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Tetrahedron
Tetrahedron 61 (2005) 10757–10773

The preparation and reaction of enolates within micro reactors

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Received 4 April 2005; revised 26 July 2005; accepted 18 August 2005

Available online 13 September 2005

Abstract—Over the past 5 years, interest in the miniaturisation of chemical synthesis has grown rapidly, however in order to facilitate transfer of the technology from its current position as a research tool to industrial applications, a core understanding of the challenges associated with transferring reactions from the macro to the micro domain is required. This paper therefore aims to broach this problem by investigating the application of micro reactors to a range of commonly employed synthetic reactions including acylation, aldol, alkylation, 1,4-conjugate addition (Michael addition) and the Knoevenagel condensation. Comparison of the results obtained with traditional batch techniques enable us to highlight some of the advantages associated with micro reaction technology.

1. Introduction

Although less common than their analytical counterparts,[1] miniaturised devices capable of performing chemical synthesis, termed micro reactors, have recently received widespread interest from both industry and academia. The desire to miniaturise synthetic reactions has been driven by a need for greater process control, not only as a means of increasing product purity and plant productivity, but also reactor safety.[2,3] With these factors in mind, the micro reactor group at Hull have successfully demonstrated the application of miniaturised systems to a range of solution phase chemistries, contributing greatly to the initial evaluation of micro reactors for synthetic applications.[4,5] This paper follows a series of communications and aims to illustrate, in detail, the challenges associated with the transfer of reactions from the macro to the micro domain, laying the foundations necessary for the ultimate goal of performing novel synthetic procedures in micro fabricated devices.[6–11]

In this context, we define a micro reactor as a device that contains a series of interconnecting channels with cross-sectional dimensions in the range of 10–500 μm. Depending on the end use of the device, a range of substrates have been employed, these include; silicon, glass, quartz, ceramics, polymers and metals.[12] However, due to its compatibility with organic solvents, high mechanical strength, temperature resistance and optical transparency, borosilicate glass is the chosen substrate for the work described herein. As Figure 1 illustrates, the devices consist of a borosilicate glass base plate, containing an etched channel network, and a top block through which reagents are delivered. Thermal bonding of the two layers affords a sealed micro reactor, with typical dimensions of 2.5 cm × 2.5 cm × 2.0 cm for electroosmotic devices[13] and 2.5 cm × 2.5 cm × 0.6 cm for pressure driven applications. Using a suitable pumping mechanism, reagents are brought together within the micro channels, where they are reacted for a specified period of time, prior to collection and analysis. In order to manipulate reagents and products within micro fabricated devices accurate pumping mechanisms are

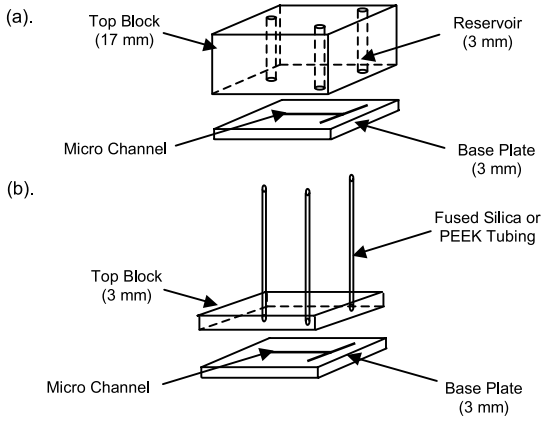

Figure 1. Exploded view of borosilicate glass micro reactors for (a) electroosmotic and (b) pressure-driven applications.

Keywords: Micro reactor; Enolate synthesis.
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doi:10.1016/j.tet.2005.08.076

required, these are loosely categorised as either mechanical or non-mechanical.[14]

1.1. Non-mechanical pumping

In the early 1990's, Manz and co-workers[15] described the use of electrokinetic flow in a miniaturised flow injection system, a concept further investigated by Dasgupta et al.[16] Harrison and co-workers[17] later applied the principle to the mobilisation of fluorescein labelled amino acids in a glass reactor manifold, whereby valve-less control of fluid at a T-shaped intersection was observed. In comparison to the use of mechanical micro pumps, field induced flow is advantageous as the electric field acts as a pump and a valve, enabling both the direction and magnitude of flow to be controlled.[18]

1.1.1. Scope and limitations of electrokinetic flow. Electrokinetic flow comprises of two physical effects; electroosmotic flow (EOF), which is responsible for the velocity of the solvent system as a whole, and electrophoretic flow (EPF), which is an additional velocity effect experienced by charged species within the solvent system. As Figure 2 illustrates, when an ionisable surface such as glass, quartz or Teflon comes into contact with a suitable solvent system, the surface is neutralised with a diffuse layer of positive ions from the bulk liquid.[12] A proportion of the counterions are adsorbed onto the surface, resulting in the formation of an immobile layer, and the remaining positive ions form a transient double layer. Application of an electric field causes the double layer to move towards the most negative electrode, inducing bulk flow within the micro channel.

Although the use of EOF has been well documented within the literature, the manipulation of fluid within open channel networks is inherently irreproducible due to hydrodynamic pressure effects.[19] Consequently, in order to obtain reproducible controlled flow, it is important to ensure that non-uniformities in velocity profile (that arise as a result of different reservoir heights) are excluded or minimised. One such approach is the fabrication of micro porous silica frits (MPS frits) within the micro channels.[20] The porous silica structure acts to reduce the cross sectional area of the micro channel in a specific region, therefore minimising pressure effects while maintaining EOF.[21] Alternatively, Fletcher et al.[22] recently reported the fabrication of a series of narrow channels (restrictions) at strategic points within the main channel network, thus providing the necessary regions of resistance. Clearly, compared to the use of micro porous silica frits, the fabrication of restrictions is more amenable to the large-scale manufacture of micro fluidic devices.

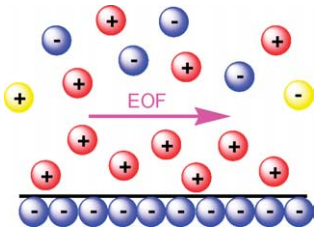


Figure 2. Schematic illustrating the principle of electroosmotic flow.

Table 1. Summary of the flow rates obtained for a series of commonly employed organic solvents

Applied field ($V\ cm^{-1}$)	Average flow rate ($\mu l\ min^{-1}$)[a]			
	MeCN	THF	DMF	EtOH
417	5.30	1.00	1.67	0.90
311	4.08	0.73	1.50	0.70
208	3.00	0.45	1.33	0.50
104	1.90	0.17	1.17	0.30

[a] ≥ 10 measurements were made at each applied field.

$$\nu_{eof} = -\frac{E_{\varepsilon\varepsilon_0}\zeta}{\eta} \quad (1)$$

ν_{eof}=electroosmotic flow velocity, E=applied field, ε=relative dielectric constant of the fluid, ε_0=the permittivity of free space, ζ=zeta potential and η=viscosity.

Equation 1. Determination of the electroosmotic flow velocity.[23]

While EOF has generally been associated with the manipulation of aqueous systems for analytical applications,[23] we have more recently demonstrated the mobilisation of polar solvent systems such as MeOH and DMF.[24] With this in mind, the flow rates of a series of common organic solvents were investigated over a range of applied fields ($V\ cm^{-1}$) (Table 1 and Fig. 3). As Table 2 illustrates, the electroosmotic flow rate is largely determined by the dielectric constant, polarity and viscosity of the solvent system (Eq. 1).[25] Consequently, the technique is restricted to the use of solvents such as alcohols, tetrahydrofuran, dimethylformamide, acetonitrile and aqueous systems.

1.2. Mechanical pumping

Most mechanical or reciprocating pumps are based on the movement of a piston or membrane, resulting in the delivery of fluids or gases in discrete aliquots. Due to the wide array of primary sources actuation of a membrane can be achieved using a variety of techniques including piezoelectric[26] and shape memory alloys.[27] As the pumping mechanism is independent of the device material any fluid can be mobilised, the flow is however, often pulsed (exceptions have been demonstrated[28]). Alternatively, external displacement pumps such as syringe pumps have found widespread use, at a research level, due to their ability to deliver stable, bi-directional flow. The main challenge

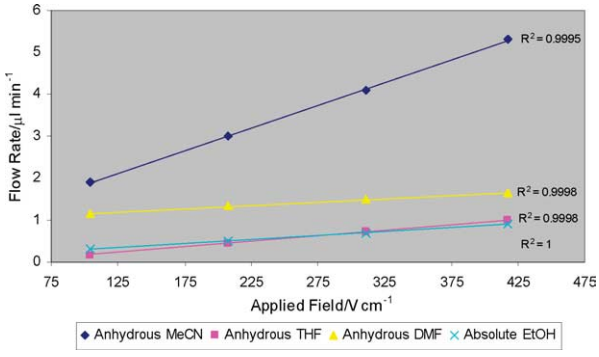


Figure 3. Graph illustrating the relationship between flow rate and applied field for a range of organic solvents.

Table 2. Relationship between the magnitude of EOF and the physical properties of a range of common organic solvents

Solvent	Dielectric constant	Viscosity (cP)	Polarity index (*P*)	Flow rate ($\mu l\ min^{-1}$)
MeCN	37.50 (20 °C)	0.38	5.8	5.30
DMF	36.71 (25 °C)	0.92	6.4	1.67
EtOH	24.55 (25 °C)	1.10	5.2	0.90
THF	7.58 (25 °C)	0.55	4.0	1.00

associated with the use of displacement pumps is obtaining low dead volume, leak free connections between the pump and device.[29] The mechanism is currently very cumbersome resulting in a system whereby the pumps dwarf the device. The low tolerance to particulates also results in the generation of high back-pressure within the system. In addition, the control of multiple inputs represents a challenge, as careful balancing of the flow rates and internal pressures is required.[30] Consequently, we believe that electrokinetic pumping is advantageous as it enables us to obtain reproducible, pulse-free, low flow rates without the generation of high back-pressures. As the pumping mechanism requires no moving parts, the technique is simple to use and free from component wear and tear making it ideal for the continuous manipulation of fluid within miniaturised systems. Therefore, unless otherwise stated, electroosmotic flow is employed for the manipulation of reagents and reaction products within the micro fabricated devices described herein.

1.3. Advantages of miniaturisation

Current production technology is based on the scale-up of successful bench-scale processes to a pilot plant, followed by a final increase in scale to achieve mass production. This approach is however fundamentally flawed as at each stage of scale-up, reactor modifications result in changes to the surface to volume ratio, which in turn have a profound effect on the thermal and mass transportation properties of the reaction. As a result of these variations, it is often necessary to re-optimise the process at each stage of scale-up; consequently the route from bench to production is both costly and time-consuming. It is therefore proposed that through the application of micro reaction technology, the transfer of reactions from the laboratory to production will be both rapid and cost effective as processes would initially be optimised on a single device and in order to increase production capacity, more devices would be employed.[3] Therefore instead of the traditional approach of scaling-up the reactor vessel, the approach of scale-out or numbering-up would be employed (Fig. 4).

From a production perspective, the scale-out approach is advantageous as it enables changes in production volume to be met by simply increasing or decreasing the number of devices employed, therefore meeting customer demand. Additionally, the use of generic reactor designs, such as those described herein, would enable custom syntheses to be performed with relative ease. Compared to a production plant where reactors are generally configured/optimised for a single function, this flexibility is both advantageous and cost effective. In addition, the predictable thermal and mass transportation properties observed within a laminar flow

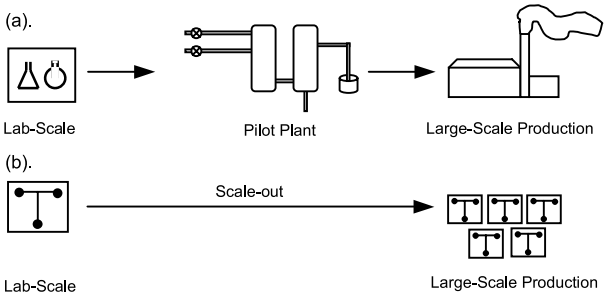
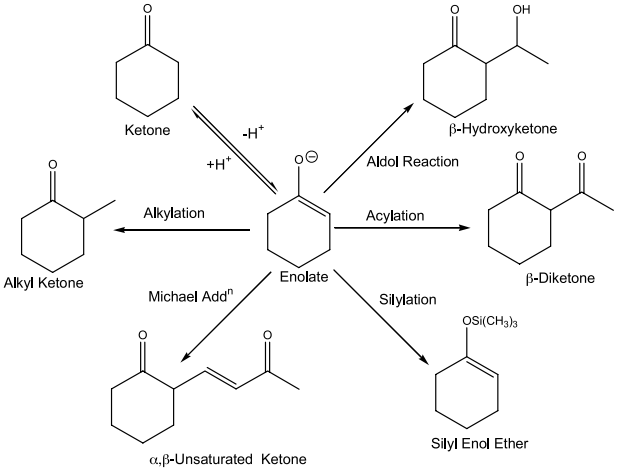


Figure 4. Schematic illustrating the (a) traditional, versus (b) miniaturised approaches to mass production.

environment result in increased reactor control.[2] In traditional large-scale reactor vessels, fluctuations in temperature and concentration are difficult to rapidly address as any alterations made take time to have an effect on the system as a whole. Along with increasing the rate of mixing, decreasing the reactor dimensions results in an inherently high surface to volume ratio. Consequently, heat generated by exothermic reactions can be dissipated rapidly, reducing the likelihood of thermal runaway or hot spot formation. As a result of the uniform reactor conditions obtained, extended reaction times are no longer required in order to obtain high conversions, resulting in fewer, but more often, no side reactions.[2,6]

2. Results and discussion

As a result of the importance of enolate chemistry in the pharmaceutical industry, the synthesis of 1,3-diketones, β-hydroxyketones, α,β-unsaturated ketones and 1,4-addition products (Scheme 1), has been used to demonstrate the key advantages associated with micro reaction technology, these include; rapid reaction optimisation, reduced reaction time, enhanced conversions, reduced by-product formation, in-situ generation of reactive intermediates and the ability to synthesise compounds that require no further purification.



Scheme 1. Illustration of the reaction diversity exhibited by an enolate.

2.1. The regioselective acylation of silyl enol ethers[7,8]

The preparation and subsequent acylation of enolates is a fundamental transformation used in organic synthesis; their ambident nature however, allows the formation of bonds at either the carbon or the oxygen. This often results in the undesirable formation of a mixture of both *O*- and *C*-acylated products, which can prove difficult to separate, resulting in low yields.[31] Consequently, a large amount of work has been undertaken in order to explore and understand those reaction conditions that promote the regioselective acylation of enolates; that is, the nature of the counterion, reaction temperature, solvent; stoichiometry of reagents, order of reagent addition and type of acylating reagent employed.[32]

Although careful selection of the aforementioned conditions has been shown to influence reaction regioselectivity, many of the 1,3-diketones prepared remain contaminated with small amounts of *O*-acylated product.[33] With this in mind, we recently demonstrated a simple technique for the regioselective synthesis of 1,3-diketones, free from any competing *O*-acylation or diacylation products. The procedure involved regeneration of enolates from silyl enol ethers[34] using a catalytic quantity of 'anhydrous' tetra-*n*-butylammonium fluoride (TBAF) **1**, followed by acylation using acyl halides (1 h) or acyl cyanides (24 h).[8] Using this approach, α-substituted ketones were found to give *C*-acylated products when treated with either acyl halides or cyanides, whereas non α-substituted ketones reacted to give *O*-acylation with acyl halides and *C*-acylation with acyl cyanides. Based on these findings, the catalytic desilylation approach was further investigated within an EOF-based micro reactor.[7]

Prior to performing an EOF-based micro reaction it is important to consider what reagent concentration, flow rate (a function of applied field) and length of experiment to use. As one of the aims of micro reaction technology is to synthesise compounds more efficiently, the use of higher reagent concentrations is desirable as this enables a greater quantity of product to be synthesised in a shorter time; consequently the limiting factor is reagent solubility (Section 2.5.2). When employing EOF, the flow rate is dependant on both the applied field and the physical properties of the reagents; as a result applied fields vary to ensure that equal flow of reagents is obtained from all reservoirs. Finally, the length of experiment is chosen in order to obtain a sufficient quantity of product for off-line analysis by GC–MS and does not reflect the residence time of reagents within the micro reactor channel; unless otherwise stated reactions are performed for 20 min.

In order to perform the acylation reaction, solutions of 'anhydrous' TBAF **1** (40 μl, 0.1 M), benzoyl fluoride **2** (40 μl, 1.0 M) and trimethyl(1-phenylvinyloxy)silane **3** (40 μl, 1.0 M) in anhydrous THF were placed in reservoirs A, B and C, respectively, (Fig. 5). The reagents were then manipulated within the device, using the following applied fields 333, 455, 333 and 0 V cm^{-1} (to reservoirs A, B, C and D, respectively), and the reaction products collected in reservoir D. Analysis of the reaction mixture by off-line GC–MS showed that 100.0% conversion of silyl enol ether

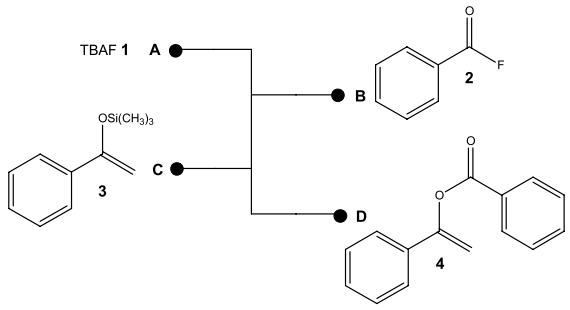


Figure 5. Schematic of the reactor manifold used for the synthesis of benzoic acid 1-phenylvinyl ester **4**.

3 to benzoic acid 1-phenylvinyl ester **4** had occurred and crucially, no *C*-acylated **5** or diacylated products were detected. Having successfully demonstrated the micro-scale synthesis of benzoic acid 1-phenylvinyl ester **4**, the kinetically slower *C*-acylation reaction (24 h in batch) was investigated.

Substitution of benzoyl fluoride **2** with benzoyl cyanide **6** (40 μl, 1.0 M) enabled the synthesis of 1,3-diphenylpropane-1,3-dione **5** to be investigated using the same micro reactor manifold. Manipulation of the reagents using 417, 318, 476 and 0 V cm^{-1}, resulted in 100.0% conversion of the enol ether **3** to 1,3-diphenylpropane-1,3-dione **5**, again no competing *O*-acylated **4** or diacylated products were observed. The generality of the technique was subsequently demonstrated using trimethyl(1-phenyl-propenyloxy)silane **7** and cyclohex-1-enyloxy(trimethylsilane) **8** to afford 2-methyl-1,3-diphenylpropane-1,3-dione **9** and 2-benzoylcyclohexanone **10**, respectively. Again, all standard solutions were prepared in anhydrous THF and the reagents introduced into the reactor as follows; 'anhydrous' TBAF **1** (40 μl, 0.1 M) in reservoir A, acylating reagent (40 μl, 1.0 M) in reservoir B, the enol ether (40 μl, 1.0 M) in reservoir C and the reaction products collected in reservoir D. Manipulation of the reagents using the applied fields reported in Table 3 resulted in 100.0% conversion to the respective 1,3-diketone. In summary, we have demonstrated a simple, regioselective technique for the acylation of an array of tetra-*n*-butylammonium enolates in an EOF-based micro reactor (Table 3); demonstrating an approach, which is clearly suited to the generation of combinatorial libraries.

2.2. The synthesis of β-hydroxyketones using silyl enol ethers[9]

Having successfully demonstrated the use of silyl enol ethers as enolate precursors with respect to regioselective acylation, the investigation was extended to incorporate the synthesis of β-hydroxyketones. In the mid 1970's, Noyori

Table 3. Comparison of the conversions obtained for the acylation of silyl enol ethers in batch and in a micro reactor

Product no.	Conversion (%)		Applied field (V cm^{-1})
	Batch	Micro reaction	
4	100.0	100.0	333, 455, 333 and 0
5	95.0	100.0	417, 318, 476 and 0
9	100.0	100.0	375, 455, 405 and 0
10	100.0	100.0	208, 409, 357 and 0

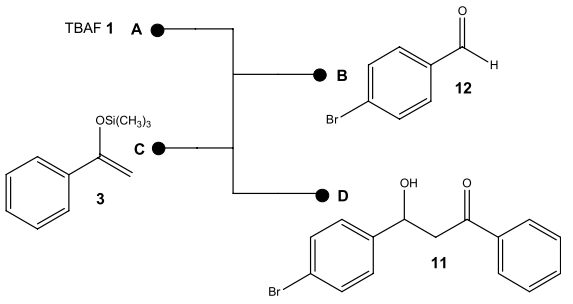


Figure 6. Schematic of the micro reactor manifold used for the synthesis of 3-(4-bromophenyl)-3-hydroxy-1-phenylpropan-1-one **11**.

et al.[35] demonstrated the aldol reaction of silyl enol ethers as a means of circumventing the dehydration step frequently associated with the aldol condensation. As the resulting β-hydroxyketone is a versatile synthon finding application for example in the synthesis of natural products derived from polyketide biosynthetic pathways, we investigated their synthesis in an EOF-based micro reactor.

The synthesis of 3-(4-bromophenyl)-3-hydroxy-1-phenylpropan-1-one **11** was investigated using anhydrous THF as the solvent system. As Figure 6 illustrates, 'anhydrous' TBAF **1** (40 μl, 0.1 M) was placed in reservoir A, 4-bromobenzaldehyde **12** (40 μl, 1.0 M) was placed in reservoir B and trimethyl(1-phenylvinyloxy)silane **3** (40 μl, 1.0 M) in reservoir C. Manipulation of the reagents using 375, 409, 381 and 0 V cm^{-1} resulted in 100.0% conversion of the silyl enol ether **3** to 3-(4-bromophenyl)-3-hydroxy-1-phenylpropan-1-one **11**. Using the aforementioned procedure, the reaction was subsequently repeated using cyclohex-1-enyloxy(trimethylsilane) **8** (40 μl, 1.0 M), whereby application of 417, 455, 476 and 0 V cm^{-1} resulted in only 1.0% conversion of the enol ether **8** to 2-[(4-bromophenyl)-hydroxymethyl]cyclohexanone **13**. Upon altering the applied fields to 417, 341, 333 and 0 V cm^{-1}, and hence increasing reagent residence time within the device, the conversion to product **13** was increased to 100.0% wrt residual enol ether **8**. As Table 4 illustrates, compared to traditional batch techniques, enhancements in conversion were obtained as a result of performing the reactions within a micro reactor; in the case of 3-(4-bromophenyl)-3-hydroxy-1-phenylpropan-1-one **11**, an increase of 20.0% was observed. Along with a reduction in reaction times, the technique is highly desirable as no dehydration products were detected.

2.2.1. Alternative silylation technique. The use of preformed enolates, in the form of silyl enol ethers,[36,37] has allowed us to successfully demonstrate the regeneration and subsequent reaction of a series of enolates within a micro reactor (Sections 2.1 and 2.2). This approach can however be disadvantageous when base sensitive molecules are employed as poor conversions result in products often contaminated with inorganic salts.[38] In order to circumvent these problems, many groups have investigated mild and efficient alternatives.[39,40] Nakamura and co-workers[41] demonstrated the use of ethyltrimethylsilylacetate (ETSA) **14** and 'anhydrous' TBAF **1** for the *O*-silylation of ketones and alcohols under nearly neutral conditions. As Scheme 2 illustrates, TBAF **1** acts catalytically with the only by-product of the reaction being ethyl acetate. Consequently, this approach was of particular interest as the reaction conditions are mild and no inorganic residues are formed during the reaction.

Table 4. Summary of the conversions obtained for the synthesis of β-hydroxyketones **11** and **13** in batch and a micro reactor

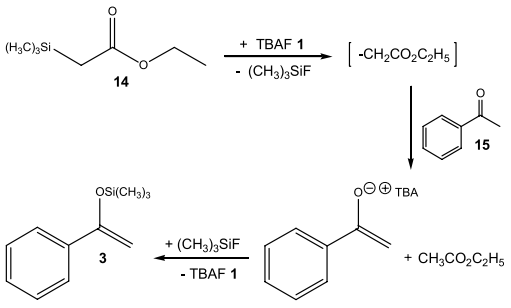
Product no.	Conversion (%)		Applied field (V cm^{-1})
	Batch	Micro reaction	
11	80.0	100.0	375, 409, 381 and 0
13	93.0	1.0	417, 341, 333 and 0
13	93.0	100.0	333, 455, 333 and 0

Prior to transferring the technique to a micro reactor, the synthesis of trimethyl(1-phenylvinyloxy)silane **3** was investigated in batch. Reaction of ETSA **14** and acetophenone **15** in the presence of 'anhydrous' TBAF **1** (0.1 equiv) afforded 56.2% conversion to enol ether **3** after only 20 min. Surprisingly however, after 2 h only 6.0% trimethyl(1-phenylvinyloxy)silane **3** remained; an observation that is attributed to competing desilylation and protonation of the tetra-*n*-butylammonium enolate. Obviously when performing the reaction in batch, the limited lifetime of the enol ether is disadvantageous, however by transferring the reaction to a micro reactor we believed that the spatial control obtained would enable us to synthesise the enol ether, generate the tetra-*n*-butyl ammonium enolate and react it to afford the desired product in high conversion.

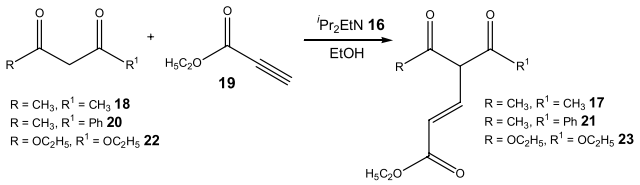
In order to demonstrate the technique, the synthesis of trimethyl(1-phenylvinyloxy)silane **3** and its subsequent reaction to afford benzoic acid 1-phenylvinyl ester **4**, was selected as a model reaction. A premixed solution of acetophenone **15** and ETSA **14** (40 μl, 1.0 M) in anhydrous THF was placed in reservoir A, a solution of 'anhydrous' TBAF **1** (40 μl, 0.1 M) in THF in reservoir B and a solution of benzoyl fluoride **2** (40 μl, 1.0 M) in THF in reservoir C. Manipulation of the reagents using 417, 417 and 0 V cm^{-1}, resulted in 100.0% conversion of acetophenone **15** to product **3**, demonstrating the potential of this technique for the in-situ synthesis of silyl enol ethers and their subsequent reaction within the micro fluidic device.

2.3. Michael addition[6]

Following the successful synthesis of a series of β-hydroxyketones, 1,3-diketones and *O*-acylated ketones within an EOF-based micro reactor, we were interested in extending



Scheme 2. Preparation of trimethyl(1-phenylvinyloxy)silane **3** using ETSA **14**/TBAF **1**.

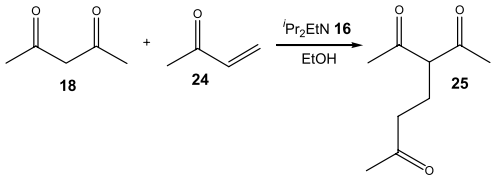


Scheme 3. Synthesis of Michael adducts **17**, **21** and **23** using diisopropylethylamine **16**.

the investigation to include the preparation of 1,3-diketone enolates. In order to demonstrate their synthetic utility, a series of 1,4-conjugate additions were investigated (Scheme 3). With the extensive range of donor and acceptor compounds featured within the literature serving to demonstrate the synthetic scope associated with the Michael reaction,[42,43] the investigation concentrated on the reaction of 1,3-diketones (donor) and α,β-unsaturated carbonyl compounds (acceptor). As the protons of 1,3-dicarbonyl compounds are relatively acidic ($^{MeCN}pK_{BH^+}$ 9–13), deprotonation was achieved using the organic base diisopropylethylamine **16**.

Prior to investigating the reactions within a micro reactor, synthetic standards of the target products were synthesised. (*E*)-4-Acetyl-5-oxohex-2-enoic acid ethyl ester **17** was prepared in 89.0% yield via the dropwise addition of 2,4-pentanedione **18** to a stirred solution of ethyl propiolate **19** and diisopropylethylamine **16** in absolute EtOH. Analysis of the product by ^{1}H NMR, indicated that the Michael adduct **17** formed was predominantly the trans isomer (>99.0% selectivity). With this in mind, the reaction was subsequently repeated using 1-phenylbutane-1,3-dione **20** to afford (*E*)-4-benzoyl-5-oxohex-2-enoic acid ethyl ester **21** in 77.0% yield and diethyl malonate **22** to give (*E*)-4-ethoxycarbonylpent-2-enedioic acid ethyl ester **23** in 82.5% yield. The generality of the technique was examined using the alkenic acceptor methyl vinyl ketone **24**, whereby 3-acetylheptane-2,6-dione **25** was obtained in 91.0% yield (Scheme 4).

Using absolute EtOH as the solvent system, the synthesis of (*E*)-4-acetyl-5-oxohex-2-enoic acid ethyl ester **17** was investigated in a micro reactor (Fig. 7). Diisopropylethylamine **16** (40 μl, 5.0 M), 2,4-pentanedione **18** (40 μl, 5.0 M) and ethyl propiolate **19** (40 μl, 5.0 M) were manipulated within the device using 417, 318, 333 and 0 V cm^{-1}. Off-line analysis of the reaction mixture showed 56.0% conversion of 2,4-pentanedione **18** to (*E*)-4-acetyl-5-oxohex-2-enoic acid ethyl ester **17**, with the remaining 44.0% being unreacted starting material **18**. This was subsequently increased to 95.0% by employing stopped flow (Flow Regime B) (for a detailed discussion of flow regimes see Section 4.2.2). The increase in conversion was



Scheme 4. Synthesis of 3-acetylheptane-2,6-dione **25** using diisopropylethylamine **16**.

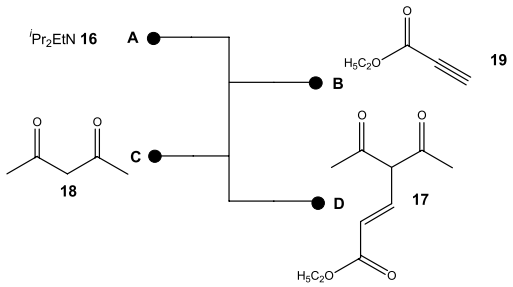


Figure 7. Schematic of the micro reactor manifold used for the synthesis of (*E*)-4-acetyl-5-oxohex-2-enoic acid ethyl ester **17**.

originally attributed to an increase in diffusive mixing between the reagent streams,[6] this is however, unlikely as micro-scale reactions are often regarded as being rate limited, not diffusion limited.[2] As both reactions were performed over the same period of time, the observed increase in conversion is attributed to an increase in residence time within the micro reactor.

Based on these initial observations, the synthesis of (*E*)-4-benzoyl-5-oxohex-2-enoic acid ethyl ester **21** was subsequently investigated using absolute EtOH as the solvent system. Standard solutions of diisopropylethylamine **16** (40 μl, 5.0 M), ethyl propiolate **19** (40 μl, 5.0 M) and 1-phenylbutane-1,3-dione **20** (40 μl, 5.0 M) were manipulated within the device using the following applied fields, 417, 318, 333 and 0 V cm^{-1}. Employing Flow Regime A resulted in 15.0% conversion of 1-phenylbutane-1,3-dione **20** to (*E*)-4-benzoyl-5-oxohex-2-enoic acid ethyl ester **21**, with the remaining 85.0% being unreacted diketone **20**. Again, application of a stopped flow regime (Flow Regime B) resulted in an increase in conversion to 34.0%, which was further increased to 100.0% by employing a longer period of stopped flow (Flow Regime C). The technique was further exemplified using the synthesis of (*E*)-4-ethoxycarbonylpent-2-enoic acid ethyl ester **23**, whereby Flow Regime A (417, 386, 381 and 0 V cm^{-1}) resulted in 40.0% conversion to product **23** compared to 100.0% as a result of employing Flow Regime B.

Having successfully demonstrated a number of conjugate additions using the alkynic acceptor ethyl propiolate **19**, the synthesis of 3-acetylheptane-2,6-dione **25** was subsequently investigated using methyl vinyl ketone **24** (Scheme 4). Using absolute EtOH as the solvent system, diisopropylethylamine **16** (40 μl, 5.0 M), 2,4-pentanedione **18** (40 μl, 5.0 M) and MVK **24** (40 μl, 5.0 M) were manipulated within the device (417, 455, 476 and 0 V cm^{-1}) and the reaction products collected in reservoir D. As a result of employing Flow Regime A, 13.0% conversion to product **25** was obtained, this was further increased to 96.0% conversion as a result of employing Flow Regime B (Table 5).

To summarise, using the Michael addition as a model reaction, we have demonstrated the ability to rapidly optimise reactions by employing a range of flow regimes in an EOF-based micro reactor. In addition, it must also be noted that as a result of the increased reaction control obtained within the micro fluidic device, no by-products were detected; compared to batch, where a competing

Table 5. Comparison of the effect of flow regime on conversion to Michael adduct in an EOF-based micro reactor

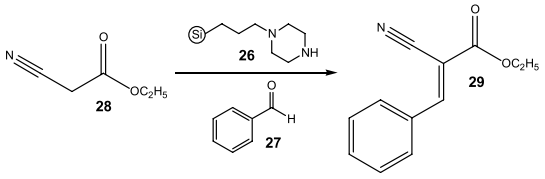
Product no.	Conversion (%)		
	Flow regime A	Flow regime B	Flow regime C
17	56.0	95.0	—
21	15.0	34.0	100.0
23	40.0	100.0	—
25	13.0	96.0	—

reaction between the base **16** and the Michael acceptor **19** was frequently observed.[44]

2.4. The use of solid-supported bases for the synthesis of analytically pure condensation products[10]

Due to the widespread pharmaceutical interest in the Knoevenagel condensation (Scheme 5), we investigated the synthesis of α,β-unsaturated compounds in an EOF-based micro reactor. As the reactions are base catalysed, one of the main disadvantages is that the reaction products require purification in order to remove the organic base and its salt. With this in mind, we proposed that by incorporating a series of supported bases (Fig. 8) into a micro fabricated device, product purity could be increased while simultaneously maintaining the advantages associated with reaction miniaturisation. In order to evaluate the use of supported reagents within an EOF-based system, a miniaturised flow reactor was designed (Fig. 9). This approach not only enabled reagents to be packed with ease but also provided a relatively inexpensive, versatile system. Using the set-up illustrated in Figure 9, 5 mg of 3-(1-piperazino)propyl-functionalised silica gel **26** (4.75×10^{-3} mmol) was packed into a borosilicate glass capillary (500 μm×3.0 cm) and micro porous silica frits placed at both ends, the capillary was then placed between two glass reservoirs. A 1:1 mixture of benzaldehyde **27** and ethyl cyanoacetate **28** (40 μl, 1.0 M) in MeCN was placed in reservoir A and MeCN in reservoir B (40 μl).

Application of 333 and 0 V cm^{-1} resulted in the mobilisation of the reaction mixture through the packed bed at a flow rate of 0.5 μl min^{-1}. Operating the device continually for 4.75 h (14×20 min runs) resulted in the synthesis of 0.025 g (0.124 mmol, 98.9%) of 2-cyano-3-phenyl acrylic acid ethyl ester **29**. The 'crude' reaction products were then analysed by NMR spectroscopy to confirm product purity.[10] The generality of the technique was subsequently investigated using 4-bromobenzaldehyde **12**, 3,5-dimethoxybenzaldehyde **30** and 4-benzyloxybenzaldehyde **31**. As Table 6 illustrates, the respective condensation products **32**, **33**, and **34** were obtained in >95.0% conversion. In addition, we investigated the condensation of malononitrile **35** with the aforementioned aldehydes to afford condensation products



Scheme 5. General scheme illustrating the use of a functionalized silica gel **26**, in the Knoevenagel condensation.

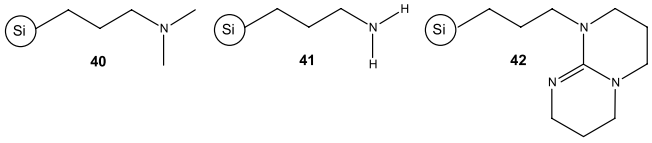


Figure 8. Schematic illustrating the silica-supported bases investigated.

36 (96.9%), **37** (96.3%), **38** (97.8%) and **39** (99.7%), respectively.

Using the synthesis of unsaturated ketone **29** as a model reaction, we also investigated the use of other supported bases, namely; 3-(dimethylamino)propyl-functionalised silica gel **40**, 3-aminopropyl-functionalised silica gel **41** and 3-(1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-*a*]-pyrimidino)propyl-functionalised silica gel **42** (Fig. 8) whereby 99.4, 100.0 and 99.3% conversion to the desired product 2-cyano-3-phenyl acrylic acid ethyl ester **29** was observed. Compared to standard batch techniques, the approach described is advantageous as the supported reagents can be recycled with ease, enabling more consistent results to be obtained. In addition, the generation of localised concentration gradients enables reactions to be driven to completion without the need to employ large quantities of catalyst. In summary, we have demonstrated the successful incorporation of a series of silica-supported bases within an EOF-based device, enabling the synthesis and characterisation of eight condensation products whereby no additional product purification was required.

2.5. Enolate alkylation

Following the successful preparation of a range of 1,3-diketone enolates using both solution phase and solid-supported organic bases, the next step was to evaluate the preparation of enolates directly from ketones such as acetophenone **15**. This was firstly demonstrated using organic peralkylated polyaminophosphazene bases (Section 2.5.1) and secondly using inorganic bases (Section 2.5.2–2.5.3).

2.5.1. Phosphazene bases. Over the past 30 years, research has been undertaken in order to increase the inherent strength (pK_{BH^+}) of organic bases[45] and although a few examples are commercially available, such as heptamethylisobiguanide,[46] however they were not well received by synthetic chemists.[47] The field was however transformed in the early 1990's by Schwesinger and co-workers[48,49] with

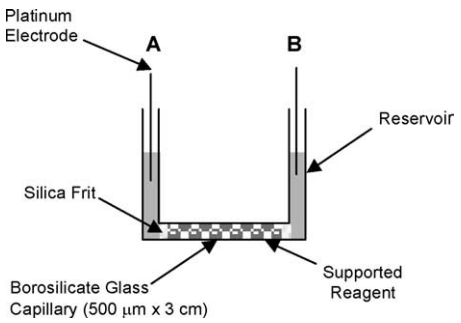


Figure 9. Schematic of the reaction set-up used for the evaluation of solid-supported reagents, in a miniaturized system.

Table 6. Summary of the conversions obtained in a micro fabricated device using 3-(1-piperazino)propyl-functionalised silica gel **26**

Product no.	Applied field ($V\ cm^{-1}$)	Flow rate ($\mu l\ min^{-1}$)	Conversion[a] (%)
29	333	0.5	99.1
32	333	0.3	99.5
33	333	0.3	94.7
34	333	0.5	95.1
36	167	1.0	96.9
37	167	0.5	96.3
38	167	0.7	97.8
39	167	1.0	99.7

[a] ≥ 10 replicates were performed for each compound.

the synthesis of a series of strong, uncharged bases, termed peralkylated polyaminophosphazenes or simply phosphazenes (Fig. 10).[50] Compared to traditional organic bases such as diisopropylethylamine **16** and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) **43**, the peralkylated phosphazene bases demonstrate a dramatic increase in basicity, of between 14.9 and 30.6 pK_{BH^+} units, representing base strengths more commonly associated with inorganic bases such as *n*-butyllithium **44** (Table 7).[51]

In order to demonstrate enolate formation within a micro reactor, the synthesis of 2-benzylcyclohexanone **47** was selected as a model reaction (Scheme 6). As a means of identifying any advantages associated with the miniaturisation of this technique, the reaction was initially performed in batch. As Table 8 illustrates, despite the fact that 2-benzylcyclohexanone **47** was successfully synthesised

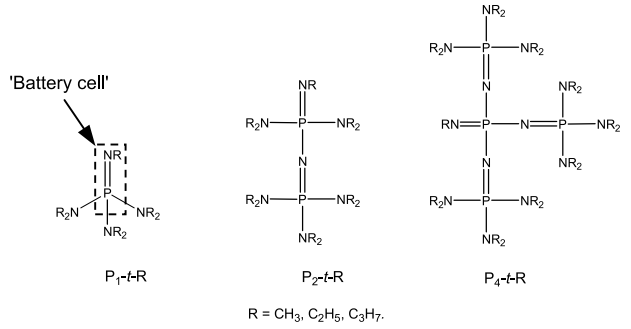
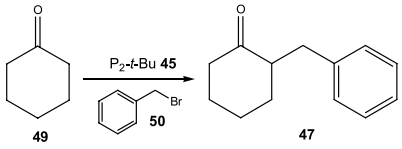


Figure 10. General structure of a series of peralkylated polyaminophosphazenes bases.

Table 7. Comparison of base strength as a function of charge delocalization for a range of organic bases

Base	$^{MeCN}pK_{BH^+}$	Charge declocalisation
DBU **43**	24.3	2
P_1-*t*-Bu	26.9	5
P_2-*t*-Bu **45**	33.5	9
P_3-*t*-Bu	38.6	13
P_4-*t*-Bu **46**	42.6	17



Scheme 6. Preparation of 2-benzylcyclohexanone **47** using P_2-*t*-Bu **45**.

Table 8. Comparison of the proportion of by-product formed in batch and a micro reactor for the alkylation of cyclohexanone **49**

Base	Conversion ratio **47**:**48**[a]	
	Batch	Micro reaction
P_2-*t*-Bu **45**	40.0:7.0	84.0:0.0
P_4-*t*-Bu **46**	15.0:40.0	N/A

[a] Remainder is unreacted starting material.

using both P_2-*t*-Bu **45** and P_4-*t*-Bu **46**, the reaction mixtures were found to contain appreciable amounts of the dialkylated product 2,2-dibenzylcyclohexanone **48**. With this in mind, we investigated the synthesis of 2-benzylcyclohexanone **47** in an EOF-based micro reactor.

Using anhydrous THF as the solvent system, cyclohexanone **49** (40 µl, 0.25 M) was placed in reservoir A, P_2-*t*-Bu **45** (40 µl, 0.25 M) in reservoir B and benzyl bromide **50** (40 µl, 0.25 M) in reservoir C (Fig. 11). The reagents were mobilised within the device using the following applied fields, 417, 455, 476 and $0\ V\ cm^{-1}$ and the reaction products collected in anhydrous THF (40 µl) at reservoir D. Analysis of the reaction products by GC–MS illustrated 84.0% conversion to product **47** (with respect to residual cyclohexanone **49**) demonstrating a significant increase in conversion compared to that obtained in batch (44.0%). The technique also proved advantageous as no dialkylation products **48** were detected when the reaction was performed in a micro reactor. This observation is attributed to the reduced reaction times employed in a micro reactor, i.e. the reaction mixture is removed from the reactor and quenched prior to the 2nd alkylation. The spatial control obtained within such a device therefore enabled by-product formation to be eliminated, enabling the synthesis of uncontaminated products.[52]

In spite of the array of examples featured within the literature, chemists remain hesitant to employ phosphazene bases, in preparative scale reactions, due to their cost (typically £21 g^{-1}). To some extent, this has been addressed by the availability of polymer-supported derivatives, which enable their efficient separation and recovery from a reaction mixture.[53] Incorporation of these supported bases into a micro fabricated device (Section 2.4) would enable the continuous synthesis of base free reaction products coupled with enhanced reaction control.

In summary, using the synthesis of 2-benzylcyclohexanone **47** as a model reaction, we have demonstrated significant

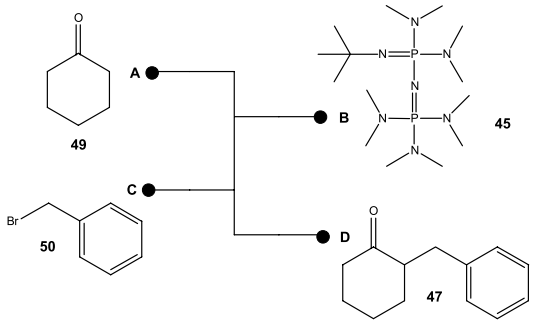


Figure 11. Schematic of the reactor manifold used for the synthesis of 2-benzylcyclohexanone **47**.

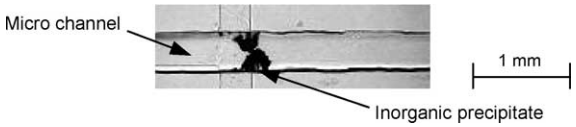


Figure 12. Optical microscope image of a blocked micro channel, caused by the precipitation of an inorganic base.

enhancements in conversion compared to batch, i.e. 84.0% cf. 40.0%, along with significantly enhancing product selectivity. In addition, the use of phosphazene bases enabled us to demonstrate the synthesis of previously inaccessible carbanions within an EOF-based micro reactor.

2.5.2. Inorganic bases. Although we have described numerous techniques for the preparation of enolates within a micro reaction environment, we are yet to discuss their preparation using inorganic bases. Again, the synthesis of 2-benzylcyclohexanone **47** was used as a model reaction for the investigation of the following bases; lithium bis(trimethylsilyl)amide **51**, sodium bis(trimethylsilyl) amide **52**, potassium bis(trimethylsilyl)amide **53**, sodium *tert*-butoxide **54**, potassium *tert*-butoxide **55**, lithium *tert*-butoxide **56**, lithium 2,2,6,6-tetramethylpiperidine **57**, lithium diisopropylamide **58**, lithium phenoxide **59**, sodium methoxide **60** and sodium ethoxide **61**.

Due to their inherent ionic nature, many reagents used in organic synthesis are largely insoluble in non-polar organic solvents. In this case, the relative insolubility of inorganic bases within solvents such as THF, DMF and MeCN (0.05–1.0 M) proved problematic, as blockage formation within the micro channels resulted in retardation of EOF (Fig. 12). These observations were initially surprising as Skelton et al.[54] had previously demonstrated the use of NaOMe **60** in MeOH, within an EOF-based device, for the synthesis of a range of stilbenes. The mobilisation of NaOMe **60** was inferred via the generation of a purple coloured intermediate (ylide) within the micro channel and the subsequent off-line detection of the respective stilbene ester. We however postulate that the base was successfully mobilised as a result of its enhanced solubility within the polar solvent system employed. Consequently, in order to further investigate the mobilisation of inorganic bases by EOF, a means of ensuring greater solubility was required.

2.5.3. Enhanced base solubility using crown ethers. In 1967, Pedersen et al.[55] demonstrated the complete dissolution of potassium permanganate in benzene by employing a stoichiometric quantity of the cyclic ether, 18-crown-6 **62**. A phenomenon that was later attributed to the separation of the metal ion from its associated ions, rendering the salt soluble in the non-polar media. With this in mind, we postulated that by solvating inorganic bases with their respective crown ether, increased solubility could be achieved; enabling their electro osmotic mobilisation in solvents such as THF. In order to evaluate this approach, we again used the preparation of 2-benzylcyclohexanone **47** in THF as a model reaction. As Figure 13 illustrates, a solution of cyclohexanone **49** and benzyl bromide **50** (40 μl, 1:1) was placed in reservoir A and a solution of base and crown ether (40 μl, 1:1) was placed in reservoir B. The reagents were manipulated within the device using 417, 455 and

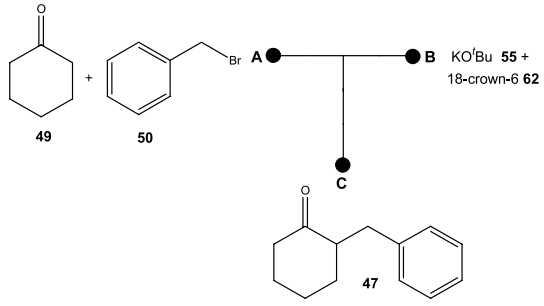


Figure 13. Typical reactor manifold used for the determination of inorganic base flow by EOF.

0 V cm^{-1} and the reaction products collected in reservoir C. As the aim of the investigation was to rationalise the problems associated with the mobilisation of inorganic bases by EOF, at this stage, the detection of 2-benzylcyclohexanone **47** (and the respective crown ether) by GC–MS was considered indicative of base mobilisation. Consequently, conversions and optimised reaction conditions are not provided. In accordance with the literature, 18-crown-6 **62** was investigated for potassiated bases, 15-crown-6 **63** for sodiated bases and 12-crown-4 **64** for lithiated bases.[55]

Using the aforementioned methodology, 0.5–1.0 M solutions of KHMDS **53**, NaO^{t}Bu **54** and KO^{t}Bu **55** were successfully mobilised by EOF. Extension of the technique to NaHMDS **52**, LiO^{t}Bu **56** and LiHMDS **51** however, proved problematic as over the course of the micro reaction, the contents of reservoir B became turbid, resulting in the partial blockage of the micro channel; an observation attributed to decomposition of the base. In order to prevent base decomposition, the reagent reservoirs were covered with a series of PTFE bungs, as illustrated in Figure 14. Using this approach, reagent turbidity was prevented, enabling the successful mobilisation of NaHMDS **52** and LiO^{t}Bu **56** by EOF.[56] In contrast, no electrokinetic flow was observed for LiHMDS **51**; with all solutions forming a gelatinous precipitate within the reagent reservoir and micro channel.

Due to the widespread application of the base sodium hydride **65**, its mobilisation by EOF was also investigated, however as NaH **65** is not strong enough to provide complete deprotonation of cyclohexanone **49**, the benzylation of phenol **66** was employed as a model reaction (Scheme 7). Using either anhydrous THF or MeCN as the solvent system, NaH **65** and 15-crown-5 **63** (40 μl, 0.5 M) were placed in reservoir A, phenol **66** (40 μl, 0.5 M) in reservoir B and benzyl bromide **50** (40 μl, 0.5 M) in reservoir C (Fig. 15). The reagents were manipulated within the micro reactor using applied fields, 417, 455, 476 and

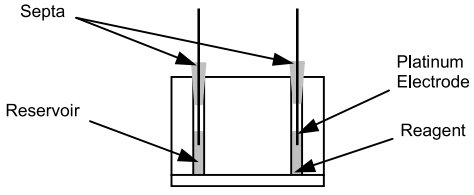
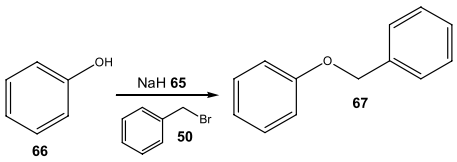


Figure 14. Schematic illustrating the reaction set-up used for moisture/air sensitive micro reactions.



Scheme 7. Synthesis of benzyloxybenzene **67** using NaH **65**.

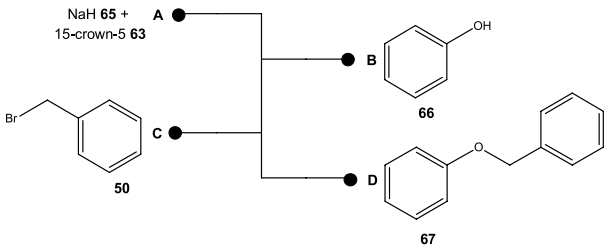


Figure 15. Schematic illustrating the reaction manifold used for the synthesis of benzyloxybenzene **67**.

0 V cm^{-1} (500, 588, 769 and 0 V cm^{-1} when employing MeCN) and the reaction products collected in reservoir D. The detection of benzyloxybenzene **67** and 15-crown-5 **63** was indicative of base mobilisation. In summary, as a result of increasing inorganic base solubility, by the addition of a stoichiometric quantity of crown ether, we have successfully demonstrated the electrokinetic mobilisation of six inorganic bases and their subsequent use for the synthesis of 2-benzylcyclohexanone **47** (Table 9).

2.6. Diastereoselective alkylation[11]

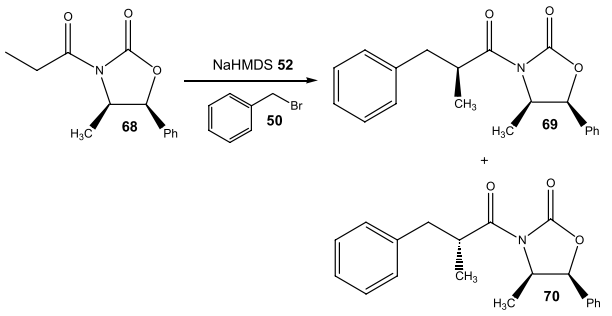
The preparation of compounds with specific stereochemistry is of great interest to pharmaceutical companies as often one enantiomer exhibits biological activity whereas the other may be inactive or even harmful. With this in mind, one such approach for the synthesis of enantiomerically pure compounds is the use of chiral auxiliaries.[57]

Based on initial observations by Skelton et al.,[54] where product stereoselectivity was found to be influenced as a result of synthesising a series of stilbene esters in a micro reactor, the effect on reaction diastereoselectivity was of interest. In order to investigate the factors that affect product diastereoselectivity, the reactions were initially performed in batch, enabling the preparation and characterisation of synthetic standards (Scheme 8). Using methodology established by Evans et al.[58] the enolate of 4-methyl-5-phenyl-3-propionyloxazolidinone **68** was alkylated, using

Table 9. Mobilisation of inorganic base/crown ether complexes by EOF

Base	Crown ether	Applied field (V cm^{-1})	EOF
KO^{t}Bu **55**	18-Crown-6 **62**	417, 455 and 0	✓
KHMDS **53**	18-Crown-6 **62**	417, 455 and 0	✓
NaO^{t}Bu **54**	15-Crown-5 **63**	417, 455 and 0	✓
NaHMDS **52**	15-Crown-5 **63**	417, 455 and 0	✓
NaH **65**	15-Crown-5 **63**	417, 455, 476 and 0	✓
NaH **65**[a]	15-Crown-5 **63**	500, 588, 769 and 0	✓
LiO^{t}Bu **56**	12-Crown-4 **64**	417, 455 and 0	✓
LiHMDS **51**	12-Crown-4 **64**	417, 455 and 0	×

[a] Performed in anhydrous MeCN.



Scheme 8. Diastereoselective alkylation of 4-methyl-5-phenyl-3-propionyl oxazolidinone **68**.

benzyl bromide **50**, to afford diastereomers **69** and **70** in an overall yield of 68.0% and a ratio of 85:15 (**69**:**70**) (at −100 °C). Although Evans et al.[69] report greater diastereoselectivities, in practise they are difficult to reproduce. With this in mind, it was postulated that due to the excellent thermal and mass transportation properties observed within micro fluidic devices, product diastereoselectivity, and reaction reproducibility, could be improved as a result of conducting the reaction in a micro reactor.

Although many reactions have been demonstrated within micro reactors at temperatures ranging from 4 to 300 °C,[59] few authors with the exception of Yoshida[60] and Schwalbe,[2] report reactions performed at reduced temperatures. Using the following experimental procedure, the synthesis of diastereomers **69** and **70** was investigated within a pressure-driven system; a standard solution of NaHMDS **52** (0.5 M) in anhydrous THF was added from syringe A (50 µl min^{-1}), a solution of 4-methyl-5-phenyl-3-propionyloxazolidinone **68** (0.5 M) in anhydrous THF was added from syringe B (50 µl min^{-1}) and a solution of benzyl bromide **50** (0.5 M) from syringe C (50 µl min^{-1}). In order to maintain the reactor temperature, the device was submerged within a CO_2–ether bath and the reaction products collected at room temperature (Fig. 16). To ensure results obtained were representative of reactions occurring within the micro fabricated device, the reaction products were quenched upon collection. Using this approach, the chiral enolate was formed within the central micro channel and reacted with benzyl bromide in the microtee, to afford diastereomers **69** and **70** in 31.0% conversion and a ratio of 94:6 (**69**:**70**). In order to increase the conversion obtained, the flow rate was firstly reduced to 20 µl min^{-1} and finally to 10 µl min^{-1}, resulting in an increase in conversion to 38.0% and 41.0% respectively. Most importantly however, the observed diastereoselectivity increased to from 94:6 to 99:1

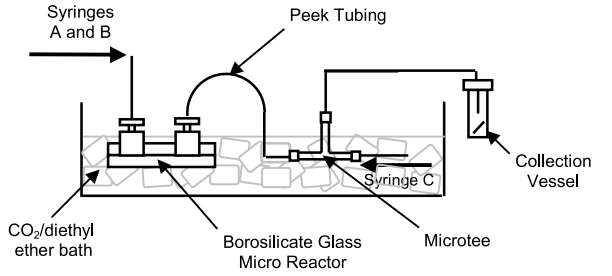


Figure 16. Schematic of the reaction set-up used for the evaluation of reduced temperature micro reactions.

Table 10. Effect of flow rate on product diastereoselectivity and conversion in a pressure-driven micro reactor

Flow Rate ($\mu l\ min^{-1}$)	Conversion (%)	Ratio (**69**:**70**)	Decomposition **71** (%)
50	31	94:6	0
20	38	99:1	0
10	41	99:1	0

(Table 10). Although these results represent initial observations and currently remain unoptimised, compared to traditional batch techniques the approach described is advantageous as no decomposition products, 3-benzyl-4-methyl-5-phenyloxazolidin-2-one **71** and 4-methyl-5-phenyloxazolidin-2-one **72**, were detected. We attribute this observation to the ability to accurately control both residence time and temperature of the reaction mixture within the micro fluidic device.

Consequently we propose that by either increasing the residence time within the device or reducing the reagent concentrations, that product conversion could be further increased. In summary, we have demonstrated a simple technique for the diastereoselective alkylation of a metal stabilised enolate, using a pressure-driven micro reactor at $-100\ ^{\circ}C$, whereby increased diastereoselectivity was observed compared to batch.

3. Conclusions

In order to demonstrate the application of micro reaction technology to chemical synthesis, the preparation and reaction of enolates was selected as it enabled a range of reactions to be investigated while maintaining a common element, i.e. deprotonation followed by nucleophilic substitution. Due to initial problems encountered with the mobilisation of inorganic bases by EOF, the use of preformed enolates, in the form of silyl enol ethers, was investigated. Using this approach, a series of tetra-*n*-butylammonium enolates were prepared using anhydrous TBAF **1** and subsequently reacted to afford 1,3-diketones, phenyl vinyl esters and β-hydroxyketones. The technique was subsequently extended to the use of organic bases whereby the Michael addition and alkylations were employed as model reactions. In addition, we demonstrated the synthesis of two carbanions using solid-supported organic bases and their subsequent reaction in the Knoevenagel condensation. Based on these observations, the use of inorganic bases was reinvestigated, this time enhancing base solubility by the addition of a stoichiometric quantity of crown ether, resulting in their successful electrokinetic mobilization. Inorganic bases were also successfully employed in a pressure-driven system demonstrating the diastereoselective alkylation of an Evans auxiliary derivative.

In conclusion, using the preparation and reaction of carbanions and enolates, we have demonstrated numerous advantages associated with micro reaction technology including; rapid reaction optimization, reduced reaction times, enhanced conversions, reduced by-product formation and the ability to generate reagents in-situ, whilst demonstrating some of the challenges associated with performing organic synthesis within micro fabricated devices.

4. Experimental procedures

4.1. Materials and methods

All materials (analytical reagent grade) were obtained from commercial suppliers and unless otherwise stated were used without further purification. Sodium hydride **65** (60% dispersion in mineral oil) was washed free of any mineral oil using *n*-hexane, to afford the purified reagent as a pale grey solid. Column chromatography was performed using Kieselgel silica gel 60 (Fluka) as the solid support and compounds eluted using mixtures of ethyl acetate and *n*-hexane of varying polarity. Thin-layer chromatography was carried out using Kieselgel 60, HF_{254} aluminium backed TLC plates (Merck), with mixtures of ethyl acetate and hexane as eluent. Visualisation was achieved using one of the following methods: exposure to short wave ultra violet light (λ 254 nm), or; development in an aqueous potassium permanganate (0.5%) and sodium carbonate (2.5%) solution, followed by heating with a hot air gun.

All NMR spectra were recorded as solutions in deuteriochloroform ($CDCl_3$) using tetramethylsilane (TMS) as an internal standard. The spectra were recorded on a Jeol GX400 spectrometer and the chemical shifts given in parts per million (ppm) with coupling constants in Hertz (Hz). The following abbreviations are used to report NMR data: s=singlet, d=doublet, t=triplet, q=quartet, dt=doublet of triplets, m=multiplet and C_0=quaternary carbon. Elemental analyses were performed using a Fisons Carlo Erba EA1108 CHN analyser. Infra-red spectra were recorded (4000–600 cm^{-1}) using a Perkin Elmer Paragon 1000 FT-IR spectrometer and peaks (ν_{max}) reported in wavenumbers (cm^{-1}). Gas-Chromatography–Mass Spectrometry (GC–MS) was performed using a Varian GC (CP-3800) coupled to a Varian MS (2000) with a CP-Sil 8 (30 m) column (Phenomenex) and ultra high purity helium (99.999%, Energas) carrier gas. Samples were analysed using one of the following methods. *Method A*. Injector temperature 200 °C, helium flow rate 1 ml min^{-1}, oven temperature 50 °C for 4 min then ramped to 250 °C at 30 °C min^{-1}, with a 3 min filament delay. *Method B*. Injector temperature 200 °C, helium flow rate 1 ml min^{-1}, oven temperature 50 °C for 1 min then ramped to 250 °C at 30 °C min^{-1}, with a 3 min filament delay. *Method C*. Injector temperature 250 °C, helium flow rate 1 ml min^{-1}, oven temperature 60 °C for 1 min then ramped to 270 °C at 35 °C min^{-1}, with a 3 min filament delay and. *Method D*. Injector temperature 250 °C, helium flow rate 1 ml min^{-1}, oven temperature 60 °C for 1 min then ramped to 270 °C at 20 °C min^{-1}, with a 3 min filament delay. All known compounds prepared had spectroscopic data consistent with the literature.

The electroosmotic micro reactions described herein were carried out using in-house fabricated borosilicate glass micro reactors with channel dimensions of 350 μm (wide)× 53 μm (deep). In order to minimise the effect of pressure gradients within the micro channels, micro porous silica frits were placed within the channels.[29] To mobilise

reagents by EOF, platinum electrodes (0.5 mm o.d.× 2.5 cm) were placed within the reagent reservoirs and voltages applied using a Paragon 3B high voltage power supply (capable of applying 0–1000 V to four outputs) (Kingfield electronics, Sheffield, UK). Automation of the HVPS using an in-house LabVIEW™ program enabled complex sequences of voltages to be investigated. To enable the results obtained to be applied to devices of different dimensions, voltages are reported as applied fields (V cm^{-1}), i.e. voltage/channel length. Prior to commencing an electroosmotic micro reaction, the micro channels were filled with anhydrous solvent in order to remove air from the micro porous silica frits and to ensure a complete circuit is formed.

The pressure driven micro reactions were performed using a device purchased from Micro Chemical Systems Ltd (Hull, UK), which consisted of a two layer borosilicate glass device with ceramic fittings (Macor) located over each of the etched micro channels (152 μm (wide)×51 μm (deep)). PTFE tubing (178 μm o.d.×2.5 cm (Supelco)) was attached to the micro reactor using PEEK microtight fittings (Upchurch Scientific); subsequent attachment to a gas-tight syringe (Hamilton) resulted in a pressure tight connection. In order to employ three input solutions and a single output, a PEEK microtee (Upchurch scientific) was incorporated into the system. The magnitude of flow was controlled using two displacement pumps (MD-1001, Bioanalytical Systems Inc.) capable of delivering fluid at flow rates of 1–100 μl min^{-1}. To monitor the progress of both EOF and pressure-driven micro reactions, experiments were conducted over a period of 20 min, after which the product reservoir was analysed by GC–MS, whereby comparison of the amount of residual starting material enabled the progression of the reaction to be determined.

4.2. Micro-scale methodology

4.2.1. Typical procedure for an electroosmotic micro reaction. After priming with THF, a standard solution of 'anhydrous' TBAF **1** (40 μl, 0.1 M) in anhydrous THF was placed in reservoir A, a solution of benzoyl cyanide **6** (40 μl, 1.0 M) in anhydrous THF was placed in reservoir B and a solution of trimethyl(1-phenylvinyloxy)silane **3** (40 μl, 1.0 M) in anhydrous THF was placed in reservoir C. The reaction products were manipulated within the device by applying an electric field to the platinum electrodes placed in each reservoir. In this case, the following applied fields were employed, 417, 318, 476 and 0 V cm^{-1}. The reaction products were collected in reservoir D, in anhydrous THF (40 μl), over a period of 20 min and analysed off-line by GC–MS. The progress of the reaction was subsequently determined by calculating the proportion of starting material converted to product (% conversion); 100% conversion to 1,3-diphenylpropane-1,3-dione **5** was observed in this case.

4.2.2. Electroosmotic flow regimes. *Flow Regime A*: Application of a constant applied field is referred to as continuous flow (unless otherwise stated this flow regime was employed); *Flow Regime B*: In this case, the field is applied for 2.5 s and no field for 5 s, the steps are subsequently cycled over a period of 20 min; *Flow Regime C*: As for Flow Regime B, with an applied field for 5 s and no field for 10 s.

4.3. Batch reactions

4.3.1. 'Anhydrous' tetra-*n*-butylammonium fluoride 1. Tetra-*n*-butylammonium fluoride trihydrate (TBAF·$3H_2O$) **73** was dried over phosphorus pentoxide under vacuum (10 mmHg) for 48 h to afford 'anhydrous' TBAF **1** as a gelatinous, colourless solid.

4.3.2. General procedure 1: synthesis of silyl enol ethers. The ketone in THF (2 ml per mmol) was added dropwise to a stirred solution of LiHMDS **51** (1.1 equiv) in THF (10 ml per mmol) over a period of 30 min at room temperature. The resulting solution was stirred for a further 15 min prior to the addition of chlorotrimethylsilane **74** (1.0 equiv) in THF (1 ml per mmol). In order to remove any residual inorganic material, the reaction mixture was concentrated in vacuo and the residue dissolved in DCM (5 ml per mmol). The reaction mixture was then filtered and the filtrate concentrated in vacuo to afford the silyl enol ether, which was stored at −10 °C and used without further purification.

4.3.3. General procedure 2: acylation using acyl halides. The silyl enol ether in anhydrous THF (2 ml per mmol) was added dropwise to a stirred solution of 'anhydrous' TBAF **1** (0.1 equiv) and acyl halide (1.0 equiv) in anhydrous THF (10 ml per mmol) under N_2, over a period of 30 min. After stirring for a further 30 min, the reaction mixture was concentrated in vacuo prior to the addition of dilute NaOH (50 ml, 0.1 M). The reaction products were extracted into ethyl acetate (3×50 ml) and the combined organic extracts were dried ($MgSO_4$), prior to concentrating in vacuo. The product was subsequently purified by silica gel chromatography.

4.3.4. General procedure 3: acylation of using acyl cyanides. The silyl enol ether in anhydrous THF (2 ml per mmol) was added dropwise to a stirred solution of 'anhydrous' TBAF **1** (0.1 equiv) and acyl cyanide (1.0 equiv) in anhydrous THF (10 ml per mmol) under N_2, over a period of 30 min. After stirring overnight, the reaction mixture was concentrated in vacuo prior to the addition of dilute NaOH (50 ml, 0.1 M). The reaction products were extracted into ethyl acetate (3×50 ml) and the combined organic extracts were dried ($MgSO_4$), prior to concentrating in vacuo. The product was subsequently purified by silica gel chromatography.

4.3.5. General procedure 4: aldol reaction of silyl enol ethers. The silyl enol ether in anhydrous THF (2 ml per mmol) was added dropwise to a stirred solution of 'anhydrous' TBAF **1** (0.1 equiv) and 4-bromobenzaldehyde **12** (1.0 equiv) in anhydrous THF (10 ml per mmol) under N_2, over a period of 30 min. After stirring overnight, the reaction mixture was concentrated in vacuo prior to the addition of distilled water (50 ml). The reaction products were extracted into ethyl acetate (3×50 ml) and the combined organic extracts were dried ($MgSO_4$), prior to concentrating in vacuo. The product was subsequently purified by silica gel chromatography.

4.3.6. General procedure 5: Michael addition. The 1,3-diketone in absolute EtOH (4 ml per mmol) was added to a stirred solution of Michael acceptor (1.0 equiv) and diisopropylethylamine **16** (2 equiv) in absolute EtOH (5 ml per mmol) and the reaction mixture stirred overnight. The reaction mixture was concentrated in vacuo and subsequently purified by silica gel chromatography to afford the respective product.

4.3.7. General procedure 6: Knoevenagel condensation. 3-(1-Piperazino)propyl-functionalised silica gel **26** (1.9 mmol N g^{-1}, 200–400 mesh) (0.10 g, 0.1 mmol) was added to a stirred solution of activated methylene (1.0 mmol) and aldehyde (1.0 mmol) in anhydrous MeCN (10 ml per mmol). After stirring overnight, the reaction mixture was filtered and the filtrate concentrated in vacuo to afford the respective condensation product.

4.3.8. Trimethyl(1-phenylvinyloxy)silane 3.[8] The reaction was carried out in accordance with general procedure 1 using acetophenone **15** (0.50 g, 4.13 mmol), LiHMDS **51** (0.77 g, 4.58 mmol) and chlorotrimethylsilane **74** (0.39 ml, 4.13 mmol) to give trimethyl(1-phenylvinyloxy)silane **3** (0.79 g, 98.0%) as a pale yellow oil; GC–MS retention time (Method A) R_T=8.55 min.

4.3.9. Benzoic acid 1-phenylvinyl ester 4.[8] The reaction was carried out in accordance with general procedure 2 using trimethyl(1-phenylvinyloxy)silane **3** (0.10 g, 0.52 mmol), TBAF **1** (0.014 g, 0.05 mmol) and benzoyl fluoride **2** (0.06 ml, 0.52 mmol) to afford benzoic acid 1-phenylvinyl ester **4** (0.12 g, 99.0%) as a pale yellow oil; GC–MS retention time (Method A) R_T=11.36 min.

4.3.10. 1,3-Diphenylpropane-1,3-dione 5.[8,61] The reaction was carried out in accordance with general procedure 3 using trimethyl(1-phenylvinyloxy)silane **3** (0.10 g, 0.52 mmol), TBAF **1** (0.02 g, 0.05 mmol) and benzoyl cyanide **6** (0.07 g, 0.59 mmol) to afford 1,3-diphenylpropane-1,3-dione **5** (0.11 g, 98.0%) as a white solid; GC–MS retention time (Method A) R_T=12.67 min.

4.3.11. Trimethyl(1-phenylpropenyloxy)silane 7.[8,62] The reaction was carried out in accordance with general procedure 1 using propiophenone **75** (1.00 g, 7.48 mmol), LiHMDS **51** (1.37 g, 8.21 mmol) and chlorotrimethylsilane **74** (1.04 ml, 7.48 mmol) to give trimethyl(1-phenylpropenyloxy)silane **7** (1.47 g, 96.0%) as a pale yellow oil; GC–MS retention time (Method A) R_T=8.92 min.

4.3.12. Cyclohex-1-enyloxy(trimethylsilane) 8.[8,37] The reaction was carried out in accordance with general procedure 1 using cyclohexanone **49** (1.00 g, 10.20 mmol), LiHMDS **51** (1.88 g, 11.22 mmol) and chlorotrimethylsilane **74** (0.95 ml, 10.20 mmol) to afford cyclohex-1-enyloxy(trimethylsilane) **8** (1.60 g, 93.0%) as a pale yellow oil; GC–MS retention time (Method A) R_T=7.40 min.

4.3.13. 2-Methyl-1,3-diphenylpropane-1,3-dione 9.[8,61] The reaction was carried out in accordance with general procedure 2 using trimethyl(1-phenylpropenyloxy)silane **7** (0.10 g, 0.48 mmol), TBAF **1** (0.013 g, 0.05 mmol) and benzoyl fluoride **2** (0.07 ml, 0.48 mmol) to afford 2-methyl-1,3-diphenylpropane-1,3-dione **9** (0.11 g, 96.0%) as a pale yellow oil; GC–MS retention time (Method A) R_T=11.67 min.

4.3.14. 2-Benzoylcyclohexanone 10.[8,63] The reaction was carried out in accordance with general procedure 2 using cyclohex-1-enyloxy(trimethylsilane) **6** (0.10 g, 0.59 mmol), TBAF **1** (0.0015 g, 0.06 mmol) and benzoyl fluoride **2** (0.06 ml, 0.59 mmol) to give 2-benzyloxycyclohexanone **10** (0.12 g, 99.0%) as a white solid; GC–MS retention time (Method A) R_T=11.20 min.

4.3.15. 2-Benzoylcyclohexanone 10.[8,63] The reaction was carried out in accordance with general procedure 3 using cyclohex-1-enyloxy(trimethylsilane) **8** (0.10 g, 0.59 mmol), TBAF **1** (0.0015 g, 0.06 mmol) and benzoyl cyanide **6** (0.08 g, 0.59 mmol) to give 2-benzyloxycyclohexanone **10** (0.11 g, 94.0%) as a white solid; GC–MS retention time (Method A) R_T=11.20 min.

4.3.16. 3-(4-Bromophenyl)-3-hydroxy-1-phenylpropan-1-one 11.[64] The reaction was carried out in accordance with general procedure 4 using trimethyl(1-phenylvinyloxy) silane **3** (0.09 g, 0.48 mmol), TBAF **1** (0.013 g, 0.048 mmol) and 4-bromobenzaldehyde **12** (0.09 g, 0.48 mmol) to afford 3-(4-bromophenyl)-3-hydroxy-1-phenylpropan-1-one **11** (0.13 g, 87.0%) as a white crystalline solid; GC–MS retention time (Method A) R_T=14.71 min.

4.3.17. 2-[(4-Bromophenyl)hydroxymethyl]cyclohexanone 13.[65] The reaction was carried out in accordance with general procedure 4 using cyclohex-1-enyloxy(trimethylsilane) **7** (0.11 g, 0.65 mmol) and 4-bromobenzaldehyde **12** (0.12 g, 0.65 mmol) to afford 2-[(bromophenyl)hydroxymethyl]cyclohexanone **13** (0.16 g, 94.0%) as a cream solid; δ_H 1.31 (1H, m, CH), 2.33 (1H, m, CH), 1.51 (1H, m, CH), 1.71 (1H, m, CH), 1.86 (3H, m, 3×CH), 2.08 (1H, m, CH), 2.33 (1H, m, CHOH), 7.69 (2H, d, J=6.8 Hz, Ar) and 7.74 (2H, d, J=6.8 Hz, Ar); δ_C 24.8 (CH_2), 27.0 (CH_2), 27.7 (CH_2), 30.7 (CH_2), 42.6 (CH), 67.9 (CHOH), 127.5 (2× CH), 128.6 (2×CH), 131.4 (C_0), 140.4 (C_0Br) and 191.1 (CO); 267 (M^++1, 15%), 266 (60), 264 (55) and 185 (100); GC–MS retention time (Method A) R_T=12.45 min.

4.3.18. (*E*)-4-Acetyl-5-oxohex-2-enoic acid ethyl ester 17. The reaction was carried out in accordance with general procedure 5 using 2,4-pentanedione **18** (0.50 g, 5.00 mmol), diisopropylethylamine **16** (1.29 g, 10.00 mmol) and ethyl propiolate (0.49 g, 5.00 mmol). The reaction mixture was concentrated in vacuo and subsequently purified by silica gel chromatography. Elution with 7% ethyl acetate in hexane afforded (*E*)-4-acetyl-5-oxohex-2-enoic acid ethyl ester **17** (0.88 g, 89.0%) as a colourless oil. (Found C, 60.78; H, 7.25, $C_{10}H_{14}O_4$ requires C, 60.60; H, 7.12%); υ_{max}/cm^{-1} 1667, 1703, 1740 and 2970; δ_H 1.34 (3H, t, J=7.0 Hz, CH_2CH_3), 2.13 (6H, s, CH_3), 4.24 (2H, q, J=7.0 Hz, CH_2CH_3), 4.24 (1H, J=7.0 Hz, COCHCO), 5.74 (1H, d, J=16.9 Hz, CH) and 7.39 (1H, d, J=16.9 Hz, CH); δ_C 14.3 (2×CH_3), 18.5 (CH_2CH_3), 61.6 (CH_2CH_3), 61.8 (COCHCO), 125.4 (CH), 141.8 (CH), 165.4 (2×CO) and 203.5 (CO_2); 199 (M^++1, 15%), 198 (27), 181 (20), 153

(30), 124 (100) and 109 (20); GC–MS retention time (Method B) $R_T = 10.21$ min (trans).

4.3.19. (*E*)-4-Benzoyl-5-oxohex-2-enoic acid ethyl ester 21. The reaction was carried out in accordance with general procedure 5 using 1-phenylbutane-1,3-dione **20** (0.25 g, 1.54 mmol), ethyl propiolate **19** (0.15 g, 1.54 mmol) and diisopropylethylamine **16** (0.40 g, 3.00 mmol). The reaction mixture was concentrated in vacuo and subsequently purified by silica gel chromatography. Elution with 5% ethyl acetate in hexane afforded (*E*)-4-benzoyl-5-oxohex-2-enoic acid ethyl ester **21** (0.31 g, 77.0%) as a pale yellow oil. (Found C, 69.48; H, 6.42, $C_{15}H_{16}O_4$ requires C, 69.22; H, 6.20%); υ_{max}/cm^{-1} 1183, 1676, 1721 and 2929; δ_H 1.34 (3H, t, $J=7.3$ Hz, CH_2CH_3), 1.96 (3H, s, CH_3), 4.23 (3H, m, CH_2CH_3 and COCHCO), 5.47 (1H, d, $J=16.8$ Hz, CH), 7.69 (1H, d, $J=16.8$ Hz, CH), 7.70 (1H, m, Ar), 7.80 (2H, m, Ar) and 7.93 (2H, m, Ar); δ_C 14.2 (CH_3), 19.1 (CH_2CH_3), 60.7 (CH_2CH_3), 96.7 (COCCO), 125.2 (CH), 128.6 (2×CH), 128.7 (2×CH), 129.7 (CH), 135.2 (C_0), 142.9 (CH), 165.5 (CO), 195.8 (CO) and 204.2 (CO_2); 261 ($M^+ + 1$, 10%), 260 (15), 181 (40) and 105 (100); GC–MS retention time (Method C) $R_T = 12.45$ min.

4.3.20. (*E*)-4-Ethoxycarbonylpent-2-enedioic acid ethyl ester 23. The reaction was carried out in accordance with general procedure 5 using diethyl malonate **22** (0.50 g, 3.10 mmol), ethyl propiolate **19** (0.30 g, 3.10 mmol) and diisiopropylethylamine **16** (0.80 g, 6.20 mmol). The reaction mixture was concentrated in vacuo and subsequently purified by silica gel chromatography. Elution with 5% ethyl acetate in hexane afforded (*E*)-4-ethoxycarbonylpent-2-enedioic acid ethyl ester **23** (0.60 g, 82.5%) as a colourless oil; δ_H 1.29 (9H, t, $J=7.4$ Hz, 3×CH_2CH_3), 4.19–4.27 (7H, m, 3×CH_2CH_3 and COCHCO), 5.88 (1H, d, $J=16.4$ Hz, CH) and 7.28 (1H, d, $J=16.4$ Hz, CH); δ_C 18.6 (3×CH_2CH_3), 61.5 (3×CH_2CH_3), 64.0 (COCHCO), 123.5 (CH), 143.0 (CH), 169.1 (2×CO) and 203.5 (CO_2); 259 ($M^+ + 1$, 5%), 258 (15), 257 (50), 255 (95), 227 (100), 212 (80), 182 (23), 167 (50), 109 (40) and 81 (15);GC–MS retention time (Method B) $R_T = 10.85$ min.

4.3.21. 3-Acetylheptane-2,6-dione 25. The reaction was carried out in accordance with general procedure 5 using 2,4-pentanedione **18** (0.50 g, 5.00 mmol), methyl vinyl ketone **24** (0.35 g, 5.00 mmol) and diisopropylethylamine **16** (1.29 g, 10.00 mmol). The reaction mixture was concentrated in vacuo and subsequently purified by silica gel chromatography. Elution with 10% ethyl acetate in hexane afforded 3-acetylheptane-2,6-dione **25** (0.77 g, 91.0%) as a colourless oil; δ_H 2.08 (2H, dt, $J=7.0$, 7.0 Hz, CH_2), 2.10 (3H, s, CH_3), 2.20 (6H, s, CH_3), 2.46 (2H, t, $J=7.0$ Hz, CH_2CO) and 3.39 (1H, t, $J=7.0$ Hz, COCHCO); δ_C 29.3 (2×CH_3), 30.0 (CH_3), 37.9 (CH_2), 40.5 (CH_2CO), 66.9 (COCHCO), 204.2 (2×CO) and 207.1 (CO); 171 ($M^+ + 1$, 5%), 170 (1), 153 (15), 128 (25), 110 (20), 95 (40) and 43 (100); GC–MS retention time (Method B) $R_T = 8.79$ min.

4.3.22. 2-Cyano-3-phenyl-acrylic acid ethyl ester 29.[66] The reaction was carried out in accordance with general procedure 6 using benzaldehyde **27** (0.106 g, 1.00 mmol), ethyl cyanoacetate **28** (0.113 g, 1.00 mmol) and 3-(1-piperazino)propyl functionalised silica gel (0.100 g, 0.10 mmol) to afford the product **29** (0.195 g, 97.0%) as a white crystalline solid; GC–MS retention time (Method C) $R_T = 6.63$ min.

4.3.23. 2-Benzylcyclohexanone 47.[67] Cyclohexanone **49** (0.50 g, 5.10 mmol) in THF was added dropwise to a stirred solution of KO^{t}Bu **55** (0.63 g, 5.61 mmol) in THF (100 ml) over a period of 30 min to afford a yellow enolate solution. The reaction mixture was stirred for a further 15 min prior to the addition of benzyl bromide **50** (0.61 ml, 5.10 mmol). After stirring overnight, the reaction mixture was concentrated in vacuo and the residual oil dissolved in ethyl acetate (50 ml) and washed with distilled water (50 ml). The aqueous layer was further extracted using ethyl acetate (2×50 ml) and the combined organic extracts dried ($MgSO_4$) and concentrated in vacuo. Purification was achieved by silica gel chromatography, whereby elution with 2.5% ethyl acetate in hexane afforded 2-benzylcyclohexanone **47** (0.85 g, 89.0%) as a pale yellow oil; GC–MS retention time (Method C) $R_T = 10.36$ min.

4.3.24. 2,2-Dibenzylcyclohexanone 48.[68] Cyclohexanone **49** (0.25 g, 2.60 mmol) in THF (10 ml) was added dropwise to a stirred solution of KO^{t}Bu **55** (0.63 g, 5.61 mmol) in THF (100 ml) over a period of 30 min to afford a yellow enolate solution. The reaction was stirred for a further 15 min prior to the addition to the addition of benzyl bromide **50** (0.61 ml, 5.10 mmol). After stirring overnight, the reaction mixture was concentrated in vacuo and the residual oil dissolved in ethyl acetate (50 ml) and washed with water (50 ml). The aqueous layer was further extracted using ethyl acetate (2×50 ml) and the combined organic extracts and the combined organic extracts dried ($MgSO_4$). Purification was achieved by silica gel chromatography, whereby elution with 20% ethyl acetate in hexane afforded 2,2-dibenzylcyclohexanone **48** (0.71 g, 85.0%) as a yellow oil; GC–MS retention time (Method A) $R_T = 14.50$ min.

4.3.25. Benzyloxybenzene 67.[69] NaH **65** (0.13 g, 5.33 mmol) in THF (10 ml) was added dropwise to a stirred solution of phenol **66** (0.50 g, 5.32 mmol) in THF (50 ml) and stirred for 5 min prior to the addition of benzyl bromide **50** (0.63 ml, 5.32 mmol). After stirring overnight, the reaction mixture was concentrated in vacuo and the residue diluted with DCM (50 ml) prior to washing with dilute sodium hydroxide (50 ml, 0.1 M). The aqueous layer was further extracted using DCM (2×50 ml) and the combined organic extracts dried ($MgSO_4$) and concentrated in vacuo. Purification was achieved by silica gel chromatography, whereby elution with 11% ethyl acetate in hexane afforded benzyloxybenzene **67** (0.70 g, 71.0%) as a pale yellow oil; GC–MS retention time (Method A) $R_T = 10.14$ min.

4.3.26. 4-Methyl-5-phenyloxazolidin-2-one 71.[70] Diphenyl carbonate **76** (10.60 g, 49.49 mmol), (1*S*, 2*R*) (+) norephedrine hydrochloride **77** (8.44 g, 44.97 mmol) and anhydrous potassium carbonate **78** (6.84 g, 49.49 mmol) were stirred at 100 °C for 6 h. The reaction mixture was subsequently cooled to 70 °C, methanol (100 ml) was added and the mixture heated to reflux for a further 30 min. The reaction mixture was concentrated in vacuo and subjected to an aqueous work up. The product was dissolved into DCM

(1×150 ml) and the organic layer washed with sodium hydroxide (2×150 ml, 1.0 M) and hydrochloric acid (2×150 ml, 1.0 M). The organic extract was subsequently dried ($MgSO_4$) and concentrated in vacuo to afford 4-methyl-5-phenyloxazolidin-2-one **71** (5.96 g, 75.0%) as an analytically pure light brown solid, which was used without further purification; GC–MS retention time (Method B) R_T=8.54 min.

4.3.27. 4-Methyl-5-phenyl-3-propionyloxazolidin-2-one 68.[71] *n*-Butyllithium **44** in hexane (4.97 ml, 2.5 M, 12.43 mmol) was added dropwise to a stirred solution of 4-methyl-5-phenyloxazolidin-2-one **71** (2.00 g, 11.30 mmol) in THF (50 ml) under N_2. The solution was maintained at −78 °C for 30 min prior to the addition of propionyl chloride **79** (1.96 ml, 22.47 mmol) and the reaction mixture warmed to room temperature and stirred overnight. The reaction mixture was concentrated in vacuo and subjected to an aqueous work up. The organic layer was neutralised using sodium hydrogen carbonate and the product extracted into DCM (3×50 ml), the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by silica gel chromatography (9% ethyl acetate in hexane) afforded the title compound **68** (2.58 g, 98.0%) as a pale yellow gum; GC–MS retention time (Method B) R_T=8.82 min.

4.3.28. (2′*S*,4*R*,5*S*)-2-(2′-methyl-3′-phenylpropionyl-4-methyl)-5-phenyloxazolidin-2-one 69.[58] NaHMDS **52** (2.63 ml, 1.0 M, 2.63 mmol) was added dropwise to a stirred solution of 4-methyl-5-phenyl-3-propionyloxazolidin-2-one **68** (0.50 g, 2.15 mmol) in THF (50 ml) under N_2 at −78 °C, the enolate was formed over a period of 20 min prior to the addition of benzyl bromide **50** (0.31 ml, 2.60 mmol). The reaction mixture was maintained at −78 °C for 40 min prior to quenching with distilled water (10 ml). The reaction mixture was concentrated in vacuo and subjected to an aqueous work up. The reaction products were extracted into DCM (4×50 ml), dried ($MgSO_4$) and concentrated in vacuo to afford a pale yellow oil. Purification was achieved by silica gel chromatography (10% ethyl acetate in hexane) to afford the diastereomer **69** (0.48 g, 59.0%) as a pale yellow oil; GC–MS retention time (Method B) R_T=12.16 min.

4.4. Micro-scale reactions[10]

4.4.1. 2-Cyano-3-phenyl acrylic acid ester 29.[66] White solid (0.025 g, 98.9%); GC–MS retention time (Method C) R_T=6.63 min.

4.4.2. 3-(4-Bromophenyl)-2-cyano acrylic acid ethyl ester 32.[72] White solid (0.012 g, 99.5%); GC–MS retention time (Method D) R_T=10.84 min.

4.4.3. 3-(3,5-Dimethoxyphenyl)-2-cyano acrylic acid ethyl ester 33.[73] White solid (0.011 g, 99.5%); δ_H 1.40 (3H, t J=7.0 Hz, CH_2CH_3), 3.85 (6H, s, 2×OCH_3), 4.39 (2H, q, J=7.0 Hz, CH_2CH_3), 6.65 (1H, m, Ar), 7.15 (2H, m, Ar) and 8.17 (1H, s, CH); δ_C 14.2 (CH_3), 55.7 (2×OCH_3), 62.8 (CH_2), 103.4 (C_0CN), 106.2 (CH), 108.6 (2×CH), 115.6 (CN), 133.1 (C_0), 155.2 (CH), 161.1 (2×C_0) and 162.5 (CO); 262 (M^++1, 20%), 261 (100), 189 (55), 161 (25) and 77 (10); GC–MS retention time (Method C) R_T=8.06 min.

4.4.4. 3-(4-Benzyloxyphenyl)-2-cyano acrylic acid ethyl ester 34. (0.021 g, 99.1%) as a cream solid (Found C, 74.51; H, 5.77; N 4.62, $C_{19}H_{17}O_3N$ requires C, 74.25; H, 5.58; N, 4.56%); δ_H 1.39 (3H, t, J=7.3 Hz, CH_2CH_3), 4.37 (2H, q, J=7.3 Hz, CH_2CH_3), 5.15, (2H, s, CH_2), 7.00 (2H, d, J=8.7 Hz, Ar), 7.40 (5H, m, Ar), 7.99 (2H, d, J=8.7 Hz, Ar) and 8.17 (1H, s, CH); δ_C 14.2 (CH_3), 62.5 (CH_2), 70.4 (C_0CN), 77.8 (CH_2O), 99.5 (C_0), 115.6 (2×CH), 124.6 (CN), 127.5 (2×CH), 128.4 (CH), 128.8 (2×CH), 133.7 (2×CH), 135.8 (C_0), 154.4, (CH), 162.9 (OC_0) and 163.1 (CO); 308 (M^++1, 5%), 307 (20), 91 (100) and 65 (20); GC–MS retention time (Method D) R_T=12.35 min.

4.4.5. 2-Benzylidene-malononitrile 36[66] Pale yellow solid (0.015 g, 100%); GC–MS retention time (Method C) R_T=5.84 min.

4.4.6. 2-(4-Bromobenzylidene)-malononitrile 37.[74] Pale yellow solid (0.035 g, 99.9%); GC–MS retention time (Method D) R_T=9.65 min.

4.4.7. 2-(3,5-Dimethoxybenzylidene)-malononitrile 38.[66] Yellow solid (0.024 g, 99.2%); GC–MS retention time (Method C) R_T=7.50 min.

4.4.8. 2-(4-Benzyloxybenzylidene)-malononitrile 39.[75] Pale yellow solid (0.024 g, 99.6%); GC–MS retention time (Method D) R_T=11.97 min.

Acknowledgements

We wish to thank Novartis Pharmaceuticals (P.W. and C.W.) and the EPSRC (C.W.) (Grant No. GR/S34106/01) for financial support. We are grateful to Dr. Tom McCreedy and Mr. Mike Bailey (The University of Hull) for help in fabricating the micro reactor devices.

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