The use of solid-supported reagents for the multi-step synthesis of analytically pure α,β-unsaturated compounds in miniaturized flow reactors†‡

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Micro reaction technology offers a safe, controllable and information rich technique suitable for the long-term production of pharmaceutical agents and fine chemicals. To date however, few of the syntheses performed using this technology have addressed the problems associated with product purification. With this in mind, we report herein the incorporation of multiple supported reagents into EOF-based miniaturized flow reactors for the two-step synthesis of analytically pure compounds. Using this approach, the successful synthesis of 20 α,β-unsaturated compounds in excellent yields (>99.1%) and purities (>99.9%) has been achieved, illustrating significant improvements compared to traditional batch techniques.

1 Introduction

Under increasing environmental and financial pressure, the chemical industry as a whole has begun exploring numerous ways of improving both the cleanliness and efficiency of many synthetic processes. One such approach is the application of micro reaction technology, whereby miniaturized reactor vessels provide controllable, information rich systems that enable reactions to be performed more rapidly,[2] efficiently[3] and selectively[4] than traditional batch-scale reactions. With these factors in mind, the use of micro reaction technology is of particular interest to the pharmaceutical industry where long term objectives include the desire to perform multiple functions (such as synthesis, detection, screening[5] and biological evaluation) within a single integrated device, resulting in an overall reduction in the time taken to discover lead compounds and subsequently transfer them to production.

Although the past ten years has seen a rapid growth in the field of micro reaction technology, with many groups demonstrating the successful synthesis of small organic compounds,[6–11] few have addressed the problems associated with the purification of reaction products prepared in continuously flowing systems.[12,13] In order to tackle this problem, we recently demonstrated the incorporation of solid-supported catalysts into miniaturized flow reactors, where the advantages of solid-supported catalysts/reagents were coupled with those of reaction miniaturization.[14,15]

As solid-supported reagents are designed to work in a similar manner to their solution phase counterparts, little reaction optimization is usually required in order to implement their use.[16,17] In comparison to solution phase reagents, however, the use of solid-supported analogues is advantageous, as they enable reaction products to be isolated with ease; consequently, supported reagents are often employed in a large excess in order to drive reactions to completion. Furthermore, by employing more than one supported reagent in the same reaction vessel, multiple transformations can be achieved.[18] Although solid-supported reagents clearly have many advantages over solution phase reagents, drawbacks of the technique include increased reaction times and mechanical degradation of the support (as a result of stirring or agitating the reaction mixture) which can make reagent recovery/recycling difficult. Consequently, by performing reactions in flow reactors,[19] the supported reagent undergoes minimal degradation, leading to extended reagent lifetimes, increased system reproducibility and simplified product isolation (Fig. 1).

In addition, from a production point of view, reaction miniaturization is advantageous, as syntheses can be readily transferred from a laboratory scale to mass production with ease. Using an approach referred to as scale-out or numbering-up,[20,21] reactions are firstly optimized within a single micro reactor, then, in order to increase production volume, the number of reactors employed is simply increased. In comparison to current production technology, scale-out is advantageous, as the thermal and mass transportation properties of the original micro reaction are maintained, facilitating the rapid transfer of a synthetic route from the laboratory scale where a single reactor is used, to mass production where multiple reactors are employed; for this approach to be

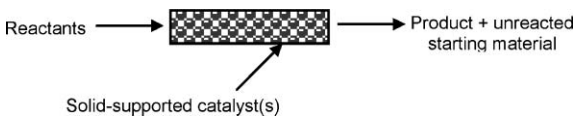

Fig. 1 Schematic illustrating the principle of employing solid-supported reagents in continuous flow reactors.

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† See ref. 1.
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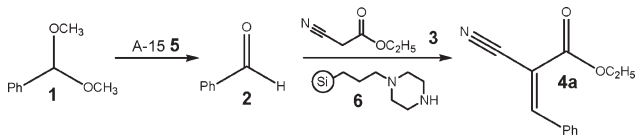


Scheme 1 General reaction scheme illustrating the multi-step synthesis of an α,β-unsaturated compound **4a**.

successful, it is important that individual reactors can be operated reproducibly. This work therefore builds on the successful base-catalyzed synthesis of α,β-unsaturated compounds[14] and the acid-catalyzed synthesis (also deprotection) of dimethyl acetals,[15] by increasing reaction complexity, enabling multi-step syntheses to be performed. As Scheme 1 illustrates, the proposed reaction sequence involves the acid-catalyzed deprotection of a dimethyl acetal **1** followed by the *in situ* base-catalyzed condensation of the aldehyde **2** with an activated methylene **3** to afford the respective α,β-unsaturated compound **4a**.[22]

2 General procedure for the synthesis of α,β-unsaturated compounds in a flow reactor

A typical procedure for the synthesis of α,β-unsaturated compounds in a miniaturized flow reactor consisted of passing a solution of dimethyl acetal and activated methylene (1.0 M respectively in MeCN) through a solid-supported acid catalyst (whereby deprotection of the dimethyl acetal afforded the respective aldehyde) followed by a solid-supported base catalyst (where the aldehyde and activated methylene condensed) to afford the desired α,β-unsaturated compound. The reaction mixture was subsequently analyzed by GC-MS, and the conversion of starting materials to product determined, *i.e.* % conversion. If any residual starting materials were detected the reaction was repeated, this time passing the starting materials over the supported catalysts at a slower flow rate; thus having the effect of increasing reagent residence time within the reactor. Once successfully optimized, the devices were operated for 2.5 h, after which work-up of the reaction product consisted simply of concentrating the sample *in vacuo*. The purity of the 'crude' product was subsequently evaluated by NMR spectroscopy, and, in the case of previously unreported compounds, elemental analysis performed; in all cases, no additional product purification was found to be necessary.

In order to mobilize reagents and products through the packed bed, electroosmotic flow (EOF) was selected as the pumping mechanism as it is simple to use, provides reproducible pulse-free flow, enables both the magnitude and direction of flow to be altered with ease and generates minimal back-pressure; an important feature with respect to the use of solid-supported reagents.[23] While EOF is widely associated with the manipulation of aqueous systems, more recently it has been applied to polar organic systems such as MeOH, MeCN and DMF.[24] In comparison to mechanical pumping techniques, electroosmotic systems are advantageous as they consist simply of the flow reactor and a power supply; automation of the system therefore enables the reaction set-up to be housed within a fume-cupboard and operated remotely.

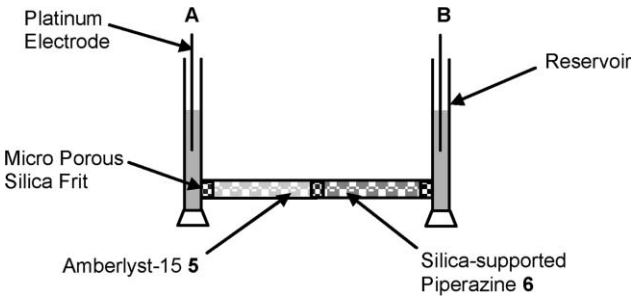


Fig. 2 Schematic illustrating the use of two solid-supported catalysts in an EOF-based continuous flow reactor.

2.1 Experimental set-up used for the evaluation of solid-supported reagents in miniaturized flow reactors

In order to evaluate the use of multiple supported reagents within an EOF-based system for the synthesis of α,β-unsaturated ketones (Scheme 1), a series of miniaturized flow reactors were constructed. As previously demonstrated,[14,15] reactions were performed using a single capillary borosilicate glass reactor, as illustrated in Fig. 2, with capillary dimensions of 500 μm (i.d.) × 3.0 cm (length). To hold the solid-supported reagents in place, a micro porous silica frit (MPS frit)[25] was placed at one end of the capillary and the Amberlyst-15 **5** (2.5 mg, 0.105 mmol) dry packed against it, the acid catalyst **5** was then held in place with another MPS frit positioned in 1.5 cm along the capillary (Fig. 2). The silica-supported base **6** (2.5 mg, 4.25×10^{-3} mmol) was subsequently dry packed up to the second MPS frit, which was again held in place by a third MPS frit. The packed capillary was subsequently primed with MeCN to remove any air, ensuring the formation of an electrical circuit. A leak-tight connection between the packed capillary and the borosilicate glass reagent reservoirs was achieved using PTFE thread seal tape (75 μm × 12 mm × 12 m). To mobilize reagents by EOF, platinum electrodes (500 μm (o.d.) × 2.5 cm (length)) were placed within the reservoirs and voltages applied using a Paragon 3B high-voltage power supply (HVPS), capable of applying 0 to 1000 V to four pairs of outputs (Kingfield Electronics, UK); automation of the HVPS was achieved using LabView™ software. Typical applied fields ranged from 167 to 333 V cm^{-1}; enabling flow rates of between 0.40 and 1.05 μl min^{-1} to be achieved.[26]

3 Results and discussion

3.1 Synthesis of 2-cyano-3-phenyl acrylic acid ethyl ester 4a

Using the set-up illustrated in Fig. 2 and 3, a solution of dimethoxymethyl benzene **1** and ethyl cyanoacetate **3** (40.00 μl, 1.0 M in MeCN) was placed in reservoir A and MeCN (40.00 μl) in reservoir B. Application of 333 V cm^{-1} to the solution in reservoir A and 0 V cm^{-1} to reservoir

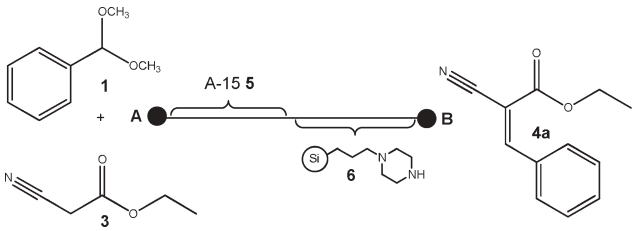


Fig. 3 Schematic illustrating the multi-step synthesis of 2-cyano-3-phenyl acrylic acid ethyl ester **4a** in an EOF-based miniaturized flow reactor.

B (ground electrode) resulted in the electroosmotic mobilization of reagents **1** and **3** through the packed bed at a rate of 0.50 μl min^{-1} (throughput of 6.0 mg h^{-1}). After 10 min, the reaction products collected from reservoir B were analyzed by GC-MS, confirming that 99.98% conversion to 2-cyano-3-phenyl acrylic acid ethyl ester **4a** had occurred.[27]

In order to demonstrate the reproducibility of the experimental set-up, the reaction was repeated a further 14 times (2.5 h in total), resulting in an average conversion of 99.99% (Table 1, % RSD = 3.5 × 10^{-3}, n = 15). After analysis by GC-MS, the reaction products were combined and concentrated *in vacuo* to afford 2-cyano-3-phenyl acrylic acid ethyl ester **4a** as a white solid (0.0150 g, 99.40%). In order to confirm product purity, the 'crude' product **4a** was analyzed by NMR spectroscopy; whereby no residual starting materials **1**, **2** and **3**, or by-products, were detected.

To confirm that the observed reaction was in fact attributed to the presence of both acid and base catalysts within the flow reactor, the synthesis of 2-cyano-3-phenyl acrylic acid ethyl ester **4a** was evaluated in the absence of Amberlyst-15 **5** and 3-(1-piperazino)propyl-functionalized silica gel **6**. Firstly, the base catalyst **6** was replaced with silica gel (Kieselgel 60), and a 1 : 1 mixture of dimethyl acetal **1** and ethyl cyanoacetate **3** mobilized through the reactor at a flow rate of 0.50 μl min^{-1}; after 10 min, the

Table 1 Illustration of system stability over 15 runs (2.5 h) for the synthesis of 2-cyano-3-phenyl acrylic acid ethyl ester **4a**

Run no.	Conversion (%)[a]
1	99.98
2	99.99
3	99.99
4	99.99
5	99.99
6	99.99
7	99.99
8	99.99
9	99.99
10	99.99
11	99.99
12	99.99
13	99.99
14	99.98
15	99.99

Mean = 99.99%, % RSD = 3.5 × 10^{-3}

[a] Calculated with respect to residual aldehyde **2**

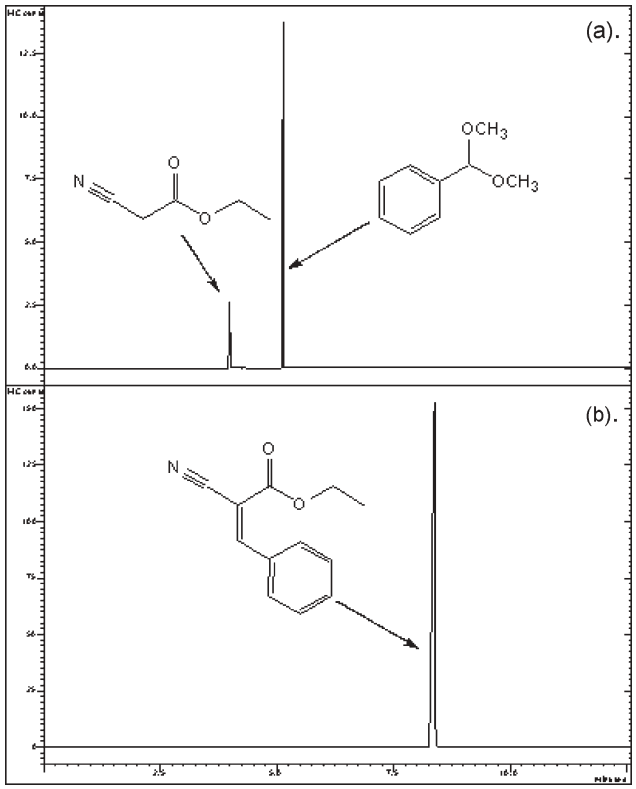


Fig. 4 Gas chromatograms illustrating the complete conversion of (a). dimethoxymethyl benzene **1** and ethyl cyanoacetate **3** to (b). 2-cyano-3-phenyl acrylic acid ethyl ester **4a** within a miniaturized flow reactor.

reaction products were diluted with MeCN and analysed by GC-MS. As expected, the reaction products only contained benzaldehyde **2** (due to acid catalyzed deprotection of dimethyl acetal **1**) and ethyl cyanoacetate **3**; importantly no 2-cyano-3-phenyl acrylic acid ethyl ester **4a** was detected. The effect of the acid catalyst **5** was subsequently investigated by replacing Amberlyst-15 **5** with polystyrene beads (2% cross-linked with divinylbenzene), again the stock solution was passed through the polystyrene beads and 3-(1-piperazino)propyl-functionalized silica gel **6**; analysis of the reaction products confirmed that the starting materials **1** and **3** remained unchanged.

Finally, the reaction was repeated using polystyrene beads and silica gel; again, as expected, analysis of the reaction products confirmed that no reaction had occurred. In summary, it was concluded that the observations presented in Table 1 are in fact attributed to the acid-catalyzed deprotection of dimethoxymethyl benzene **1**, followed by the base-catalyzed condensation of benzaldehyde **2** and ethyl cyanoacetate **3** to afford 2-cyano-3-phenyl acrylic acid ethyl ester **4a**; and importantly, not as a result of performing the reaction in an electric field.

In order to compare the efficiency of miniaturized flow reactors with traditional batch techniques, the synthesis of 2-cyano-3-phenyl acrylic acid ethyl ester **4a** was subsequently performed using the traditional one-pot approach. In brief, 3-(1-piperazino)propyl-functionalized silica gel **6**

(2.5 mg, 4.25 × 10^{-3} mmol) and Amberlyst-15 **5** (2.5 mg, 1.05 mmol) were added to a solution containing dimethoxymethyl benzene **1** (0.011 g, 0.075 mmol) and ethyl cyanoacetate **3** (0.08 g, 0.075 mmol) in MeCN (75.0 μl) (1.0 M respectively) and stirred for 2.5 h. In order to monitor the progress of the reaction, aliquots of the reaction mixture (1.0 μl in 100.0 μl MeCN) were analyzed every 10 min, by GC-MS. As Fig. 5 illustrates, after 30 min complete deprotection of dimethoxymethyl benzene **1** to benzaldehyde **2** was achieved, however even after a further 1.5 h only 2.9% conversion to 2-cyano-3-phenyl acrylic acid ethyl ester **4a** had occurred. In comparison, by performing the reaction in a miniaturized flow reactor, with a residence time of 1.0 min, 0.015 g (0.075 mmol, 99.40%) of 2-cyano-3-phenyl acrylic acid ethyl ester **4a** was synthesized in excellent purity over the same 2.5 h period. In addition, by employing scale-out methodology, the quantity of material synthesized can be increased by simply employing an array of reactors in parallel.

The observed reduction in reaction time can be partly explained by the formation of localized concentration gradients within the flow reactor, as although only small quantities of catalyst are employed (2.5 mg per reagent), when the starting materials are passed through the reactor they are, in fact, exposed to a large excess of catalyst. In addition, within a packed reactor, the diffusion distance between any starting materials and the supported catalyst is greatly decreased compared to within traditional stirred reactors; consequently, conversions >99% can be achieved in minutes, in contrast with >24 h in a traditional stirred reactor. Furthermore, compared to the one-pot approach, the preparation of packed columns is also advantageous, as the supported catalysts remain spatially resolved (Fig. 2) enabling their reuse either separately or in alternative reaction sequences.

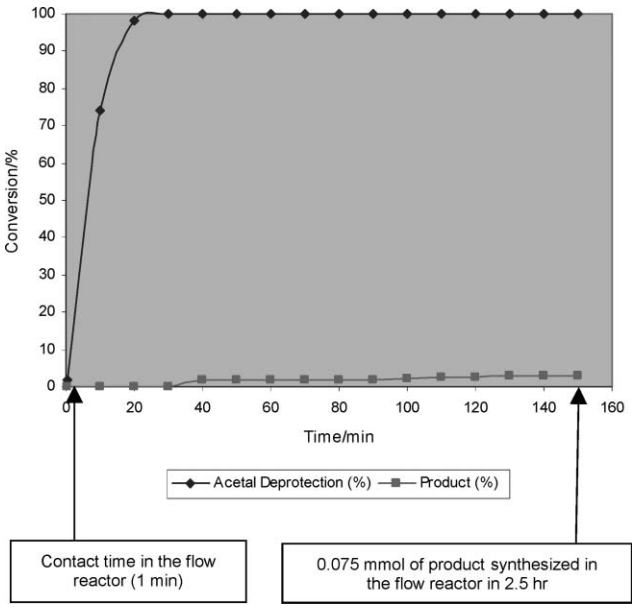


Fig. 5 Graph illustrating the progress of a two-step reaction using the one-pot approach.

3.2 Synthesis of α,β-unsaturated compounds in an EOF-based miniaturized flow reactor

Using the synthesis of 2-cyano-3-phenyl acrylic acid ethyl ester **4a** as a model reaction, the advantages associated with incorporating multiple supported catalysts into miniaturized flow reactors have been clearly illustrated. As a means of demonstrating the versatility of this technique, the investigation was extended to demonstrate the reactions of substituted aldehydes. Again, Amberlyst 15 **5** and 3-(1-piperazino)propyl-functionalized silica gel **6** were employed as the catalysts, enabling the synthesis of α,β-unsaturated ketones **4a** to **4j** in excellent yield (Table 2). The generality of the technique was further investigated, employing malononitrile **7** as the activated methylene, and, as Table 3 illustrates, α,β-unsaturated compounds **8a** to **8j** were again synthesized in excellent yields (>99.2%). Evaluation of the resulting 'crude' products by GC-MS and NMR spectroscopy once more confirmed that all products were synthesized in analytical purity without the need for additional purification steps.

3.3 Catalyst turnover

As previously mentioned, when employing solid-supported reagents, in either stirred or shaken reactor vessels, degradation of the support material can lead to problems with reagent recovery and reuse; as a means of overcoming this problem, we investigated the use of miniaturized continuous flow reactors. Using this approach, a combinatorial array of α,β-unsaturated compounds were synthesized in excellent yield and purity (Tables 2 and 3), whereby separation of the reaction products from the supported catalyst was achieved with ease. With this in mind, our attention turned to assessing the recyclability of the supported catalysts employed in the aforementioned device. In order to ascertain the technique's efficiency, the same 2.5 mg portions of Amberlyst-15 **5** and 3-(1-piperazino)propyl-functionalized silica gel **6** were used for the synthesis of all 20 α,β-unsaturated compounds. As illustrated by Table 4, this equates to the synthesis of 2.13 mmol of α,β-unsaturated product using only 1.05 × 10^{-2} mmol of acid **5** and 4.25 × 10^{-3} mmol of base **6**, demonstrating catalyst turnovers of 203 and 501 times, respectively. Most importantly, over the course of the investigation, no sign of reagent degradation or reduced reaction efficiency was observed; consequently, the flow reactor will be employed in further studies. Notably, although the catalysts remain active in a traditional stirred reactor, to perform 20 separate syntheses using the same portion of catalytic material (5 mg in total) would be unfeasible due to difficulties associated with the filtration and recovery of small quantities of supported material.

In summary, by incorporating multiple solid-supported catalysts into a miniaturized flow reactor an array of α,β-unsaturated compounds have been synthesized in excellent yield and purity without the need for additional, off-line, purification steps. In addition, we have demonstrated the ability to recycle solid-supported catalysts, enabling reaction reproducibility that is currently unobtainable in traditional stirred/shaken reactors (Table 4).

Table 2 Summary of the conversions obtained for the synthesis of α,β-unsaturated ketones **4a** to **4j** using Amberlyst-15 **5** and 3-(1-piperazino)propyl-functionalized silica gel **6** in a miniaturized flow reactor

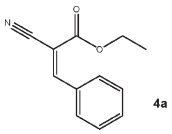
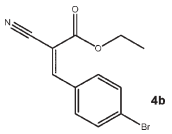
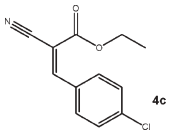
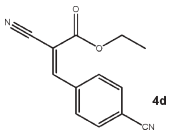
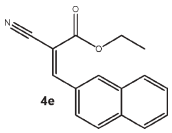
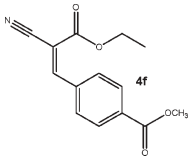
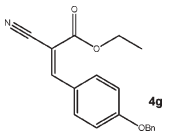
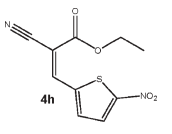
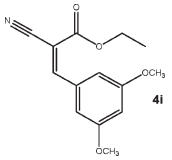
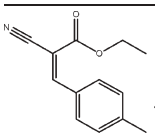
Product	Flow rate/μl min^{-1}	GC-MS purity (%)[a]	Yield (%)
 **4a**	0.50 (1.00)[b]	99.99 (3.0×10^{-3})[c]	99.40 (0.0150)[d]
 **4b**	0.80 (0.63)	99.99 (1.2×10^{-3})	99.76 (0.0338)
 **4c**	0.65 (0.77)	99.99 (1.25×10^{-3})	99.56 (0.0227)
 **4d**	0.84 (0.60)	99.99 (8.0×10^{-4})	99.65 (0.0284)
 **4e**	0.84 (0.60)	99.99 (8.0×10^{-4})	99.80 (0.0298)
 **4f**	0.65 (0.77)	100.00 (0.0)	99.68 (0.0253)
 **4g**	0.48 (1.04)	99.99 (2.6×10^{-4})	99.10 (0.0219)
 **4h**	0.75 (0.67)	99.99 (6.0×10^{-4})	99.65 (0.0234)
 **4i**	0.55 (0.91)	99.99 (8.0×10^{-4})	99.53 (0.0213)

Table 2 Summary of the conversions obtained for the synthesis of α,β-unsaturated ketones **4a** to **4j** using Amberlyst-15 **5** and 3-(1-piperazino)propyl-functionalized silica gel **6** in a miniaturized flow reactor (*Continued*)

Product	Flow rate/μl min^{-1}	GC-MS purity (%)[a]	Yield (%)
 **4j**	0.89 (0.56)	99.99 (2.5×10^{-3})	99.30 (0.0284)

[a] GC-MS conversion determined with respect to residual aldehyde. [b] the number in parentheses represents the period of time, in min, that the starting materials are in contact with each supported reagent. [c] the number in parentheses represents the RSD, whereby $n = 15$. [d] the number in parentheses represents the isolated yield in g.

Table 3 Summary of the conversions obtained for the synthesis of α,β-unsaturated compounds **8a** to **8j** using Amberlyst-15 **5** and 3-(1-piperazino)propyl-functionalized silica gel **6** in a miniaturized flow reactor

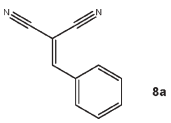
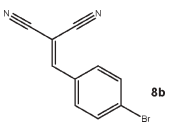
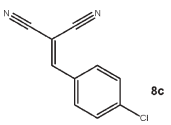
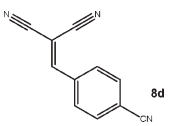
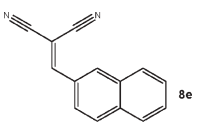
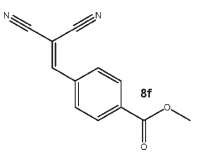
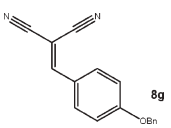
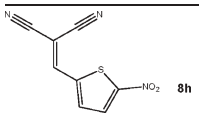
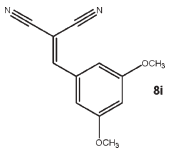
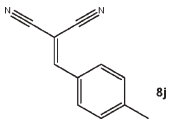
Product	Flow rate/μl min^{-1})	GC-MS purity (%)[a]	Yield (%)
 **8a**	0.53 (0.94)[b]	99.99 (7.0×10^{-4})[c]	99.42 (0.0121)[d]
 **8b**	0.95 (0.53)	99.99 (5.0×10^{-4})	99.36 (0.0312)
 **8c**	0.65 (0.77)	99.99 (4.6×10^{-4})	99.40 (0.0179)
 **8d**	0.83 (0.60)	99.99 (7.0×10^{-4})	99.55 (0.0222)
 **8e**	0.84 (0.60)	99.99 (2.6×10^{-3})	99.22 (0.0255)
 **8f**	0.67 (0.75)	99.99 (1.06×10^{-4})	99.53 (0.0211)
 **8g**	0.40 (1.25)	100.00 (0.0)	99.36 (0.0155)

Table 3 Summary of the conversions obtained for the synthesis of α,β-unsaturated compounds **8a** to **8j** using Amberlyst-15 **5** and 3-(1-piperazino)propyl-functionalized silica gel **6** in a miniaturized flow reactor (*Continued*)

Product	Flow rate/μl min^{-1})	GC-MS purity (%)[a]	Yield (%)
 **8h**	1.04 (0.48)	100.00 (0.0)	99.90 (0.0263)
 **8i**	0.50 (1.00)	99.99 (5.6 × 10^{-4})	99.66 (0.0177)
 **8j**	1.05 (0.50)	99.99 (2.5 × 10^{-4})	99.62 (0.0319)

[a] GC-MS conversion determined with respect to residual aldehyde. [b] the number in parentheses represents the period of time, in min, that the starting materials are in contact with each supported reagent. [c] the number in parentheses represents the RSD, whereby $n = 15$. [d] the number in parentheses represents the isolated yield in g.

3.4 Catalyst screening

Having demonstrated the ability to continuously synthesize an array of α,β-unsaturated compounds within an EOF-based flow reactor, the investigation was extended to look at the use of other solid-supported acids and bases. As illustrated in Table 5, nine combinations of polymer-supported acids (Amberlyst-15 **5**, polymer-supported *p*-toluenesulfonic acid **9** and ytterbium polystyrylsulfonate(III) **10**) and silica-supported bases (3-(1-piperazino)propyl-functionalized silica gel **6**, 3-(dimethylamino)propyl-functionalized silica gel **11** and 3-(1,3,4,6,7,8-hexahydro-2*H*-pyrimidino)propyl-functionalized silica gel **12**) were packed into a series of miniaturized flow reactors (Fig. 6).

In order to evaluate these catalyst combinations, the synthesis of 2-cyano-3-phenyl acrylic acid ethyl ester **4a** was again selected as the model reaction. To perform a reaction, a solution of dimethoxymethyl benzene **1** and ethyl cyanoacetate **3** (40 μl, 1.0 M in MeCN) was placed in reservoir A and MeCN (40 μl) in reservoir B; application of 333 and 0 V cm^{-1}, respectively, resulted in mobilization of the reagents through the packed-bed at flow rates in the range of 0.4 to 0.5 μl min^{-1} (Table 5). All reaction products were subsequently analyzed by GC-MS after 10 min (≥99.99% conversion w.r.t. residual benzaldehyde **2**) and the reactors operated for a total of 2.5 h (15 runs) per catalyst combination. In all cases, concentration of the reaction products *in vacuo* afforded 2-cyano-3-phenyl acrylic acid ethyl ester **4a** as a white crystalline solid (≥99.26% yield).

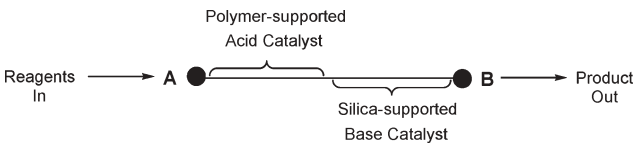


Fig. 6 Schematic illustrating the reaction set-up used to screen the solid-supported catalysts.

These results not only demonstrate the generality of the technique with respect to the nature of catalyst used but also the support material employed.

4 Conclusions

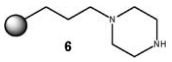
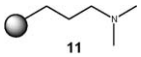
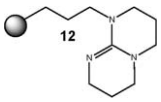
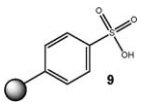
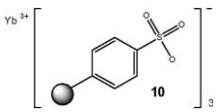
In conclusion, we have demonstrated a simple and efficient technique for the incorporation of multiple supported reagents into miniaturized flow reactors, resulting in a system suitable for the continuous flow synthesis of analytically pure compounds; using this approach, 20 α,β-unsaturated compounds (**4a–4j** and **8a–8j**) were synthesized in near quantitative yield and purity *via* a two-step synthesis.

Compared to standard batch techniques, the application of miniaturized flow reactors proved advantageous, as it is possible to synthesize compounds in high yield and purity without the need for additional purification steps. Furthermore, the ease with which supported reagents are

Table 4 Illustration of reagent recycling demonstrated in a miniaturized EOF-based flow reactor

	Supported reagent/mmol	Product/mmol	Turnover number
Amberlyst-15 **5**	1.05 × 10^{-2}	2.13	203
3-(1-Piperazino)propyl-functionalized silica gel **6**	4.25 × 10^{-3}	2.13	501

Table 5 Illustration of the results obtained for the synthesis of 2-cyano-3-phenyl acrylic acid ethyl ester **4a** using various polymer-supported acids and silica-supported bases

			
Amberlyst-15 **5**	0.50[a] 99.99%[b] 3.0 × 10^{-3}[c] 99.40%[d] 0.0150 g[e]	0.45 99.99% 9.6 × 10^{-4} 99.26% 0.0134 g	0.49 99.99% 7.4 × 10^{-4} 99.32% 0.0148 g
	0.47 99.99% 5.1 × 10^{-4} 99.30% 0.0140 g	0.42 99.99% 4.9 × 10^{-4} 99.53% 0.0126 g	0.41 99.99% 7.4 × 10^{-4} 100.0% 0.0123 g
	0.45 99.99% 3.5 × 10^{-4} 99.27% 0.0136 g	0.40 99.99% 7.4 × 10^{-4} 99.50% 0.0120 g	0.50 99.99% 6.1 × 10^{-4} 99.34% 0.0150 g

[a] Electroosmotic flow rate (μl min^{-1}). [b] Average GC Conversion ($n = \geqslant 15$). [c] % RSD ($n = \geqslant 15$). [d] Yield (%). [e] Isolated yield (g).

recycled provides reaction reproducibility unobtainable in traditional stirred or shaken reactor vessels. In addition, the formation of localized concentration gradients within the flow reactor enables reactions to be driven to completion more rapidly than in stirred/shaken reactors, a point clearly illustrated in Fig. 4.

Consequently, whether milligrams of a compound are required for biological evaluation or tonnes for the production of fine chemicals, the flexibility associated with micro reaction technology enables these differences in scale to be bridged with ease.

Acknowledgements

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26 The total volume of the flow reactor was calculated to be 0.5 μl; therefore when operating the reactor at flow rates in the range of 0.40 to 1.05 μl min^{-1} contact times of 1.25 to 0.5 min were obtained.
27 In all cases, the acid-catalyzed deprotection of the dimethyl acetal was found to proceed in quantitative conversion; consequently, the percentage conversion to the α,β-unsaturated compound was based on residual aldehyde.

