% ethyl acetate in pentane) afforded 58.0 mg of **3c** and **4c** isomers as colourless oils (52% combined yield, 58:42, respectively).

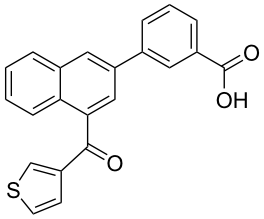
(**3c**) $^1$H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, *J* = 8.1 Hz, 1H), 7.92 (d, *J* = 8.1 Hz, 1H), 7.84 (d, *J* = 8.1Hz, 2H), 7.53–7.66 (m, 3H), 7.37–7.52 (m, 4H), 4.50 (s, 2H), 3.23 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 199.2, 137.8, 135.7, 133.7, 133.3, 132.8, 130.4, 129.6, 129.4, 128.7, 128.2, 126.8, 126.2, 125.5, 125.4, 72.1, 58.3. Anal. Calcd. for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84; found, C, 82.34, H, 5.60. HRMS calcd. for $C_{19}H_{16}O_2$: 276.1150; found 276.1154.



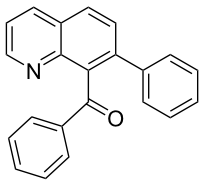
**[3-(Methoxymethyl)naphthalen-1-yl]-phenylmethanone** (**4c**). $^1$H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, *J* = 8.1Hz, 1H), 7.98 (d, *J* = 1.1 Hz, 1H), 7.93 (d, *J* = 8.1 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 2H), 7.10 (t, *J* = 7.1 Hz, 1H), 7.58 (d, *J* = 1.1 Hz, 1H), 7.45–7.56 (m, 4H), 4.66 (s, 2H), 3.46 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 197.9, 138.2, 136.7, 134.4, 133.7, 133.3, 130.5, 130.4, 129.4, 128.5, 128.3, 127.3, 127.1, 126.7, 125.6, 74.2, 58.3. Anal. Calcd. for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84; found C, 82.39; H, 5.62. HRMS calcd. for $C_{19}H_{16}O_2$: 276.1150; found 276.1153.



**[2-(Phenyl)naphthalen-1-yl](thiophen-3-yl)-methanone** (**3d**). Following the general MACOS benzannulation protocol, 2-(2-(thiophen-3-yl)-ethynyl)-benzaldehyde (**1d**) and phenylacetylene were reacted and 650 μL of the crude reaction mixture were collected. Purification by flash chromatography (15% ethyl acetate in hexane) afforded 63.7 mg of **3d** as a pale-yellow oil (62% yield). $^1$H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, *J* = 8.1 Hz, 1H), 7.96 (d, *J* = 8.1 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.61 (d, *J* = 8.1 Hz, 1H), 7.48–7.58 (m, 3H), 7.38–7.47 (m, 3H), 7.21–7.34 (m, 3H), 7.12–7.15 (m, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 198.6, 143.5, 140.3, 137.1, 136.4, 135.3, 132.4, 130.4, 129.6, 129.4, 128.3, 128.1, 127.6, 127.5, 127.3, 127.2, 126.4, 126.2, 125.5. Anal. Calcd. for $C_{21}H_{14}OS$: C, 80.22; H, 4.49; found C, 79.79; H, 4.13. HRMS calcd. for $C_{21}H_{14}OS$: 314.0765; found 314.0759.

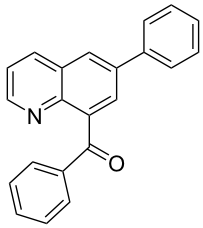


**3-[4-(Thiophene-3-carbonyl)naphthalen-2-yl]-benzoic acid** (**4e**). Following the general MACOS benzannulation protocol, 2-(2-(thiophen-3-yl)-ethynyl)-benzaldehyde (**1d**) and 3-ethynyl-benzoic acid were reacted and 700 μL of the crude reaction mixture were collected. Purification by flash chromatography (10% methanol in dichloromethane) afforded 75.0 mg of **4e** as a yellow oil (60% yield). $^1$H NMR (400 MHz, $CDCl_3$): δ 8.17 (s, 1H), 8.10 (d, *J* = 8.1 Hz, 1H), 7.93–8.00 (m, 2H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.48–7.63 (m, 4H), 7.33–7.43 (m, 2H), 7.15 (s, 1H). $^{13}$C NMR (150 MHz, $CDCl_3$): δ 192.7, 171.3, 143.4, 140.6, 136.7, 135.7, 135.3, 134.6, 132.6, 130.8, 130.3, 129.7, 129.4, 129.1, 128.4, 128.1, 127.3, 127.2, 127.0, 126.6, 126.4, 125.5. HRMS calcd. for $C_{22}H_{14}O_3S$: 358.0664; found 358.0666.

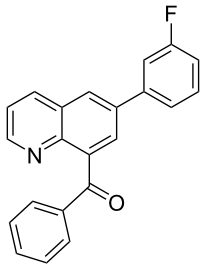


**Phenyl-(7-phenylquinolin-8-yl)-methanone** (**3f**). Following the general MACOS benzannulation protocol, 2-(2-phenylethynyl)-nicotinaldehyde (**1f**) and phenyl acetylene were reacted and 780 μL of the crude reaction mixture were collected. Purification by flash chromatography (20% ethyl acetate in pentane) afforded 77.8 mg of **3f** and **4f** isomers as pale-yellow oils (64% combined yield). (**3f**) $^1$H NMR (400

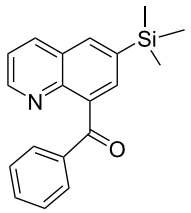
MHz, $CDCl_3$): δ 8.88 (dd, *J* = 4.1, 1.5 Hz, 1H), 8.25 (d, *J* = 8.1 Hz, 1H), 8.01 (d, *J* = 8.1 Hz, 1H), 7.66–7.73 (m, 3H), 7.40–7.47 (m, 4H), 7.20–7.33 (m, 5H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 198.8, 151.1, 146.6, 140.5, 139.3, 137.9, 137.4, 135.7, 133.0, 129.6, 129.3, 128.7, 128.6, 128.3, 128.2, 127.7, 127.0, 121.4. HRMS calcd. for $C_{22}H_{15}NO$: 309.1154; found 309.1145.



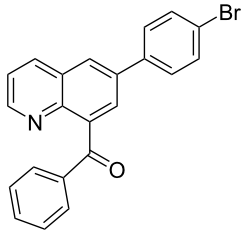

**Phenyl-(6-phenylquinolin-8-yl)-methanone** (**4f**). $^1$H NMR (400 MHz, $CDCl_3$): δ 8.86 (dd, *J* = 4.1, 1.5 Hz, 1H), 8.29 (dd, *J* = 8.1, 1.5 Hz, 1H), 8.16 (d, *J* = 2.0 Hz, 1H), 8.03 (d, *J* = 2.0 Hz, 1H), 7.92 (dd, *J* = 8.1, 1.5 Hz, 2H), 7.75 (dd, *J* = 8.1, 1.5 Hz, 2H), 7.59 (t, *J* = 7.1 Hz, 1H), 7.49–7.56 (m, 2H), 7.40–7.49 (m, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 197.7, 150.8, 145.6, 139.8, 139.5, 138.7, 137.7, 136.2, 133.3, 130.3, 129.1, 128.5, 128.3, 128.1, 127.9, 127.5, 127.1, 122.0. Anal. Calcd. for $C_{22}H_{15}NO$: C, 85.40; N, 4.53; H, 4.89; found C, 84.98; N, 4.32; H, 4.62. HRMS calcd. for $C_{22}H_{15}NO$: 309.1154; found 309.1143.



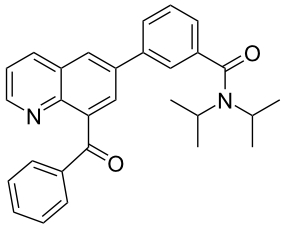

**[6-(3-Fluorophenyl)quinolin-8-yl](phenyl)methanone** (**4g**). Following the general MACOS benzannulation protocol, 2-(2-phenylethynyl)-nicotinaldehyde (**1f**) and 1-ethynyl-3-fluorobenzene were reacted and 750 μL of the crude reaction mixture were collected. Purification by flash chromatography (25% ethyl acetate in pentane) afforded 63.8 mg of **4g** as a colourless oil (54% yield). $^1$H NMR (400 MHz, $CDCl_3$): δ 8.87 (dd, *J* = 4.0, 1.5 Hz, 1H), 8.29 (dd, *J* = 8.1, 1.5 Hz, 1H), 8.15 (d, *J* = 2.0 Hz, 1H), 7.99 (d, *J* = 2.0 Hz, 1H), 7.90 (dd, *J* = 8.1, 1.5 Hz, 2H), 7.60 (t, *J* = 7.1 Hz, 1H), 7.40–7.56 (m, 6H), 7.10–7.17 (m, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 197.6, 163.3 ($^1J^{13}$C-$^{19}$F = 245.0 Hz), 151.1, 145.7, 141.8, 141.7, 140.1, 137.6, 137.5, 136.2, 133.4, 130.6 ($^3J^{13}$C-$^{19}$F = 8.5 Hz), 130.2, 128.4, 127.5, 127.3, 123.1, 122.1, 114.9 ($^2J^{13}$C-$^{19}$F = 22.0 Hz), 114.4 ($^2J^{13}$C-$^{19}$F = 23.0 Hz). Anal. Calcd. for $C_{22}H_{14}FNO$: C, 80.72; N, 4.28; H, 4.31; found C, 80.77; N, 4.56; H, 4.09. HRMS calcd. for $C_{22}H_{14}FNO$: 327.1059; found 327.1046.




**Phenyl-[6-(trimethylsilyl)quinolin-8-yl]methanone** (**4h**). Following the general MACOS benzannulation protocol, 2-(2-phenylethynyl)-nicotinaldehyde (**1f**) and TMS acetylene were reacted and 800 μL of the crude reaction mixture were collected. Purification by flash chromatography (20% ethyl acetate in pentane) afforded 70.0 mg of **4h** as a pale-brown oil (58% yield). $^1$H NMR (400 MHz, $CDCl_3$): δ 8.82 (dd, *J* = 4.1, 1.5 Hz, 1H), 8.21 (dd, *J* = 8.1, 1.5 Hz, 1H), 8.11 (d, *J* = 1.6 Hz, 1H), 7.84–7.87 (m, 3H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.38–7.44 (m, 3H), 0.38 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 198.5, 151.0, 146.4, 138.9, 138.3, 137.9, 136.0, 135.5, 133.2, 132.1, 130.2, 128.3, 127.5, 121.7, 0.87. Anal. Calcd. for $C_{19}H_{19}NOSi$: C, 74.71; N, 4.59; H, 6.27; found C, 74.93; N, 4.62; H, 6.07. HRMS calcd. for $C_{19}H_{19}NOSi$: 305.1236; found 305.1232.




**[6-(4-Bromophenyl)quinolin-8-yl]-phenylmethanone** (**4i**). Following the general MACOS benzannulation protocol, 2-(2-phenylethynyl)-nicotinaldehyde (**1f**) and 1-bromo-4-ethynylbenzene were reacted and 700 μL of the crude reaction mixture were collected. Purification by flash chromatography (20% ethyl acetate in pentane) afforded 70.0 mg of **4i** as a colourless oil (52% yield). $^1$H NMR (400 MHz, $CD_2Cl_2$): δ 8.83 (dd, *J* = 4.1, 1.5 Hz, 1H), 8.35 (dd, *J* = 8.1, 1.5 Hz, 1H), 8.21 (d, *J* = 2.0 Hz, 1H), 8.00 (d, *J* = 2.0 Hz, 1H), 7.85 (dd, *J* = 8.1, 1.5 Hz, 2H), 7.60–7.76 (m, 4H), 7.44–7.56 (m, 3H), 7.34 (q, *J* = 9.0 Hz, 1H). $^{13}$C NMR (150 MHz, $CD_2Cl_2$): δ 197.3, 150.7, 145.4, 140.0, 138.5, 137.8, 137.5, 136.2, 133.2, 132.1, 129.8, 128.9, 128.4, 128.3, 127.2, 126.9, 122.3, 122.1. HRMS calcd. for $C_{22}H_{14}BrNO$ $[M+H]^+$: 388.0337; found 388.0337.



**3-(8-benzoylquinolin-6-yl)-*N,N*-diisopropylbenzamide** (**4j**). Following the general MACOS benzannulation protocol, 2-(2-phenylethynyl)-nicotinaldehyde (**1f**) and 3-ethynyl-N,N-diisopropylbenzamide were reacted and 840 μL of the crude reaction mixture were collected. Purification by flash chromatography (30% ethyl acetate in pentane) afforded 72.0 mg of **4j** as a colourless oil (40% yield). $^1$H NMR (600 MHz, $CD_2Cl_2$): δ 8.81 (dd, *J* = 3.8, 1.6 Hz, 1H), 8.35 (dd, *J* = 8.1, 1.6 Hz, 1H), 8.25 (d, *J* = 2.1 Hz, 1H), 8.03 (d, *J* = 2.1 Hz, 1H), 7.84 (dd, *J* = 8.1, 1.6 Hz, 2H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.70 (s, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.44–7.52 (m, 3H), 7.35 (d, *J* = 8.1 Hz, 1H), 3.90 (br s, 1H), 3.54 (br s, 1H), 1.55 (s, 6H), 1.16 (s, 6H). $^{13}$C NMR (150 MHz, $CD_2Cl_2$ 10 °C): δ 197.6, 170.2, 150.7, 145.5, 140.2, 140.0, 139.9, 138.1, 137.8, 136.3, 133.3, 129.9, 129.2, 128.5, 128.4, 127.5, 127.4, 127.2, 124.9, 124.6, 122.2, 51.0, 45.7, 20.4. HRMS calcd. for $C_{29}H_{28}N_2O_2$: 436.2151; found 436.2147.

## Supporting Information

Spectra for compounds made in this manuscript are available as supporting information.

### Supporting Information File 1

NMR spectra of compounds **1d**, **2j**, **3c**, **3d**, **3f**, **4c** and **4e**–**j**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-5-35-S1.pdf]

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# Acid-mediated reactions under microfluidic conditions: A new strategy for practical synthesis of biofunctional natural products

Katsunori Tanaka and Koichi Fukase*

Review

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Address:
Department of Chemistry, Graduate School of Science, Osaka University, 1-1 Machikaneyama, Toyonaka, Osaka, 560-0043, Japan

Email:
Koichi Fukase* - koichi@chem.sci.osaka-u.ac.jp

* Corresponding author

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## Abstract

Microfluidic conditions were applied to acid-mediated reactions, namely, glycosylation, reductive opening of the benzylidene acetal groups, and dehydration, which are the keys to the practical synthesis of *N*-glycans and the immunostimulating natural product, pristane. A distinctly different reactivity from that in conventional batch stirring was found; the vigorous micromixing of the reactants with the concentrated acids is critical especially for the "fast" reactions to be successful. Such a common feature might be due to the integration of all favorable aspects of microfluidic conditions, i.e., efficient mixing, precise temperature control, and the easy handling of the reactive intermediate by controlling the residence time. The microfluidic reactions cited in this review indicate the need to reinvestigate the traditional or imaginary reactions which have so far been performed and evaluated only in batch apparatus, and therefore they could be recognized as a new strategy in synthesizing natural products of prominent biological activity in a "practical" and a "industrial" manner.

## Introduction

A continuous flow microreactor, an innovative technology, has been used to realize efficient mixing and fast heat transfer in organic syntheses [1-26]. The flow system allows the reaction to be quenched immediately after the formation of the unstable products. Furthermore, once the reaction conditions are optimized for a small-scale operation, the same conditions are directly applicable to large-scale synthesis under the flow process. We have been applying these advantageous features of the microfluidic systems to the "key" but "problematic" acid-mediated reactions under the conventional batch apparatus, in practically preparing bioactive natural products [27-33]. Our successful examples are cation-mediated reactions, such as α-sialylation [28,32], β-mannosylation [31], and reductive opening of the benzylidene acetal groups in sugars [30], for which improved procedure under the microfluidic conditions enabled the preparation of key synthetic intermediates for oligosaccharides on a

multi-gram scale, eventually leading to a total synthesis of the asparagine-linked oligosaccharide (*N*-glycan) [32]. A significant improvement has also been achieved for dehydration, which resulted in the industrial scale-synthesis of the immunostimulating natural terpenoid, pristane, of about 500–1000 kg in a year [29]. In this account, we review these acid-mediated reactions and discuss the new aspects of using microfluidic systems for controlling the hitherto difficult reactions in conventional organic synthesis; microfluidic reactions can offer a direct and practical route to the desired compounds without the usual scale-up problems associated with mixing efficiency and the temperature control. They can therefore be regarded as one of the new strategies for the practical synthesis, or in favorable cases, the industrial synthesis of the bioactive natural products.

## Review

### 1. Application of microfluidic systems to the synthesis of asparagine-linked oligosaccharides

Among the various types of oligosaccharide structures, asparagine-linked oligosaccharides (*N*-glycans) are prominent in terms of diversity and complexity [34]. It is becoming clear that they are involved in a variety of important physiological events, such as cell-cell recognition, adhesion, signal transduction, quality control, and circulatory residence of proteins [35-38]. However, isolating large quantities of structurally pure *N*-glycans from natural sources is difficult. Thus, chemical synthesis provides an attractive opportunity to evaluate their biological functions. Although a number of new chemical and/or combined methods employing biological technology have actively been investigated [39,40], an efficient approach to these complex oligosaccharides has yet to be established in terms of (i) selectivity in the glycosyl bond formations, i.e., β-mannosylation and α-sialylation, and (ii) a non-tedious purification process during each step of glycosylation and deprotection. Our interests in elucidating unknown biological functions of mammalian *N*-glycans of the diverse structures, have motivated us to establish a practical and library-directed synthesis of the complex-type *N*-glycans on solid-support [32]; the initial target of our strategy is a sialic acid-containing *N*-glycan with asymmetric branching chains (Figure 1), which is difficult to obtain from natural sources. To prepare the target *N*-glycan as well as other diverse structures of this family in an efficient manner, we designed fragments **a**–**d** with *N*-phenyltrifluoroacetimidate as the leaving group, which can be efficiently glycosylated on solid-support to construct the *N*-glycan structures. Herein, two challenging glycosyl bond formations, i.e., β-mannosylation and α-sialylation, were carried out in advance in solution, by the aid of the microfluidic systems (Figure 1) [28,31,32]. The problem of the key protecting group manipulation, i.e., the reductive opening of benzylidene acetal group, for the large-scale preparation of the fragment **b** [30] could also be circumvented under

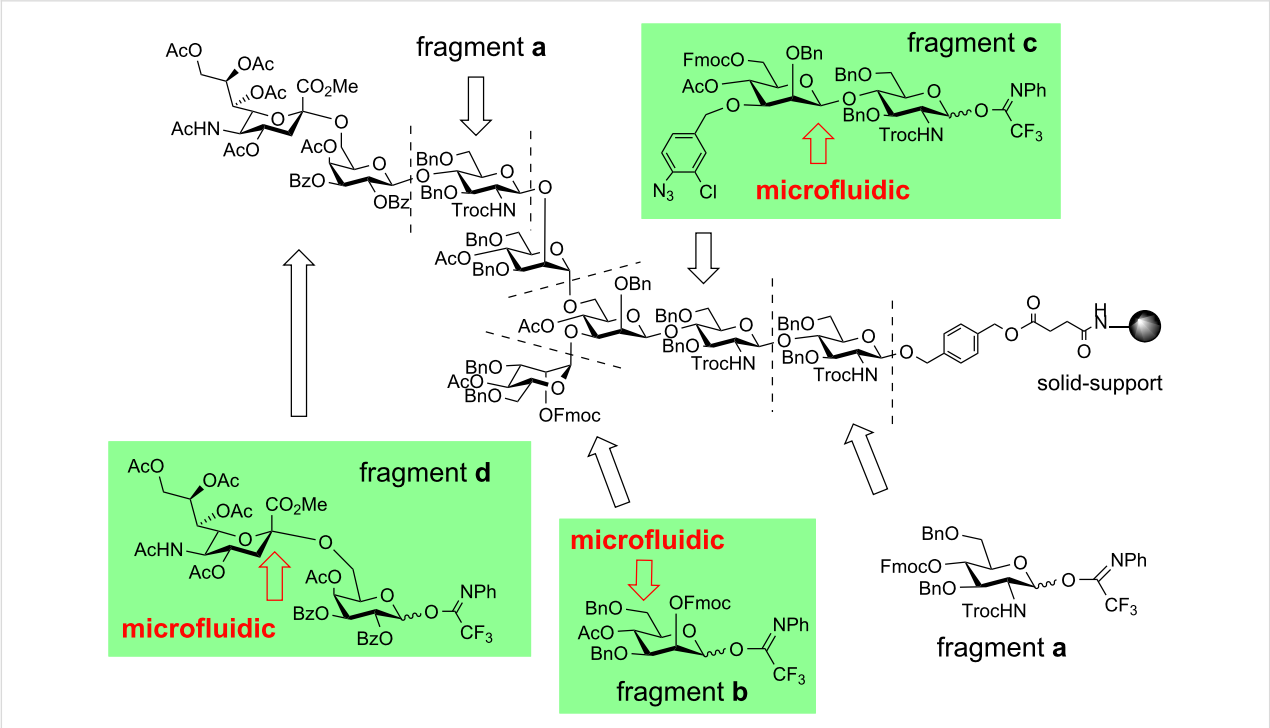



**Figure 1:** Synthetic strategy for asparagine-linked oligosaccharide on solid support and application of microfluidic systems to fragment synthesis.

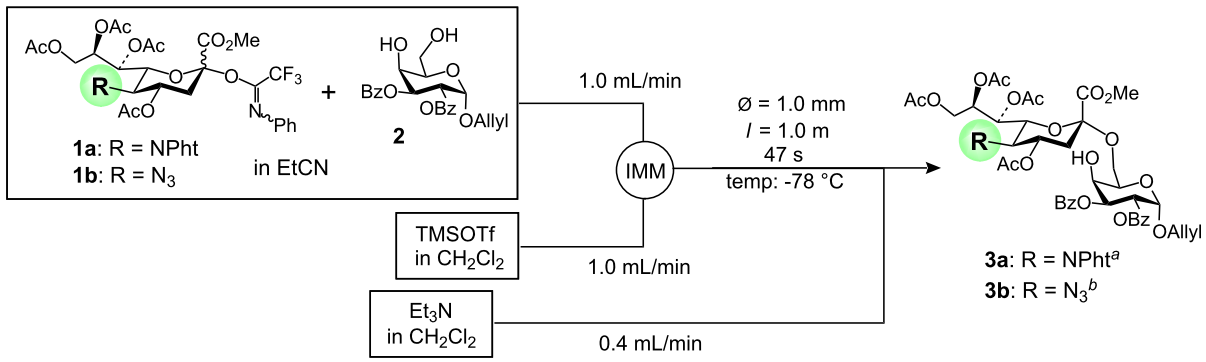
the microfluidic conditions, as will be discussed in the following sections.

## Microfluidic α-sialylation

We have previously developed an efficient α-sialylation by utilizing the highly reactive sialyl donors having C-5 cyclic imides (Table 1), especially *N*-phthalimide **1a**, by virtue of the "fixed-dipole moment effects" (α-only, 92% on 50 mg scale) [41]. The scale-up in a batch process, however, significantly decreased the yield and selectivity. Thus, a 100 mg scale reaction of **1a** gave only 60% of α-sialoside accompanied by a significant amount of a glycal by-product. The decrease in sialylation efficiency might be due to the high reactivity of the donor **1a**. For such a case, precise reaction control is very difficult under the conventional batch process conditions, especially when the reaction is scaled-up. Thus, the disorder of the reaction factors in the scaled-up batch reaction, i.e., (i) precise temperature control, (ii) mixing efficiency between acceptor, donor, and Lewis acid, and (iii) reaction time, might lead to the glycal production. In order to circumvent these problems, we used a continuous flow microreactor. An application of the microfluidic system to the glycosylation reaction was first reported by Seeberger and co-workers on α-mannosylation [18]. We also have established an efficient microfluidic glycosylation in combination with the affinity separation method [27].

For the present microfluidic sialylation, a propionitrile solution of sialyl donor **1a** and acceptor **2** with various concentrations was mixed with TMSOTf solution in dichloromethane at −78 °C using an IMM micromixer [42] with a channel width of 40 μm at a flow rate of 1.0 mL/min (Table 1). After the reaction mixture was allowed to flow at −78 °C for an additional 47 seconds through a reactor tube (Ø = 1.0 mm, *l* = 1.0 m), the mixture was quenched by another flow of excess triethylamine dissolved in dichloromethane by using a T-shaped mixer at −78 °C. When the concentrations of the donor **1a**, acceptor **2**, and TMSOTf were adjusted to 0.15 M, 0.1 M, and 0.08 M, respectively, disaccharide **3a** was obtained in only 14% yield and a large amount of the acceptor **2** was recovered (entry 1). However, we were pleased to find that the yield of **3a** dramatically increased (88%) when the concentration of the Lewis acid was increased to 0.15 M (entry 2). Finally, the desired α-sialoside **3a** was obtained in quantitative yield by increasing the concentration of the donor **1a** to 0.2 M (entry 3). Thus, the microfluidic reaction successfully controlled the high reactivity of the sialyl donor **1a** for α-sialylation. Obviously, vigorous and rapid mixing of the substrates with the high concentrations of the acid is responsible for the success of the microfluidic sialylation; the trend is completely different from that of the corresponding batch reaction, since the decomposition of the donor has long been regarded as a severe problem under such drastic conditions [41]. The use of excess amounts of donor **1a** and/or TMSOTf in batch reaction did not improve the sialylation yield, but rather resulted in a large amount of glycal production. Apparently, the efficient micromixing between substrates and the high concentration of the acid should accelerate the reaction, while the rapid heat transfer prevented the undesired hydrolysis and glycal formation. The "flow system"

**Table 1:** Optimization of α(2-6)-sialylation using IMM micromixer.




| Entry | Donor **1a**,**b** (M) | Acceptor **2** (M) | TMSOTf (M) | Yield of **3a**,**b** (%) | α : β[d] |
|---|---|---|---|---|---|
| 1 | 0.15 (**1a**) | 0.1 | 0.08 | 14[c] | α only |
| 2 | 0.15 (**1a**) | 0.1 | 0.15 | 88 | α only |
| 3 | 0.2 (**1a**) | 0.1 | 0.15 | >99 | α only |
| 4 | 0.2 (**1b**) | 0.1 | 0.15 | >99 | 20 : 1 |

[a]Batch results: 92%, α-only on 50 mg scale; 60%, α : β = 97 : 3 on 100 mg scale. [b]Batch results: 90%, α : β = 9 : 1 on 100 mg scale. [c]Mainly, glycal derived from **1a** and acceptor **2** were recovered by TLC analysis. [d]Based on $^1$H NMR analysis.

also enabled the residence time to be controlled before the decomposition of sialoside **3a** under the strongly acidic conditions. This new aspect under microfluidic conditions was found to be general to the acid-mediated reactions, and similar results can be seen in the following sections.

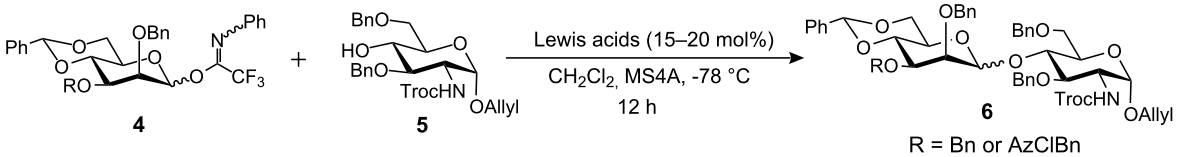
Unfortunately, the selective deprotection of the *N*-phthalyl group in the presence of the C-1 methoxycarbonyl in **3a** was troublesome on the 1–2 g reaction scale. As an alternative to the *N*-phthalyl function, we also employed the C-5 azide group in sialyl donor **1b** because this azide group should direct similar "fixed-dipole moment effects", but should be easier to convert to naturally occurring *N*-substituents of neuraminic acids, i.e., *N*-acetyl or *N*-glycolyl groups (see structure in Figure 1) [32]. As anticipated, sialylation between **1b** and galactosyl acceptor **2** in the presence of TMSOTf as an activator and 4Å molecular sieves in propionitrile provided **3b** in 90% yield with good α-selectivity (α : β = 9 : 1 on 100 mg scale). Furthermore, applying the continuous microfluidic sialylation, which was established for the *N*-phthalyl derivative **1a** (Table 1, entry 3), improved both the yield and α-selectivity (entry 4): **3b** was obtained quantitatively with near perfect α-selectivity (α : β = 20 : 1). The α and β stereoisomers were easily separated by chromatography on silica-gel, and the pure α-isomer was readily converted to the desired imidate fragment **d** (Figure 1) using the general procedure. Hence, we successfully prepared fragments **d** on the 5–10 g scale [32].

## Microfluidic β-mannosylation

Stereoselective formation of the β-mannoside linkage, a key glycosylation in the synthesis of the βMan(1→4)GlcNTroc fragment **c** of *N*-linked glycans, is another challenging topic in oligosaccharide synthesis. Various methods, such as intramolecular aglycon delivery (IAD) or glycosylation with 4,6-*O*-benzylideneacetal-protected α-mannosyltriflates, have recently been reported and successfully applied to β-mannoside synthesis [31,39,40,43-45]. We also have achieved excellent β-selectivity in the reaction of 4,6-*O*-benzylidenemannopyranosyl-*N*-phenyltrifluoroacetimidate (**4**) with *N*-Troc-glucosamine acceptor **5** (R = Bn, 93% yield, β : α = 95 : 5 on 20 mg scale) using the bulky and dual Lewis acid/cation trap reagent, $TMSB(C_6F_5)_4$ (Table 2, entry 1) [46,47].

Nevertheless, it is difficult to apply our β-mannosylation protocol to a few gram-scale synthesis of the βMan(1→4)GlcNTroc fragment **c** because the scaled-up glycosylation requires a large quantity of the bulky $TMSB(C_6F_5)_4$ activator, which has limited commercial availability [46,47]. Therefore, from a practical viewpoint for preparing the fragment **c** as a starting material, we refocused on applying the more common TMSOTf as a glycosyl activator because our earlier experiments indicated that TMSOTf shows a good yield and β-selectivity on a 20 mg scale (90% yield, β : α = 93 : 7) (entry 2) [46]. However, the efficiency of glycosylation catalyzed by TMSOTf is extremely sensitive to the reaction scale as well as the addition speed of the Lewis acid (entries 2–5). When TMSOTf was added dropwise to a solution of mannosyl donor **4** and acceptor **5** at −78 °C, the yield of β-mannoside **6** gradually decreased as the reaction scale increased (entries 2–4). On a 50 mg scale, 63% of β-disaccharide **6** was isolated, whereas only 27% of β-isomer **6** was obtained on a 500 mg scale (entries 3 and 4). For an unknown reason, slow addition of a Lewis acid in the larger scale reactions inhibited the glycosylation process at an earlier stage [31]. Moreover, even the subsequent addition of the TMSOTf catalyst did not activate the glycosylation between the remaining starting materials. These results cannot be clearly explained based on presently available data. On the other hand, when the acid was added to the initial solution of **4**

**Table 2:** β-Mannosylation under batch conditions.




| Entry[a] | Lewis acids | Addition of LA | scale (mg) | Yield (%)[b] | β : α[c] |
|---|---|---|---|---|---|
| 1 | $TMSB(C_6F_5)_4$ | dropwise | 20 | 88 | 95 : 5 |
| 2 | TMSOTf | dropwise | 20 | 84 | 93 : 7 |
| 3 | TMSOTf | dropwise | 50 | 63[d] | NA |
| 4 | TMSOTf | dropwise | 500 | 27[d] | NA |
| 5 | TMSOTf | in one portion | 900 | 61[d] | 4.9 : 1 |

[a]Reaction is performed using 1.5 equiv of donor **4** relative to acceptor **5**. [b]Isolated yields for β-isomer. [c]Based on $^1$H NMR analysis. [d]Additionally, acceptor **5**, its silylated derivative, and decomposed products of **4** were obtained by TLC analysis.

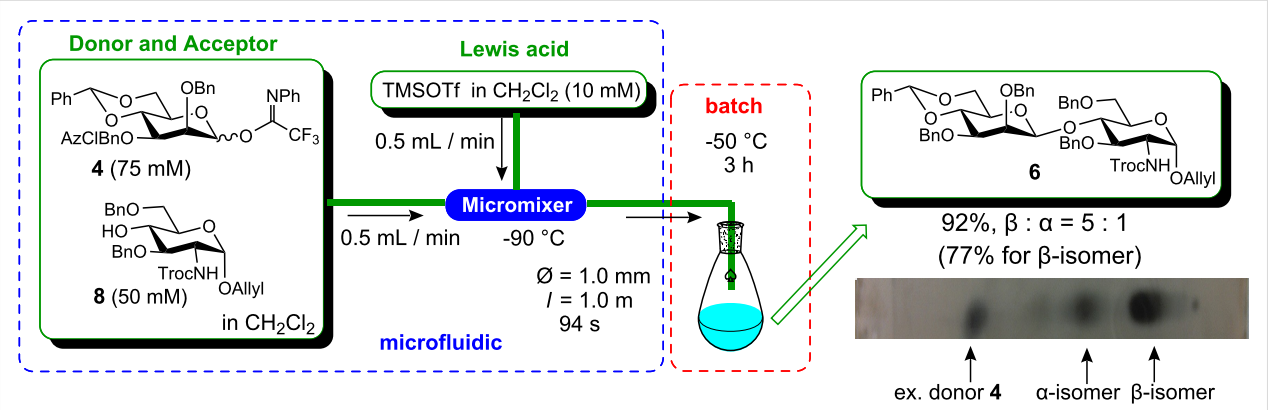



**Figure 2:** β-Mannosylation using an integrated microfluidic/batch system. Yield and β/α-ratio are analyzed by $^1$H NMR and HPLC.

and **5** in one portion, mannosylation proceeded smoothly (entry 5). However, the β-selectivity decreased to 4.9 : 1, presumably due to the exothermic nature of the reaction, i.e., heat is generated while rapidly mixing, which leads to an overall decrease in the isolated yield of β-disaccharide **6** (61% on 900 mg scale). Therefore, we decided to examine the microfluidic conditions based on the observations shown in Table 2, which indicate that the success of the current glycosylation depends on the fast addition and the efficient mixing with the Lewis acid to produce the active intermediates at the low temperature, which subsequently and slowly reacted with the acceptor **5** in batch apparatus.

We initially constructed the microfluidic system shown in Figure 2, based on our previous experiences with microfluidic α-sialylation [28,32]. In addition to the aspects mentioned above, an attractive feature of the microfluidic reaction is that the reaction can be readily optimized under the flow process [18]; the optimal conditions, i.e., concentrations of the substrates, mixing speed, temperature, and residence time, are rapidly determined using a small quantity of materials. For this optimization, we have used the Comet X-01 micromixer [48] with a channel width of ca. 500 μm, where the micromixing with IMM mixer (40 μm) caused the significant solution blockage problems due to the low solubility of both the donor **4** and the acceptor **5** in dichloromethane at very low temperature of −78 to −90 °C. Rapid screening of more than 30 conditions in a combinatorial fashion led to a new reaction system where the microfluidic system is integrated with a conventional batch apparatus (Figure 2) [31]. Namely, the reaction solution resulting from efficient micromixing between the reactants at a low temperature, was subsequently inserted into the batch system, and then was conventionally stirred in a flask for a few hours to complete the reaction. Although it is theoretically possible to maintain an indefinite residence time by increasing the reactor tube length, under certain conditions, i.e., when the reaction has to proceed for more than an hour, employing an extremely long tube is impractical. The optimal conditions in the integrated microfluidic/batch apparatus as depicted in Figure 2, i.e., micromixing at −90 °C and a batch reaction at −50 °C for 3 h, provided α/β-mannoside **6** (R = Bn) in 92% yield and with a moderate β-selectivity (β : α = 5.0 : 1). Under the established conditions, mannosylation proceeds gradually in the flask, by TLC analysis. It should be noted that although the β-selectivity was somewhat lower than that observed in the small-scale batch reaction (Table 2, entry 2), the isolated β-mannoside **6** could be obtained with similar efficiency (77% for microfluidic reaction versus 84% for 20 mg scale batch reaction) [31]. Moreover, under the established conditions, the compound **6** was reproducibly obtained even in the scaled-up synthesis by simply preparing stock solutions of substrates and reagents, and then continuously pumping them into the integrated microfluidic/batch system. Thus, the reproducibility and scaled-up preparation of **6**, and hence the fragment **c**, is noteworthy from the viewpoint of preparing an important synthetic intermediate for complex *N*-glycans.

## Microfluidic reductive opening of sugar 4,6-*O*-benzylidene acetals

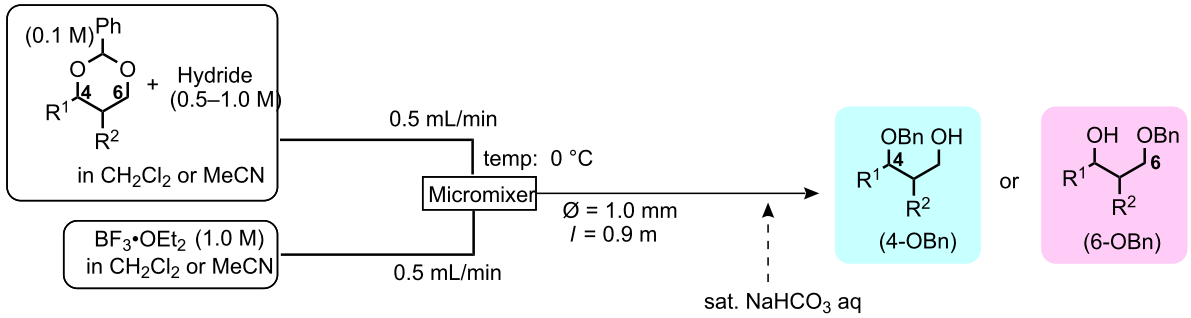
The microfluidic conditions can also be applied to an efficient procedure for the reductive opening of 4,6-*O*-benzylidene acetals [30], a key functional group manipulation toward fragment **b** for our *N*-glycan synthesis. Reductive opening of sugar 4,6-*O*-benzylidene acetals by the combination of acid/hydride reagents is one of the most useful transformations in the field of carbohydrate chemistry [49], not only for our current *N*-glycan case, since the benzyl-protected derivatives at either the C4- or C6-hydroxyl can be selectively prepared by the choice of reagent and/or solvent systems [50,51].

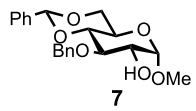
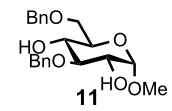
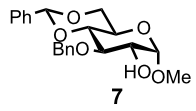
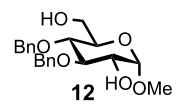
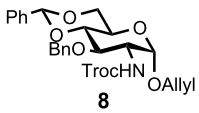
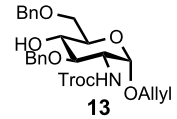
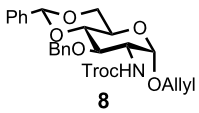
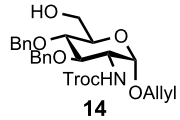
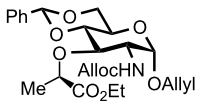
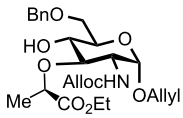
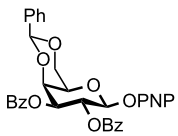
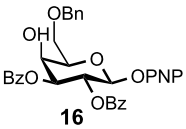
The typical procedure of the reductive opening of the acetals involves the very slow addition of the acid to a mixture of the

substrate and excess hydride reagent at 0 °C, followed by continuous stirring at room temperature for another few hours to ensure the completion of the reaction. Since the reaction is exothermic, it is important to control the addition speed of the acid in order to prevent concomitant acid-catalyzed hydrolysis of the benzylidene groups. However, the yields are not always reproducible, especially when the reaction is performed in a large scale, giving rise to the hydrolyzed by-products, 4,6-*O*-diols. The precise temperature control and the mixing efficiency between the substrate, acid, and hydride source are critical for this transformation. In order to facilitate the synthetic procedure, therefore, we used a continuous flow microreactor.

Optimal conditions for reductive opening of 4,6-*O*-benzylidene acetals by a microfluidic system, similar to the α-sialylation and the β-mannosylation protocols, were examined using the glucose 4,6-*O*-benzylidene acetal **7** (Table 3). Benzylidene acetal **7** (0.1 M) and $Et_3SiH$ (1.0 M) dissolved in $CH_2Cl_2$ were mixed with various concentrations of $BF_3{\cdot}OEt_2$ in $CH_2Cl_2$ (0.1–1.0 M) at 0 °C using a Comet X-01 micromixer [48] at the flow rate of 0.5 mL/min. After the reaction mixture was allowed to flow at room temperature for approximately 90 seconds

**Table 3:** Reductive opening of benzylidene acetals under microfluidic conditions.




| Entry | Substrate | Reducing agent | Solvent | Product | Yield (%, microfluidic)[a] | Yield (%, batch)[a,b] |
|---|---|---|---|---|---|---|
| 1 |  **7** | $Et_3SiH$ (1.0M) | $CH_2Cl_2$ |  **11** | 93[c] (6-OBn) | 58 |
| 2 |  **7** | $BH_3{\cdot}Et_2NH$ (0.5M) | $CH_2Cl_2$ |  **12** | 100 (4-OBn) | 90 |
| 3 |  **8** | $Et_3SiH$ (1.0M) | $CH_2Cl_2$ |  **13** | 91 (6-OBn) | 83 |
| 4 |  **8** | $BH_3{\cdot}Et_2NH$ (0.5M) | $CH_2Cl_2$ |  **14** | 100 (4-OBn) | 86 |
| 5 |  **9** | $BH_3{\cdot}Et_3N$ (0.5M) | MeCN |  **15** | 100 (6-OBn) | NA[d] |
| 6 |  **10** | $Et_3SiH$ (1.0M) | $CH_2Cl_2$ |  **16** | 91 (6-OBn) | 62 |

[a]Isolated yields. [b]Reaction was performed at 100–500 mg scale. [c]4-*O*-Benzyl derivative was obtained in 5% yield. [d]60–70% Yields for the case of corresponding *N*-Troc derivative. [e]PNP: *p*-nitrophenol.

through a reactor tube (Ø = 1.0 mm, *l* = 0.9 m), the mixture was quenched by saturated $NaHCO_3$ solution at 0 °C.

When 0.1 M solution of $BF_3{\cdot}OEt_2$ in $CH_2Cl_2$ was used, only a hydrolyzed compound was obtained in about 50% yield accompanied with recovery of the starting material **7**. However, the yield of 6-*O*-benzyl derivative **11** dramatically increased when the concentration of $BF_3{\cdot}OEt_2$ was increased up to 1.0 M; the desired **11** was obtained in 93% yield together with 5% of the 4-*O*-benzyl derivative **12**, and no hydrolyzed by-product was detected (Table 3, entry 1). Surprisingly, the reaction with a more concentrated $BF_3{\cdot}OEt_2$ solution ($BF_3{\cdot}OEt_2$ : $CH_2Cl_2$ = 1 : 1) also provided **11** in quantitative yield. The reaction is very rapid and **11** was obtained within a minute after mixing with the acid in the micromixer device. These results are in marked contrast to those of the batch reaction, which requires dilution of the Lewis acid and longer reaction time in order to keep the hydrolysis to a minimum. Very similar to the microfluidic α-sialylation described above, the rapid and vigorous mixing with the highly concentrated acid was critical for the acid-mediated microfluidic reaction to be successful.

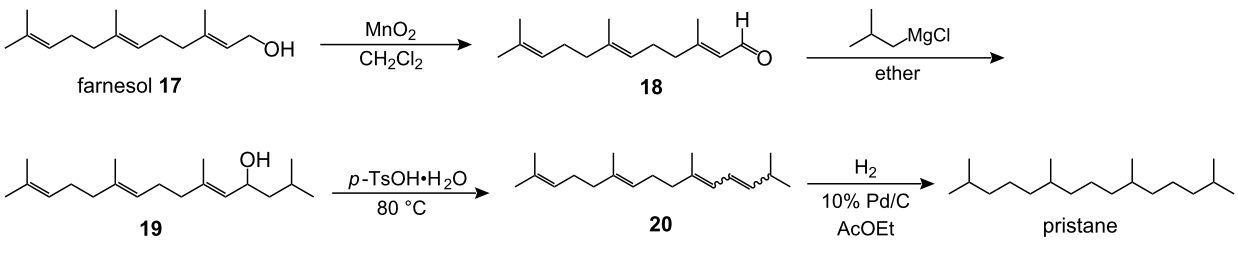
Gratifyingly, by applying the established conditions above, the glucose, glucosamine, and galactose 4,6-*O*-benzylidene acetals **7**–**10** were selectively transformed into the corresponding 4- or 6-*O*-benzyl derivatives **12**–**16** in nearly quantitative yields (entries 2–6). Thus, the treatment of **7** with $BH_3{\cdot}Et_2NH$ selectively provided 4-*O*-benzyl derivative **12** in quantitative yield (entry 2). The benzylidene group of glucosamine derivative **8** was also selectively cleaved under the microfluidic conditions by utilizing either $Et_3SiH$ or $BH_3{\cdot}Et_2NH$ as a hydride source to provide the 6- and 4-*O*-benzyl derivatives **13** and **14** in excellent yields, respectively (entries 3 and 4). The $BH_3{\cdot}Et_3N$ in MeCN system was also applicable to the microflow reduction of muramic acid derivative **9**, which contains a lactic acid ester at the C3-hydroxyl, affording 6-*O*-benzyl derivative **15** as a single isomer (entry 5). Finally, the selective reduction of galactose derivative **10** gave the 6-*O*-benzyl derivative **16** in 91% yield (entry 6). It is worthwhile mentioning that the established microfluidic reaction reproducibly provided the *O*-benzylated compounds **11**–**16** in greater than 90% yields in all cases, out of the three experiments performed in each entry of Table 3. Furthermore, no special dehydration procedures, such as pre-drying of the reaction apparatus and the solvents by molecular seives, are necessary, making the present microflow reaction a practical procedure for large-scale synthesis [30]. Based on the established microfluidic protocol, fragment **b** for the *N*-glycan synthesis, was continuously and reproducibly obtained even on a 10-gram scale [32].

The successful application of the microfluidic systems to the three hitherto "difficult" acid-mediated reactions under the conventional batch conditions, namely, α-sialylation, β-mannosylation, as well as reductive opening of sugar 4,6-*O*-benzylidene acetals, significantly facilitated the large scale preparation of the *N*-glycan fragments **b**–**d**. A stock of these key synthetic intermediates eventually led to the first solid-supported synthesis of the sialic acid-containing complex-type *N*-glycan (Figure 1) [32].

## 2. Microfluidic dehydration: a process synthesis of immunoactivating natural product, pristane

2,6,10,14-Tetramethylpentadecane (pristane) is a saturated isoprenoid isolated from the basking shark, *Cetorhinus maximus* [52-56]. This hydrocarbon oil is known to induce tumorigenesis in mice and arthritis and lupus nephritis in rats, and has been widely used as an adjuvant for monoclonal antibody production in mouse ascites [57-59]. However, in 2002, the basking shark was listed on Article II of the Washington Convention (Convention on International Trade in Endangered Species of Wild Fauna and Flora), and since then, the availability of pristane from a natural source became very limited. Therefore, an efficient chemical synthesis of pristane has been long desired.

When considering the synthesis of this simple hydrocarbon in a non-stereoselective manner, one can immediately come up with a commonplace route, i.e., oxidation of farnesol **17**, alkylation, dehydration, and hydrogenation, as shown in Scheme 1. The




**Scheme 1:** Synthesis of pristane.

synthesis is quite simple when 50 mg of the sample is prepared, but it suddenly becomes difficult when 200 kg of this hydrocarbon is required in a year with more than 98% purity. Namely, the preparation of 5 kg of pristane in about a week is necessary in order to supply enough material in the market.

The challenging step in Scheme 1 is the acid-catalyzed dehydration of allylic alcohol **19**. When the reaction was performed in 100 mg scale using a catalytic amount of *p*-TsOH in benzene at 80 °C, the corresponding diene **20** was obtained in 55% yield as its (*E*)- and (*Z*)-stereoisomers, which was transformed to pristane by hydrogenation. However, when the scale was raised to 100 g, various cation-mediated by-products, such as the cyclized products or the alkyl group-migrated compounds were produced. As expected, these hydrocarbons were very difficult to separate from the desired diene **20**, even by repeated distillation or by silica gel chromatography, although the latter is not realistic for kilogram-scale purification.

Inspired by the successful application of the microfluidic systems to the acid-mediated reactions during the *N*-glycan synthesis described above, we examined the microfluidic dehydration under the following conditions (Figure 3) [29]: Allylic alcohol **19** (1.0 M in THF) was mixed with a solution of *p*-TsOH (various concentrations of 0.2–1.0 M in THF : toluene = 1 : 1) at 90 °C using an IMM micromixer [42] at each flow rate of 0.3 mL/min. After the reaction mixture was allowed to flow for additional 157 seconds through a reactor tube (Ø = 1.0 mm, *l* = 1.0 m) at 90 °C, the mixture was quenched by a saturated $NaHCO_3$ solution at room temperature.

When 0.2 M solution of *p*-TsOH was used, only a trace amount of **20** was obtained and the starting material **19** was largely recovered. However, we again found that the yield of the dehydrated compound depends on the concentration of the acid; **20** was finally obtained in 80% yield (total yield from farnesol **17**) at an acid concentration of 1.0 M. The common features observed for the microfluidic α-sialylation and the reductive opening of the benzylidene acetals, and opposed to the conventional batch reactions, can also be applied to the current dehydration; namely, the success of "very fast" acid-mediated reactions under the microfluidic conditions owes to the rapid micromixing with the concentrated acid. It is noted that under the established microfluidic conditions, the formation of other by-products could not be detected by TLC analysis.

Having established the optimal conditions for dehydration, the kilogram synthesis of pristane was examined (Scheme 1 and Figure 3) [29]. The crude alcohol **19**, derived from 8 kg of farnesol **17** without any purification process, was subjected to the key microfluidic dehydration under the conditions established in Figure 3. For such a large-scale microfluidic reaction, we again introduced Comet X-01 [48], which we know from the previous examples, exhibited similar mixing efficiency to the IMM micromixer and avoids the blocking problem by using the relatively large tube hole (ca. 500 μm). This is especially useful for a synthetic process in which an easily crystallized material, such as TsOH, is used at high concentration. Therefore, this mixer, together with its availability at a low price, is well suited for establishing a micro chemical plant. As shown in Figure 3, we arranged 10 micromixers in a row and achieved the eight

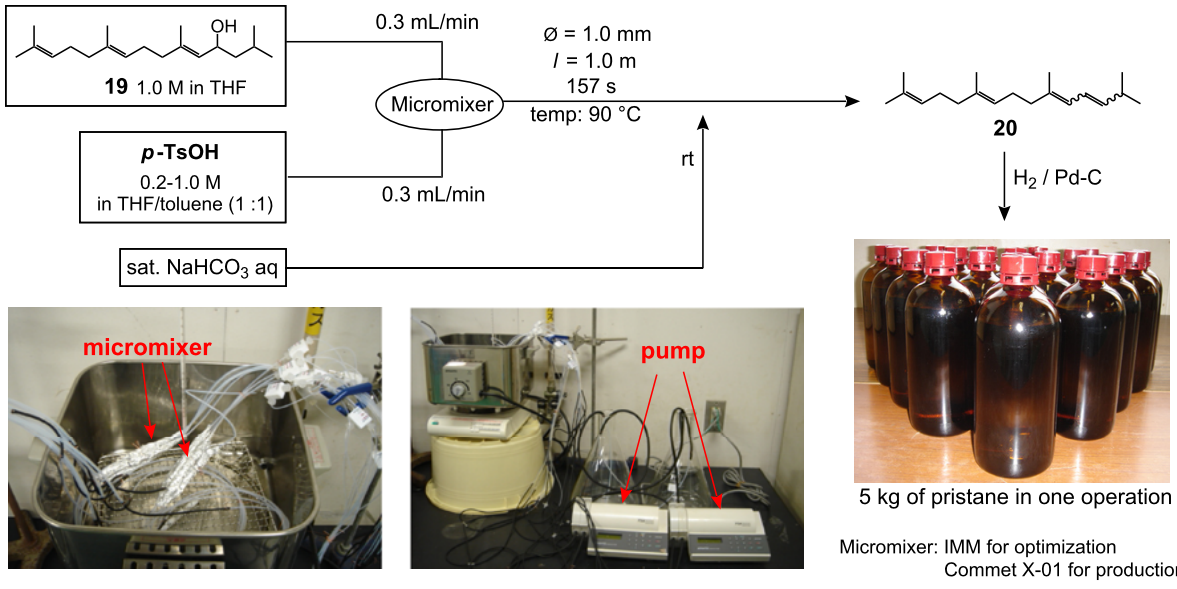
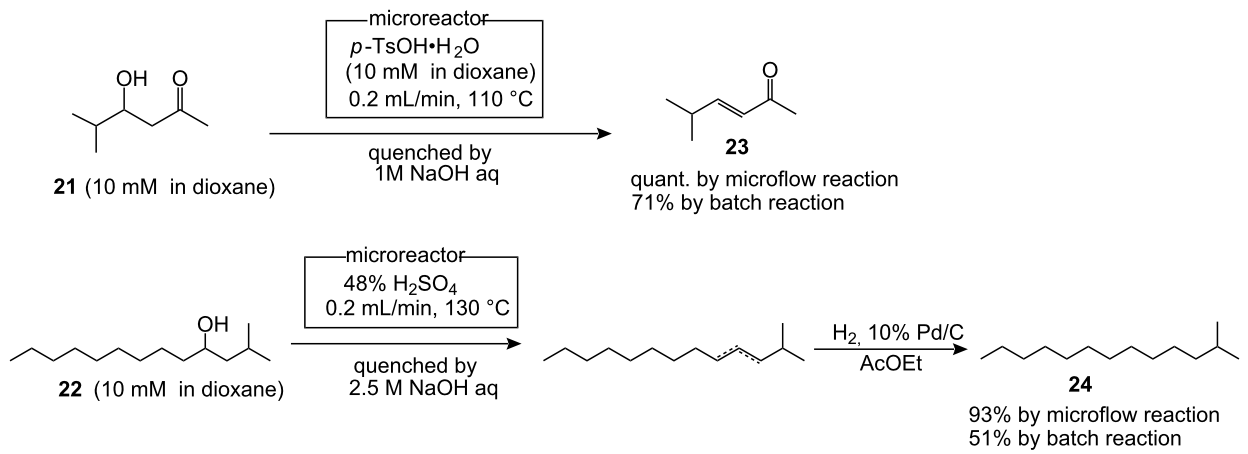



**Figure 3:** Process synthesis of pristane via microfluidic dehydration as a key step.




**Scheme 2:** Microfluidic dehydration.

kilogram-scale dehydration during 3–4 days. It is noted that the present micro chemical plant does not require any special apparatus or devices and such a simple system in Figure 3 continuously performed efficient dehydration. The resulting solution eluted from the micromixing system was quenched with a saturated $NaHCO_3$ solution, extracted with ethyl acetate, concentrated, and the mixtures were shortly passed through a silica gel pad in order to remove the hydrophilic by-products, affording the pure diene **20**.

Finally, the hydrogenation provided pristane in 50–55% overall yields (ca. 5 kg) with >99% purity based on gas chromatography analysis. Since the present pristane synthesis involves only one simple purification step by filtration with a silica gel pad, we believe that our protocol is superior to the hitherto known synthesis, which involves purification by tedious multiple distillation at the final stage. Indeed, the synthetic pristane formed by this route is confirmed to induce antibody production in mouse ascites twice as efficiently as natural pristane or the other synthetic products, due to non-negligible contamination of the other hydrophobic compounds [52-56].

In order to evaluate the efficiency of dehydration under the microfluidic conditions, the reactivity of β-hydroxyketone **21** and alkanol **22** were also tested (Scheme 2) [29]. Gratifyingly, both substrates provided the corresponding dehydrated products **23** and **24** in almost quantitative yields under the conditions established in Figure 3. For both cases, the conventional batch reaction gave lower yields of the products due to recovery of the starting materials and formation of other by-products. Therefore, an efficient and general protocol for dehydration was realized by using the micromixing system.

## Conclusions

In conclusion, we have achieved efficient glycosylation, reductive opening of the benzylidene acetal groups, and dehydration under microfluidic conditions. During our research in applying the microfluidic systems to these acid-mediated reactions, a distinctly different reactivity from that in the conventional batch stirring was found: vigorous micromixing of the reactants with the concentrated acids is critical especially for the "fast" reactions to be successful. Such a common feature might be due to the integration of all favorable aspects of microfluidic conditions, namely, efficient mixing, precise temperature control, and the easy handling of the reactive intermediate by controlling the residence time. As can be seen from the three examples cited in this review, rapid determination of the reaction conditions is another aspect of using the microfluidic conditions in a combinatorial fashion. The efficiency of the acid-mediated microfluidic reactions cited in this review, together with the other successful flow reactions reported by us and the other researchers, indicate the need to reinvestigate the traditional or imaginary reactions which have so far been performed and evaluated only in batch apparatus, and therefore have not been widely utilized for organic synthesis. In other words, such reactions could be refocused as "new generation reactions". The authors strongly believe that the microfluidic reactions could be recognized as a new strategy for the synthesis of natural products of the prominent biological activity in a "practical" and a "industrial" manner.

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# Continuous flow enantioselective arylation of aldehydes with ArZnEt using triarylboroxins as the ultimate source of aryl groups

Julien Rolland[1], Xacobe C. Cambeiro[1], Carles Rodríguez-Escrich[1] and Miquel A. Pericàs[*1,2]

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Address:
[1]Institute of Chemical Research of Catalonia; Avinguda Països Catalans, 16; 43007 Tarragona, Spain and [2]Departament de Química Orgànica, Universitat de Barcelona; 08028 Barcelona, Spain

Email:
Miquel A. Pericàs[*] - mapericas@iciq.es

* Corresponding author

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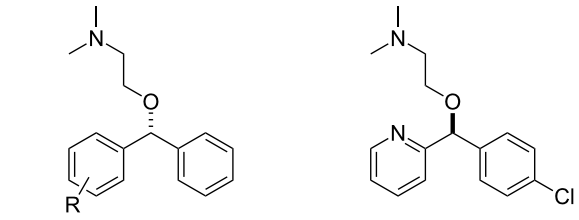
## Abstract

A continuous flow system for the synthesis of enantioenriched diarylmethanols from aldehydes is described. The system uses an amino alcohol-functionalized polystyrene resin as the catalyst, and the arylating agent is conveniently prepared by transmetallation of triarylboroxins with diethylzinc.

## Introduction

Diarylmethanols constitute the basic scaffold in several important drugs such as antihistamines and muscle relaxants (*R*)-neobenodine, (*R*)-orphenadrine or (*S*)-carbinoxamine (Figure 1) [1]. Despite the apparent simplicity of the structures, their asymmetric synthesis is not trivial. For instance, access to these structures through enantioselective reduction of the corresponding ketones can become troublesome when both aryl groups are similar in their electronic and steric properties [2-4].

On the other hand, enantioselective arylation of aldehydes with organozinc reagents appears as a most convenient alternative,




R = *p*-methyl: (*R*)-neobenodine
R = *o*-methyl: (*R*)-orphenadrine

(*S*)-carbinoxamine

**Figure 1:** Biologically active diarylmethanol derivatives.

since the initial aldehyde undergoing addition presents two very different groups (namely, a H atom and an aryl group) and hence offers good opportunities for enantiocontrol [5-7].

Whereas the catalytic enantioselective addition of diethylzinc to aldehydes has been thoroughly studied, progress in the control of the analogous asymmetric arylation has been hampered by the fact that $Ar_2Zn$ species are several orders of magnitude more active than their dialkyl counterparts [8]. In this way, when diphenylzinc has been used as the arylating species in these processes, the background, non catalyzed reaction gives rise to a racemic product, which significantly erodes the global enantioselectivity of the reactions [6,9].

The most successful approach to overcome this difficulty comes from the Bolm laboratory and has been based on the use of the comparatively less reactive mixed species PhEtZn, easily prepared from a mixture of $Ph_2Zn$ and $Et_2Zn$ [10-13]. With this strategy, it has become possible to achieve good levels of enantioselectivity in the arylation reaction, although usually at the cost of low catalytic activity, high catalytic loadings being required for the achievement of satisfactory yields [14,15]. In contrast, β-amino alcohol **1** (Figure 2), developed in our laboratory [16], showed high activity and enantioselectivity in the ethylation [16], methylation [17], and arylation [18] of a wide family of substrates at low catalyst loadings.

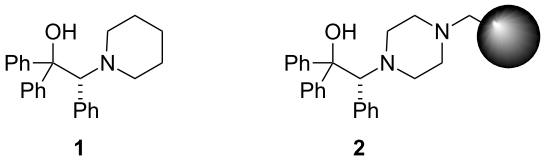
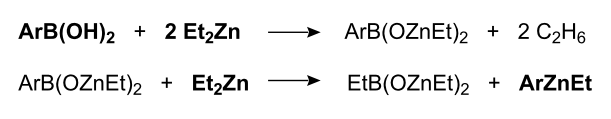



**Figure 2:** Structures of (*R*)-1,1,2-triphenyl-2-(piperidin-1-yl)ethanol (**1**) and its polystyrene-immobilized analogue **2**.

In recent times, we have developed strategies for the immobilization of analogues of **1** onto solid supports [19-22]. Among the ligands resulting from these studies, the polystyrene-supported catalyst **2** displayed levels of catalytic activity and selectivity comparable to those of the homogeneous model **1**. Noteworthy, this catalytic resin has allowed the development of the first catalytic enantioselective arylation of aldehydes employing an insoluble catalyst [22], and has been used as the basis for a single-pass, continuous flow highly enantioselective ethylation of aldehydes characterized by very short residence times (down to 2.8 min) [23]. According to these precedents, we considered that **2** could be a good candidate for a planned continuous enantioselective production of diarylmethanols.

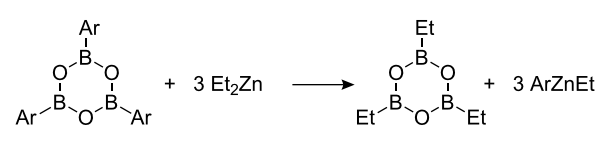
When a large scale production of diarylmethanols involving the enantioselective transfer of aryl groups from zinc to aldehydes is considered, the cost of the arylating agent becomes an important issue. From this perspective, substantial efforts have been devoted to improve the economy of this process, by replacing the expensive $Ph_2Zn$ by other, more convenient, aryl sources.

To this end, the use of arylboron species has provided particularly good results. In contrast to what happens with diarylzinc reagents, a wide variety of arylboronic acids are commercially available at a convenient price, and these species have been explored as the ultimate source of aryl groups [24-29]. In these approaches generally good results have been obtained, but at the expense of using a large excess of diethylzinc for the transmetallation step, since two non-productive equivalents of the reagent are consumed in the initial reaction with the boronic acid (Scheme 1).




**Scheme 1:** Generation of the mixed ArZnEt species from a boronic acid and $Et_2Zn$.

On the other hand, triarylboroxins, easily prepared from the corresponding arylboronic acids by thermally induced dehydration under vacuum, have recently been applied with success as the starting materials for the preparation of the ArZnEt species to be used in the reaction [30-32] (Scheme 2). This represents a highly atom-economical approach since, in principle, no sacrificial excess of diethylzinc is needed for the transmetallation process and up to a 74% of the molecular mass of triphenylboroxin (the less favourable example) can be transferred to the reacting carbonyl compound.




**Scheme 2:** Generation of the mixed ArZnEt species from a triarylboroxin and $Et_2Zn$.

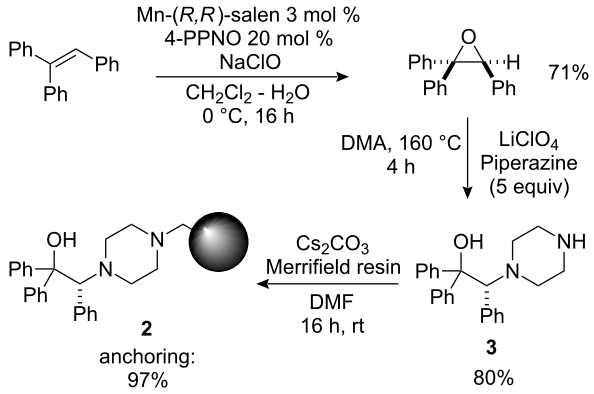
It is to be mentioned that other strategies for the preparation of mixed alkylarylzinc species from cheap organometallic reagents have been developed in recent times and could probably be also used for the same purpose [33-35].

Flow chemistry [36-39] is increasingly seen as a promising methodology for the clean and economic production of complex substances. According to this, the field is experiencing a fast growth both in methodological aspects [40-43] and in applications [44-51]. In any case, examples of continuous flow enantioselective processes [52] are still scarce [22,53-57] in spite of the enormous potential of this methodology. Herein, we report the development of a continuous flow system for the preparation of enantioenriched diarylmethanols using triarylboroxins as the ultimate aryl group source.

# Results and Discussion

## Preparation of the immobilized catalyst

Resin **2** was prepared in three steps from commercially available triphenylethylene according to a reported procedure [21]. In the key steps, enantiomerically pure triphenylethylene oxide [58] is submitted to regioselective and stereospecific ring-opening with piperazine, and the resulting diamino alcohol **3** is subsequently supported onto a slightly cross-linked (1% DVB) Merrifield resin by direct treatment at room temperature in DMF in the presence of cesium carbonate (Scheme 3).

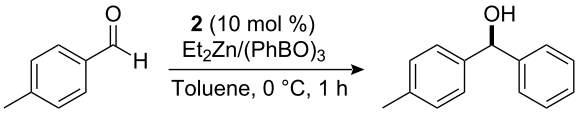



**Scheme 3:** Synthesis of the immobilized amino alcohol **2**.

## Evaluation of resin **2** under batch conditions

Prior to the continuous flow experiments, resin **2** was tested under batch conditions as a catalyst for the enantioselective phenylation of tolualdehyde using triphenylboroxin as the phenyl source (Scheme 4). In these studies, emphasis was put on the determination on the minimal ratio between triphenylboroxin and diethylzinc able to suppress competing ethyl transfer processes, and on the minimal amount of arylating species leading to complete conversion of the starting aldehyde.

Employing with **2** the reaction conditions previously optimized for the homogeneous ligand **1** [30], the addition product was obtained in slightly lower yield and enantioselectivity (entry 1, Table 1). This is probably due to the fact that the triethylboroxin co-product can trigger a non-enantioselective pathway for the arylation reaction; in fact, a decrease in the amount of $(PhBO)_3$, as well as an increase in the amount of $ZnEt_2$ employed for the transmetallation, allowed us to obtain the product in a somewhat better *ee*, although at the expense of a lower yield (entries 2 and 4). In the optimal conditions, when 2.5 equiv of $ZnEt_2$ and 0.4 equiv of $(PhBO)_3$ were used (entry 3), the diarylmethanol product was obtained in 73% yield and 89% *ee*.




**Scheme 4:** Phenylation of tolualdehyde catalyzed by **2**.

**Table 1:** Optimization of batch conditions for the phenylation of tolualdehyde with triphenylboroxin with **2** as the catalyst.[a]

| Entry | $(PhBO)_3$ (equiv) | $ZnEt_2$ (equiv) | Yield (%) | *ee* (%) |
|---|---|---|---|---|
| 1 | 0.6 | 2.4 | 90 | 83 |
| 2 | 0.4 | 2.0 | 62 | 85 |
| 3 | 0.4 | 2.5 | 73 | 89 |
| 4 | 0.4 | 3.0 | 72 | 88 |

[a]All reactions run at 0 °C for 1 h at 0.2 M concentration of tolualdehyde.

# Continuous flow system

## System set-up

For the continuous flow experiments, a system similar to that previously described for the enantioselective ethylation of aldehydes [23] was used (Figure 3). The flow reactor consists of a vertically mounted, fritted and jacketed low-pressure chromatography Omnifit glass column (10 mm bore size and a 70 mm maximal bed height) completely filled with the swollen resin. During operation, the reagents were pumped in through the bottom end of the column using two different piston pumps (one for the aldehyde substrate in toluene and one for the PhZnEt plus triethylboroxin mixture in toluene). Both flows were mixed in a T-shaped piece placed immediately before the reactor, in order to minimize the amount of background, non-enantioselective addition reaction before contact with the supported catalyst. Additionally, a supply of dry toluene was connected to both pumps, for swelling the resin and washing the tubing before and after the reaction. Isothermal operation was secured by circulation of a cooling fluid at the desired operation temperature through the column jacket. Finally, a collecting flask containing ammonium chloride solution was set in order

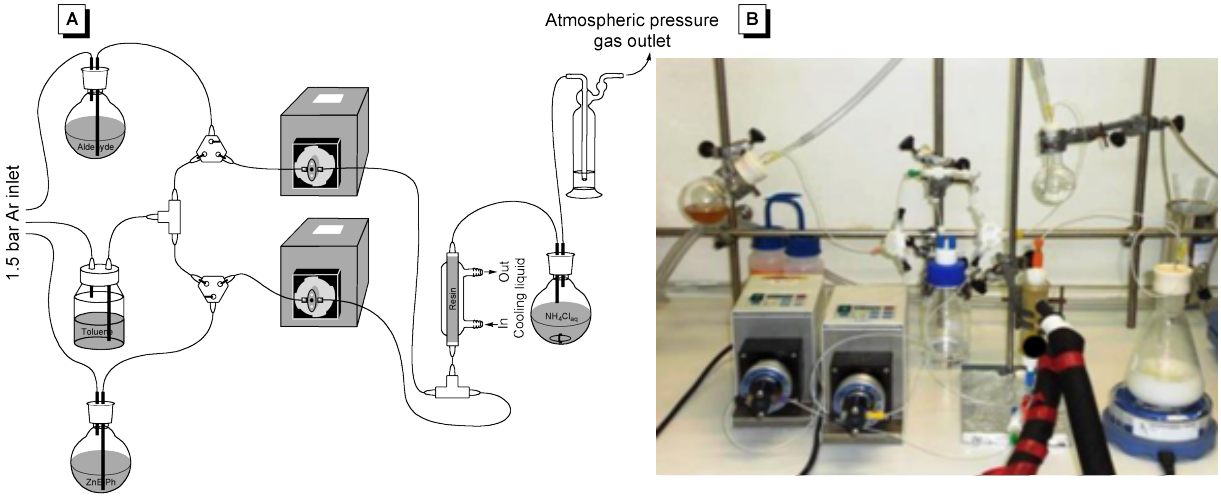



**Figure 3:** Experimental set-up for the continuous flow experiments. (A) Schematic representation and (B) Actual system.

to hydrolyze residual ethylating/arylating agents and thus prevent the non catalyzed reaction taking place in the event that conversion of the continuous flow catalytic reaction was not complete.

## Optimization of the process

Optimization of reaction parameters under continuous flow conditions was performed again on the phenylation reaction of *p*-tolualdehyde. The results of this study are summarized in Table 2. Bearing in mind the strong acceleration usually observed when reactions are run under continuous flow conditions, due to the higher effective concentration of the catalyst, the use of a smaller excess of diethylzinc than under batch conditions was initially tested at 0 °C (entry 1). However, this resulted in low levels of conversion and enantioselectivity. As already observed under batch conditions, the use of a higher excess of diethylzinc led to increased conversion without loss of *ee* and no significant formation of side products (entry 2). On the other hand, increasing the reaction temperature to 20 °C led to an unacceptable decrease in enantioselectivity (entry 3). A further improvement of the performance of the system could be achieved by setting the reaction temperature to 10 °C (entries 4–6). Working at this temperature and adjusting the aldehyde:boroxin:diethylzinc ratio to 1:0.6:2.5 the product was obtained in 83% *ee*, with complete conversion and no significant decrease in yield due to the formation of byproducts (entry 6). It is worth mentioning that, in this way, the flow system could be operative for several hours without any significant degradation of the catalytic activity. For example, after 4 h, 3.2 g of (*S*)-phenyl(4-tolyl)methanol were obtained (80% yield) with 81% *ee*.

## Scope of the continuous flow arylation

As previously demonstrated for catalyst **1**, this method can be used for the preparation of diarylmethanols with a wide variety of substituents, regardless of their electronic properties, provided that an adequate combination of aldehyde and arylating agent is chosen [30]. Thus, aryl(phenyl)methanols,

**Table 2:** Optimization of the reaction conditions for the continuous flow process.[a]

| Entry | $(PhBO)_3$ (equiv) | $ZnEt_2$ (equiv) | T (°C) | Conv (%)[b] | Yield (%)[b] | *ee* (%)[c] |
|---|---|---|---|---|---|---|
| 1 | 0.4 | 1.6 | 0 | 40 | 36 | 76 |
| 2 | 0.4 | 3.0 | 0 | 71 | 59 | 78 |
| 3 | 0.4 | 3.0 | 20 | 99 | 82 | 67 |
| 4 | 0.4 | 2.5 | 10 | 84 | 72 | 81 |
| 5 | 0.5 | 2.7 | 10 | 95 | 83 | 83 |
| 6 | 0.6 | 2.5 | 10 | 99 | 91 | 83 |

[a]All the reactions were performed with 1.1 g of resin, 0.24 mL/min total flow rate and 0.55 M maximal concentration of $(PhBO)_3$.
[b]Conversion and yield determined by GC with tridecane as internal standard.
[c]*ee* determined by HPLC with a chiral column (for details see Supporting Information File 1).

with the aryl group bearing electron-withdrawing substituents, can be prepared easily by phenylation of the corresponding aldehyde. On the other hand, if a diarylcarbinol has to be prepared where one of the aryl groups bears electron donating substituents, the phenylation of the electron rich benzaldehyde is not efficient, so that the use of an electron rich boroxin in combination with benzaldehyde is preferred (Scheme 5).

We have summarized in Table 3 the results of the continuous flow arylation of a family of aldehydes. This study was done under the set of experimental conditions previously optimized for the phenylation of *p*-tolualdehyde (see Table 2, above), and the results given in the table refer to instant conversion and enantioselectivity after given reaction times.

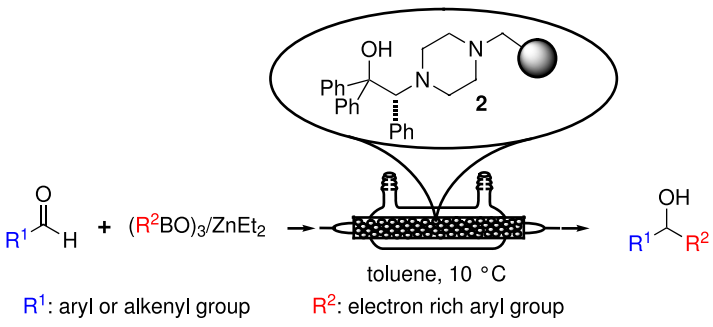
In all the studied cases tested, except in the phenylation of α-methylcinnamaldehyde (entry 5), the reaction could be run for some hours without significant decrease in the conversion of the starting aldehydes, thus allowing the preparation of enantioenriched carbinol products in multigram scale. Most attention was devoted to the use of PhZnEt (from triphenylboroxin and diethylzinc) in combination with different aromatic aldehydes (entries 1–4). Among these cases, the best results were obtained with *p*-tolualdehyde (entry 1). With *o*-fluorobenzaldehyde (entry 2), *p*-chlorobenzaldehyde (entry 3) and 2-naphthaldehyde (entry 4) conversions were excellent over the whole flow experiments (3 or 4 h), although enantioselectivities were slightly lower [30]. When an α,β-unsaturated aldehyde, such as α-methylcinnamaldehyde was used (entry 5), a fast reaction took initially place, although conversion was observed to slowly decrease after 2 h. Finally, (4-$MeOC_6H_4$)ZnEt [from tri(*p*-methoxyphenyl)boroxin and diethylzinc] could also be used in the continuous flow process with excellent conversion and moderate enantioselectivity (entry 6).

It is interesting to note that, although enantioselectivities were not as high as those obtained with the homogeneous catalyst **1** under batch conditions with the same arylating agents [30], or even with the heterogeneous catalyst **2** used under batch conditions with PhZnEt generated from diethylzinc and the very expensive diphenylzinc [22], the addition products could be easily crystallized in order to improve their enantiomeric purities. For instance, phenyl(4-tolyl)methanol could be obtained in pure form, in 76% yield and 93% *ee* after a single crystallization and 4-chlorophenyl(phenyl)methanol in 67% yield and 86% *ee* after the same process.

## Conclusion

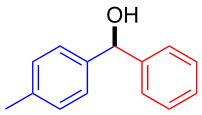
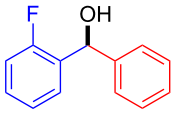
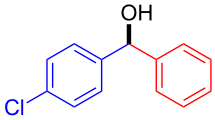
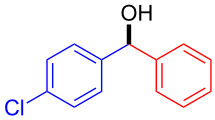
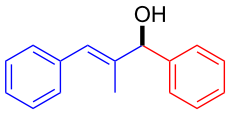
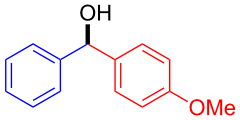
In summary, the first single-pass, continuous flow enantioselective arylation of aldehydes has been developed. In this manner, enantioenriched diarylmethanols can be prepared in large scale through a simple and efficient process. The system has been optimized for the use of arylboroxins as an atom economical, cheap and readily available source of aryl groups. The simple procedures required for the purification and enantioenrichment of the resulting carbinols converts this flow process into a convenient alternative for the multigram production of these compounds.

The observed decrease in the enantioselectivity induced by the catalyst in comparison to its homogeneous analogue **1**, suggests some participation of triethylboroxin in a competing, non-enantioselective catalytic event. In fact, boroxins present adjacent atoms with complementary Lewis base (O) and Lewis acid (B) character that could coordinate the reactant molecules (aldehyde and arylethylzinc) in an arrangement suitable for reaction. In this sense, it is noteworthy that when control experiments were done by using resin **2** under batch conditions with the $Ph_2Zn/Et_2Zn$ combination of reagents for the generation of PhZnEt, the observed enantioselectivities were comparable to those recorded with the homogeneous catalyst **1**. Thus, further improvement of the present continuous flow system could possibly be achieved with the use of alternative sources of the arylating species [33-35].




**Scheme 5:** Continuous flow enantioselective preparation of diarylmethanols.

**Table 3:** Substrate scope in the continuous flow arylation of aldehydes.[a]

| Entry | Product | Time (h) | Conv (%) | % *ee* |
|---|---|---|---|---|
| 1 |  | 1<br>2<br>3<br>4<br>Overall[b] | 99<br>98<br>98<br>98<br>80[d] (76)[e] | 83<br>82<br>81<br>79<br>81 (93)[e] |
| 2 |  | 1<br>2<br>3<br>Overall[b] | 99<br>99<br>99<br>91[d] | 58<br>56<br>53<br>55 |
| 3 |  | 1<br>2<br>3<br>4<br>Overall[b] | 99<br>99<br>99<br>99<br>78[d] (67)[e] | 72<br>70<br>67<br>65<br>68 (86)[e] |
| 4 |  | 1<br>2<br>3<br>4<br>Overall[b] | >99<br>>99<br>>99<br>>99<br>93[d] | 81<br>74<br>70<br>69<br>70 |
| 5 |  | 1<br>2<br>3<br>Overall[b] | 99[c]<br>>99[c]<br>82[c]<br>82[d] | –<br>–<br>–<br>66 |
| 6 |  | 1<br>2<br>3<br>4<br>Overall[b] | 99<br>>99<br>>99<br>97<br>83[d] | 57<br>60<br>62<br>67<br>63 |

[a]Reaction conditions as in Table 2. For determination of conversion and *ee* see Supporting Information File 1.
[b]Data for the whole flow experiment.
[c]Determined by $^1$H NMR.
[d]Isolated yield.
[e]After a single recrystallization.

# Experimental

## General procedure for the arylation of aldehydes under batch conditions

A solution of $ZnEt_2$ (257 mg, 2.08 mmol) in dry toluene (1 mL) was added via cannula to a suspension of phenylboroxin (104 mg, 0.333 mmol) in toluene (1 mL). The mixture was immediately warmed up to 60 °C in a preheated bath, in a closed system, and stirred in these conditions for 30 min before it was allowed to cool down to room temperature.

Meanwhile, catalyst **2** ($f$ = 0.467 mmol/g, 180 mg, 0.083 mmol) was swollen with toluene (2 mL) for 30 min and then cooled to 0 °C. The $ZnEt_2$/$(PhBO)_3$ mixture was added and the resulting suspension was stirred for further 30 min.

After this time, tolualdehyde (100 mg, 0.83 mmol) was added and the reaction mixture was stirred at the same temperature for 1 h. Then, a saturated aqueous solution of $NH_4Cl$ was added to stop the reaction. The resin was removed by filtration and the biphasic mixture was diluted with dichloromethane and separated. The aqueous layer was extracted with dichloromethane and the combined organic layers were washed with aqueous $NaHCO_3$ solution, dried with $Na_2SO_4$, filtered and concentrated under reduced pressure to obtain the product as a yellow oil.

Flash chromatography through silica gel with hexane-ethyl acetate mixtures afforded the pure phenyl(4-tolyl)methanol in pure form as a white solid (119 mg, 72% yield, 89% *ee*).

Conversion and GC yield were determined by GC analysis of samples of the organic solution before it was concentrated, with a HP-5 column. Enantiomeric excess was determined by HPLC analysis of the pure product with an AD-H column. Exact conditions for this and other products are given in Supporting Information File 1.

## General procedure for the phenylation of tolualdehyde in continuous flow conditions

The continuous flow system was set up as described in Figure 3. The column was filled with 1.1 g of resin, and it was swollen with a 0.24 mL·min$^{-1}$ flow of dry toluene for 30 min. After that, a 1.1 M solution of the arylating agent, prepared as described above with $(PhBO)_3$ (3.77 g, 12.1 mmol) and $Et_2Zn$ (6.23 g, 50.4 mmol) in toluene (33 mL), was connected to one of the pumps, at 0.12 mL·min$^{-1}$, while toluene (0.12 mL·min$^{-1}$) was kept in the other one, and the column was cooled down to 10 °C. These conditions were kept for a further 1 h, in order to form the amino alcohol-Zn complex. Then, a 0.61 M solution of tolualdehyde (2.42 g, 20.16 mmol) in toluene (33 mL) was connected to the second pump, keeping the same flow.

The product eluting of the column was collected in a flask containing a vigorously stirred aqueous $NH_4Cl$ solution, in order to stop the reaction.

The reaction progress was monitored by taking samples of approximately 50 μL and analyzing them by GC. The samples were treated with aqueous $NH_4Cl$, extracted with dichloromethane and filtered through $Na_2SO_4$ before they were injected in the GC apparatus. These same samples were analyzed by HPLC in order to determine the *ee* (see Supporting Information File 1 for further detail).

After 4 h, both reactants were stopped and the system was washed by pumping toluene again for 30 min. The biphasic mixture containing the product was extracted with dichloromethane, washed with aqueous $NaHCO_3$, dried with $Na_2SO_4$ and concentrated under reduced pressure. After flash chromatography on silica gel, 3.2 g of the product (80% yield) was obtained as a white solid, with 81% *ee*. A single crystallization from hexane afforded 2.4 g (76% yield) with 93% *ee*.

## Supporting Information

Supporting information contains GC and HPLC conditions for the analysis of the diarylmethanol products.

### Supporting Information File 1

Conditions for the analysis of the diarylmethanols by GC and HPLC.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-5-56-S1.pdf]

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# Flow through reactors for organic chemistry: directly electrically heated tubular mini reactors as an enabling technology for organic synthesis

Ulrich Kunz* and Thomas Turek

Full Research Paper

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Address:
Institute of Chemical Process Engineering, Clausthal University of Technology, Leibnizstr. 17, D-38678 Clausthal-Zellerfeld (Germany)

Email:
Ulrich Kunz* - kunz@icvt.tu-clausthal.de

* Corresponding author

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## Abstract

Until recently traditional heating in organic chemistry has been done with oil heating baths or using electric heat exchangers. With the advent of microwave equipment, heating by microwaves was rapidly introduced as standard method in organic chemistry laboratories, mainly because of the convenient possibility to operate at high temperature accompanied by accelerated reaction rates. In the present contribution we discuss the method of heating small, continuously operated reactors by passing electric current directly through the reactor wall as an enabling technology in organic chemistry. The benefit of this method is that the heat is generated directly inside the reactor wall. By this means high heating rates comparable to microwave ovens can be reached but at much lower cost for the equipment. A tool for the comparison of microwave heating and traditional heating is provided. As an example kinetic data for the acid catalyzed hydrolysis of methyl formate were measured using this heating concept. The reaction is not only a suitable model but also one of industrial importance since this is the main production process for formic acid.

## Introduction

Continuously operated small reactors for organic synthesis have gained much interest during the last years. Micro reaction technology is now well known and applied in many laboratories [1, 2], with many examples of its application in organic synthesis [3-6]. One aspect still preventing widespread use is the high cost of most microreactors and the peripheral equipment which is necessary for heat and flow control. Most of these reactors are indirectly heated, by fluid-supplied heating jackets or by electric heating cartridges and jackets. Beside oil baths and electric heaters microwave ovens are now widely present in the organic chemist's laboratory [7]. In many cases shorter reaction times have been reported compared to the traditional heating methods. The question of a specific microwave effect is under current discussion, but for many chemical reactions it is evident that microwave heating is just another way transferring heat into the reaction mixture [8,9]. The constructions of closed

vessels used as reactors in microwave ovens allow operation under pressure. Thereby the reaction temperature obtainable can be much higher than in traditionally heated open vessels and beakers, leading to shorter reaction times. This fact, in combination with the very convenient use of microwave ovens comparable to kitchen equipment and safe operation in a closed cabinet, are the reasons for the success of this technology.

The high cost and dimensions in the sub millimeter range led us to the question: what other methods are available to heat small flow through reactors conveniently and rapid at low cost?

# Results and Discussion

## Heating concept

In addition to microwaves, heating by other electromagnetic fields was recently introduced into organic synthesis. Magnetic particles were heated by the interaction with an electromagnetic field in the frequency range of long radio waves (< 100 kHz) [10]. Both traditional and these novel methods have disadvantages. The disadvantages of the traditional heating methods are:

- Oil baths have large volumes of oil, are bulky and heat up rather slowly. The synthesis flasks have to be cleaned from adhering oil.
- Electric heating baskets are electrically isolated for safety reasons, so the heat transfer to the glass flask is rather limited, making these devices slow in operation. Due to the electric insulation the heating wire inside may have a much higher temperature than the surface of the heated flask. This may be an ignition source for organic solvent vapors.

Heating with electromagnetic devices like microwave ovens or inductive heaters has other disadvantages:

- Only a small part of the energy taken from the AC power line is transferred as heat into the chemical reactor.
- The equipment is expensive because it requires well-controlled electromagnetic field generation.
- Cheap thermocouples cannot be used as sensors for temperature measurement and control.
- Temperature sensors cannot always be fixed directly into the reaction mixture because of limited chemical or mechanical stability.
- Operation under high pressure is limited by the properties of the construction materials for the reactors which have to be transparent for electromagnetic waves.
- Homogeneous temperature distribution in the synthesis flasks is not always ensured since not all of these devices have a stirrer or mixer.
- Penetration depth of electromagnetic waves is limited.
- Shielding of the heating chamber is required to prevent electromagnetic waves entering the environment.

In this paper we provide an example of a much simpler method to heat small flow reactors. From our point of view the easiest way to transfer heat is to heat the reactor wall directly by passing electric current through the reactor wall itself. By resistive heating of the wall the heat transfer is facilitated because heat transfer has only to occur from the reactor wall to the reaction mixture. Additional heat transfer from an outer heating source to the reactor wall is avoided. Moreover the heat is transferred very uniformly across the whole surface area of the reactor, thus enlarging the effective heat transfer surface area, avoiding hot spots and preventing overheating of sensitive reactants. The response of the reactor to changes in the heating current is fast due to the low mass of the heating resistor, which is just the reactor wall.

This heating method is not new, it is well known to every plumber to melt the ice in frozen water pipes just by connecting the ends of the pipe with a welding transformer and let the electric current generate heat. Surprisingly, this heating method is seldom used in chemistry or other technical applications. One example is the injector liner in mass spectrometers or gas chromatograph mass spectrometers. This injector tube is a capillary with a few cm length which is heated by an electric current [11]. Another application is the preheating of liquid in cars e.g. for preheating the motor cooling fluid [12]. But in the device described the resistor wire is coiled onto a tube which is used for conducting the fluid. The tube itself is not used as the heating element. Heating micro reactors made of finely structured plates by electric current is also mentioned in the literature, [13,14] but to our knowledge resistive direct heating of the reactor wall is not yet used widely as a method to heat chemical reactors. A reason for this might be that high currents at low voltages are needed. This is necessary because the resistance of metal tubes or sheets used for reactor construction is low (in the milliohm range). Usually this is encountered with big losses in the switching semiconductors and in the wires used for connecting the electric circuit. Only recently lightweight switching power supplies with high load currents and high efficiency became available. Today the switching of high currents in the range of several 10 to 100 A without big losses is possible with metal oxide field effect transistors (MOSFET) having very low saturation voltages and on-resistances in the milliohm range. Based on the availability of modern electronic components the reactor concept of resistive heating is still limited to small reactors, that means diameters in the range of several millimeters and lengths to several 0.1 m up to 1–2 m are possible. From cost aspects micro reactors made of thin metal plates with channel dimensions in the sub millimeter range in

combination with their sensitivity to mechanical failure like plugging, are not really an enabling technology for organic chemistry. Thus, the use of standard metal tubes in the aforementioned dimension range appears to be much more attractive. These dimensions fit the trend to use micro reactors or mini reactors for continuous chemical production perfectly.

Recently we introduced this concept as an attractive method for organic reactions with preliminary measurements [15]. In this paper we give a detailed description of the system and possible applications in organic synthesis.

## Experimental set up

For the experimental evaluation of this heating concept we prepared different reactors which were heated by an electric current. The reactors were investigated in an apparatus depicted in Figure 1. The reaction mixture from reservoir (1) was pumped by a pump (2) to the inlet of the reactor (3). The reactors were made from 1/8″ or 1/4″ standard stainless steel tubing. The electric heating current was fed to the reactor by soldered solid 4 mm diameter copper wires which were also used to fix the reactor on a mounting base plate. The copper wires were connected with plugs for easy exchange of the different reactors. Heating current was delivered by a low voltage/high current power (5 V, 120 A) supply (4) controlled by a fast acting temperature controller (5). This temperature controller included a switching pulse width modulator with a frequency of approximately 30 Hz to ensure fast response of the low mass heater [16]. The reactor outlet temperature was regulated taking a thermocouple (7) as a measure. This thermocouple is located in the middle of the liquid stream leaving the reactor. Thereby the temperature of the liquid is adjusted, not the wall temperature of the reactor. To allow operation at high pressure inside the tube the outlet was attached with a capillary to introduce a pressure drop. Conversion was measured with a detector (9) connected directly behind the capillary before the reactor outlet (8). All electric connections within the heater supply lines were made of 10 $mm^2$ flexible insulated copper wire to minimize resistive losses in the conductors.

# Experimental

## Power efficiency and dynamic behavior of the system

For these purposes a reactor made of 1/8″ stainless steel tubing (3.18 mm × 0.56 mm with a length of 50 cm) was used. The chosen material was 1.4404 stainless steel. For the reactor design it is necessary to know the specific electric resistance. A value of 0.724 Ω $mm^2$ $m^{-1}$ was measured at 25 °C. Before the reactor was used for reaction experiments the electric power consumption was estimated. For this purpose a flow of 10 mL water per min was pumped through the tube and the heating power was set to 100%. The water flow was used to cool the tube to prevent overheating. This mode of operation can only be used for a few seconds, because finally the water will evaporate,

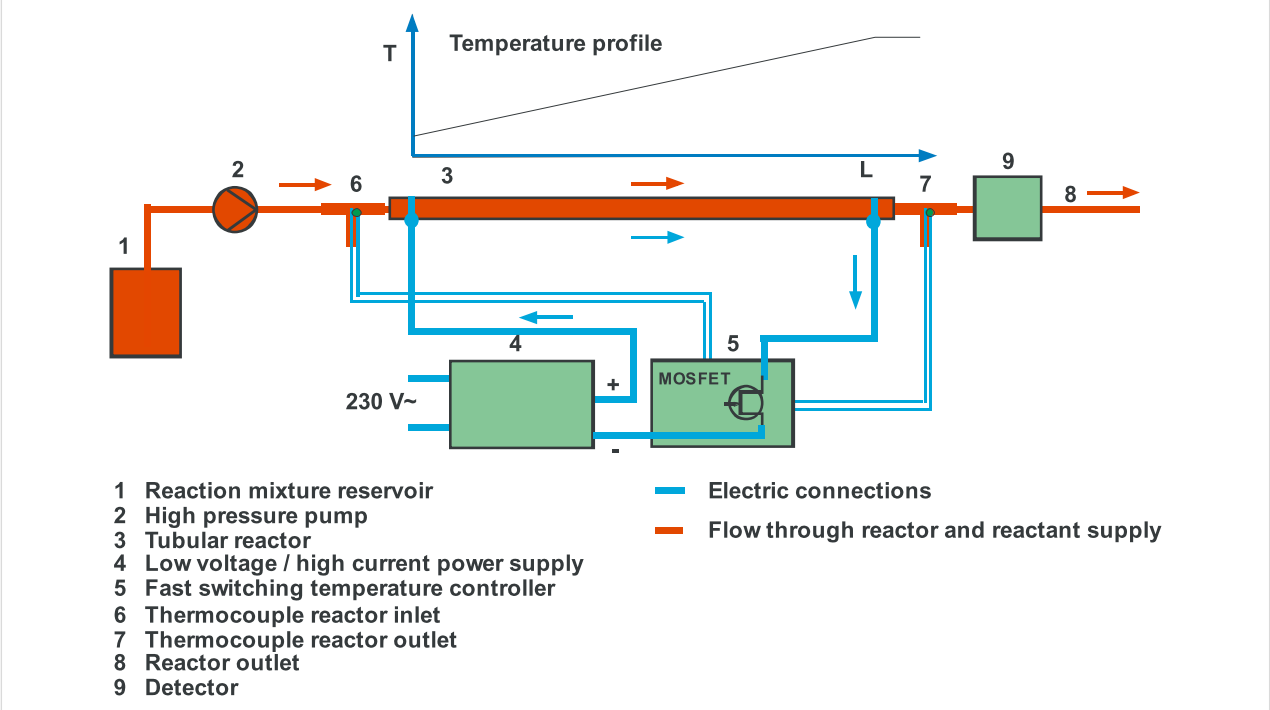



**Figure 1:** Experimental setup for heating tubular flow reactors by passing electric current directly through the reactor wall. The characteristic linear temperature profile along the reactor length is also given.

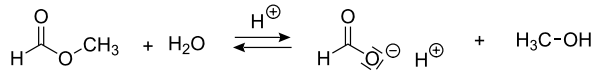
but this time is long enough to measure the characteristic data. The measured electric current flowing through the tube was 56.66 A, while a voltage at the tube of 4.45 V was determined. This gives a power uptake of the tube of 252 W. All this power is transferred into heat. The voltage drop of 0.55 V is mainly caused by the voltage drop of the power MOSFET switch which is used to actuate the heating current. The voltage drop of the copper cables can be neglected. The loss of the power switch is 31 W which is approximately 10% of the power taken from the power supply, thus the power supply has an efficiency of 90%. This leads to a power consumption from the 230 V ~ AC line of about 314 W to deliver the power of 283 W for the heated tube and the 31 W for the power switch. The power consumption of the temperature controller is about 1 W and can be neglected. Thus the overall efficiency is roughly 80%. To give an impression for a reachable temperature increase: with a power of 252 W the temperature of a water flow of 50 mL $min^{-1}$ can be increased by 72 °C. This is more than sufficient for the flow regime of the planned experiments with a flow rate of the reaction mixture between 1 and 10 mL $min^{-1}$.

Subsequently, the dynamic behavior with respect to temperature changes was studied. With the pump, water was fed at different flow rates between 1 and 10 mL $min^{-1}$ through the reactor. Times were measured until the reactor outlet temperature had reached a steady value. Outlet temperatures were chosen in the range of 30 to 90 °C. The desired reactor outlet temperature was reached in about a few seconds almost irrespective of the flow rate. The heating time was hard to measure accurately due to the rapid heating. It is evident that with the high heating power and the small flow rates very short response times can be achieved to make a reaction mixture reach a desired temperature. Due to the linear temperature profile which is caused by the interaction of the constant volumetric heat generation inside a volume element of the reactor wall and the flowing liquid, a gentle rise of the temperature without overheating can be reached. Although gentle, the heating rate is fast, comparable with heating rates of microwave ovens.

The data given above demonstrate the dynamic behavior of the heating power. Also important for the performance of a chemical reaction is the residence time of the reaction mixture in the reactor. With the tube dimensions given above the residence time is 10 s at a flow rate of 10 mL $min^{-1}$. That means that a reaction mixture can be heated within 10 s to a desired outlet temperature. It should be noted that the linear temperature profile for a set outlet temperature is constant, independent of the flow rate within the above given flow regime. If the tube is filled with inert solid material the free volume can be reduced by about a factor of two, which means that the residence time at the given flow rate of 10 mL $min^{-1}$ is about 5 s. This approach is cheaper than to use high priced capillary tubing and is easier to handle in case of blockage. Such a high heating rate resulting in a linear temperature profile cannot be reached by traditional heating methods in an easy way.

## Kinetic measurements

The applicability for kinetic measurements is demonstrated using a simple organic model reaction. We chose the hydrolysis of methyl formate with an ion exchange resin as an acidic heterogeneous catalyst. We chose a polymer catalyst because polymers are well defined materials which can be functionalized easily with many active groups. This leads to a wide variety of materials, including composites, suitable as catalysts or for anchoring active sites leading to a large number of composites [17-24]. The reaction scheme for the model reaction is given in Scheme 1.




**Scheme 1:** Acid catalyzed hydrolysis of methyl formate.

This reaction was chosen for several reasons:

- Due to the low boiling point of the ester (32 °C) kinetic measurements in traditional equipment are limited to an upper temperature of about 25 °C, otherwise the vapor pressure would lead to loss of reactant in an open system. Measurements at temperatures higher than 32 °C are not possible at all.
- The progress of the reaction can be measured easily online by determining the electrical conductivity of the reaction mixture leaving the reactor. Electrical conductivity is directly proportional to the formation of formic acid and thus proportional to conversion. As a measure for conversion the conductivity of the reaction mixture at the reactor outlet was used.
- The reaction follows first order kinetics (within the concentrations we have chosen), which facilitates the determination of kinetic parameters.
- The reaction is of industrial importance. It is the main process for production of formic acid.

For the kinetic measurements two directly electrically heated and independently temperature regulated tubes in series were used. The same power supply delivers enough current for both tubes. The first tube had a diameter of 1/8″ and a length of 50 cm. This tube was used as a non catalytic preheater. The second tube was 100 cm in length and had a diameter of 1/4″. It was filled with an ion exchange resin catalyst (Amberlyst 70,

mean particle diameter 0.8–1 mm, ion exchange capacity 0.7 mmol $mL^{-1}$). The measurements were done by continuously feeding a mixture of 940 mL water, 490 mL methanol and 123 mL methyl formate to the first tube. This corresponds to an ester concentration of 1.275 mol $L^{-1}$. This concentration was chosen because in many industrial organic syntheses the concentration of the reactant is about 1 mol $L^{-1}$ [25]. During all measurements the outlet temperature of the preheater was set to the desired reaction temperature value. The outlet temperature of the catalytic reactor was set to the same temperature to allow isothermal operation. In most experiments the reaction temperature was set at much higher values than the boiling temperature of the ester at ambient pressure. This could be done since the reactor outlet was connected with an adjustable flow control valve and a capillary which were used to keep the reaction mixture under pressure in a liquid state. Even at a reaction temperature of 80 °C the ester does not vaporize because the mixture is under pressure. Most of the heating was done by the preheater: the catalytic reactor only needed to compensate heat loss to the environment. This concept, using a preheater, which contained no catalyst, and a flat, almost isothermal temperature profile along the catalytic reactor, prevents thermal damage from the polymer resin catalyst. In addition to this the temperature difference between the reactor wall and the reaction mixture was measured. This was done by thermocouples inside the reactor and with an infrared camera observing the temperature profile at the outer surface of the reactor. Both independent measurements as well as mathematical modeling of the temperature profiles reveal that the temperature difference between inside and outside of the preheater tube are much below 10 °C [26]. The catalytic reactor was operated at a much lower temperature gradient. The determined difference is not a problem for the resin catalyst. It is a feature of this reactor heating concept that the heating is fast with high power, but gentle because the heat is introduced into the reaction mixture along the whole reactor length with a linear rising temperature profile. Even sensitive compounds in a homogeneous reaction mixture will not be damaged because the temperature gradients are low.

Before performing the experiments the conversion at low temperature was estimated in a batch experiment. At a temperature of 10 °C negligible conversion was observed for several hours, so this temperature was set to approximate zero conversion. Then for three different flow rates conversion in dependence of the reactor temperature was measured. The results of these measurements are depicted in Figure 2. It can be seen that complete conversion can be reached at approximately 80 °C and a residence time of about one minute. The measurements were used to determine reaction rate constants and the activation energy.

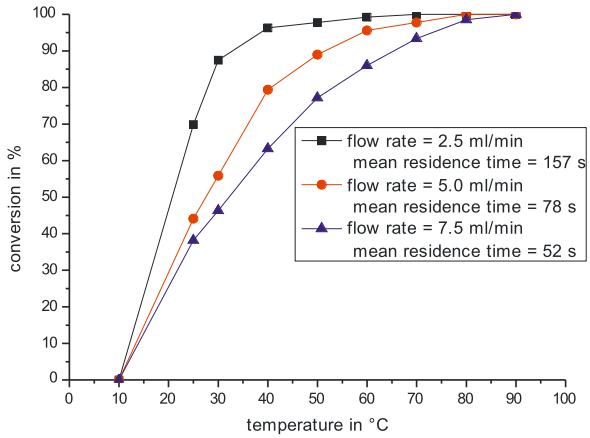



**Figure 2:** Conversion as a function of temperature for 3 different residence times.

As the reaction is first order the reaction rate constants can easily be calculated by

$$k = \ln\left(c_0 / c\right) / \tau \qquad (1)$$

where τ is the mean residence time during the experimental run. $c_0$ is the initial concentration of the ester and $c$ is the current concentration, both in mol $L^{-1}$. From the experiments 19 values for the reaction rate constant $k$ could be calculated which were used to prepare an Arrhenius plot. This plot (Figure 3) was used to estimate the activation energy and the pre-exponential factor.

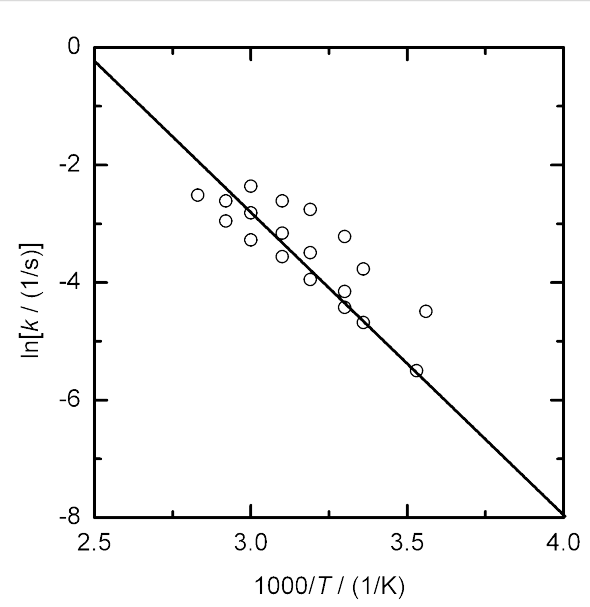



**Figure 3:** Arrhenius plot for the measured rate constants.

To some extent the values for k scatter. This could be based on the conductivity cell which was used for measuring the conversion as it had no temperature control. Measured values showed some influence on fluid temperature. From the Arrhenius plot an activation energy of 43.0 kJ $mol^{-1}$ and a pre exponential factor of $3.27\times10^5$ $s^{-1}$ was determined. The directly heated tubular reactors have low mass and act fast to new temperature settings. After a waiting time of 5 to 6 residence times (which corresponds to a few minutes) the new temperature values have stabilized and measurements can be taken from the conductivity cell. The system demonstrates that directly heated small reactors can be used very efficiently in a convenient way. The chosen model reaction is only slightly exothermic. With reactions of much higher heat production the temperature profile at high conversion will be no longer linear. But this is not a big disadvantage, because it is well known to those skilled in the art that kinetic measurements can be done easily at low conversion. In such a case the reactor is operated in a differential mode to measure reaction rates at nearly constant feed concentrations. The simplest ways to do this are to lower the residence time in the continuously operated tubular reactor by using a higher flow rate or the dilution of the reaction mixture by a solvent.

## Conclusion and Outlook

A simple system was used for heating continuously operated small tubular reactors by passing electric current directly through the reactor wall. All components are standard laboratory equipment with much lower cost compared to heating devices using electromagnetic fields or finely structured micro reactors. The voltages necessary for heating are low and all parts can be touched without the risk of electric shock. Additional insulation is unnecessary either for electric safety or for heat management, leading to a system where all tube connectors can be reached easily. This makes the device handy for facilitating changes of the reactors which could be necessary for the adjustment of residence time or catalyst exchange. Even contamination by residues of previous reactions is not a problem. The reactors are cheap standard tubes, so they can be discarded and replaced by new ones. With the design guidelines given here it is easy to set up a continuously operated mini reactor for chemical reactions using readily available laboratory equipment. In this sense it is an enabling technology allowing the use of continuous reactors at low cost, enlarging the portfolio of enabling technologies for organic synthesis [27]. Performing a simple organic reaction demonstrates that the concept of directly electrically heated tubular reactors is convenient in use and gives high heating rates. The pressure resistant system allows operation well beyond the boiling temperatures of most solvents. Due to the use of low diameter stainless steel tubing, pressures up to even more than 100 bar are feasible. The applicability for kinetic measurements at temperatures above the normal boiling point was shown for the heterogeneously catalyzed hydrolysis of methyl formate. As an example the activation energy and rate constants for an industrial ion exchange resin catalyst were determined. The system gives the opportunity to adjust accurately high heating rates with traditional resistive electric heating. This feature makes the device a tool well suited to compare the influence of heating rates on chemical reactions. Further studies will focus on the comparison of heating within microwave ovens and this method as well as the application in organic flow synthesis.

## Supporting Information

### Supporting Information File 1

Photograph of the current connector.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-5-70-S1.tif]

### Supporting Information File 2

Photograph of the mounted reactor current connector.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-5-70-S2.tif]

### Supporting Information File 3

Photograph of the preheater connection.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-5-70-S3.tif]

### Supporting Information File 4

Photograph of the reactor setup.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-5-70-S4.tif]

### Supporting Information File 5

Photograph of the thermocouple connection.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-5-70-S5.tif]

### Supporting Information File 6

Photograph of different tubular reactors.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-5-70-S6.tif]

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