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Evaluation of the Heterogeneously Catalyzed Strecker Reaction Conducted Under Continuous Flow

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Building on our experience of micro-reaction technology, we present herein the evaluation of an integrated borosilicate glass micro reactor in which 51 α-aminonitriles were synthesized via a series of continuous solution-phase and heterogeneously catalyzed reaction steps, affording analytically pure products in yields > 99.6 %. As an extension to this, the ability to selectivity synthesize aldehydic Strecker products in the presence of ketonic functionalities was also investigated, concluding with the chemoselective synthesis of 2-(4-acetylphenyl)-2-(phenethylamino)acetonitrile whereby the desired product was obtained in 99.8 % yield and quantitative purity.

Introduction

Micro-reaction technology provides a new method of executing chemical reactions, affording a means of performing synthetic transformations in such a way that lengthy optimization stages are no longer required in order to obtain production volumes traditionally met through the time-consuming route of scale-up. The technique not only enables rapid transfer of processes, but also provides a simple answer to variable production volumes through the implementation of few or many reactors depending on product demand. With this in mind, the field of continuous flow synthesis is growing year on year with many research groups reporting alternative ways to perform common organic transformations with increased control, safety and predictability. Whilst several interesting molecules have been prepared using such technology, the multiple reaction steps investigated have more often than not consisted of single steps, performed in series i.e. where the reaction products are purified off-line (batch-wise) between each reaction and as such are not performed in a truly continuous manner. Alternatively reactors have been devised where solution-phase reactions are performed in separate modules to heterogeneously catalyzed reactions, leading to the need for multiple interconnections, resulting in potential points of failure within the system. Building on experience gained through performing an array of synthetic transformations under continuous flow, we present herein the development and evaluation of an integrated borosilicate glass micro reactor in which solution phase and heterogeneously catalyzed reaction steps are performed in series to afford the target molecules in excellent purity.

In its original form, the Strecker reaction consisted of the condensation of carbonyl-containing compounds with amine salts, in the presence of alkaline cyanides under buffered aqueous conditions, with the resulting products undergoing hydrolysis to afford the desired α-amino acid.[1] The tedious nature of product isolation compared with the synthetic utility of the resulting α-aminonitriles in the preparation of 1,2-diamines, 2-amino alcohols, imidazoles, thiadiazoles[2,3] and pre-biotic precursors to nucleic acids and porphyrins,[4] has, however, led to the development of a plethora of alternative methodologies. These range from the use of organic solvents and alternative cyanide sources,[5] to the use of Lewis acid catalysts,[6–9] guanidine HCl,[10] ionic liquids,[11,12] catalyst-free[13] examples and even those conducted at elevated pressures (0.6 GPa).[14] Despite these advancements, the reaction still suffers from numerous drawbacks including the use of elevated reaction temperatures, extended reaction times, expensive homogeneous catalysts, an excess of the cyanide source and variable yields, which preclude the use of the Strecker reaction on a production scale.

In addition, a major shortcoming of the multi-component Strecker reaction is the competing cyanohydrin formation that can occur,[15] as depicted in Scheme 1. When employing aliphatic aldehydes, the respective aldimines form rapidly; therefore the potential of cyanohydrin formation is low, leading to good/moderate selectivity for the α-aminonitrile. In comparison, however, the aldimines of aromatic aldehydes form slowly, leaving the aldehyde available for *O*-TMS cyanohydrin formation, and possible hydrolysis to the respective cyanohydrin, resulting in poor reaction selectivity. With this in mind, we postulated that in those cases where rapid *O*-TMS cyanohydrin formation is favored, sequential reagent addition would allow for the selective synthesis of the desired α-aminonitrile. However, to achieve

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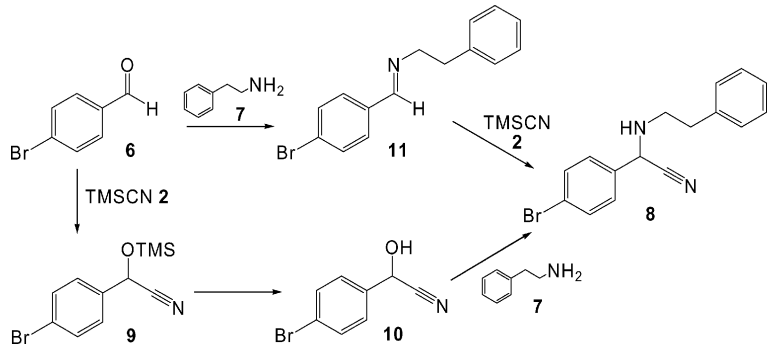


Scheme 1. Illustration of the model reaction selected for evaluation under continuous flow, depicting some of the possible by-products obtained and the reaction pathways followed in a one-pot transformation.

this in a stirred reaction vessel would require careful monitoring of the reaction, in order to confirm aldimine formation was complete prior to the addition of the cyanide source; leading to reactant specific conditions rather than the development of a general methodology. Micro reaction technology,[16] however, offers an interesting solution to this problem, affording enhanced control over physical properties such as mixing, reaction time and temperature,[17] enabling sequential reagent addition to be performed with ease. The use of a homogeneous catalyst within a continuous system would, however, mean that even if reaction selectivity could be obtained, via sequential addition of reagents, the reaction products would still require purification in order to remove, and potentially recycle, the catalytic material.[18] To circumvent this problem, many authors have reported the use of solid-supported catalysts,[19] which has been shown to increase the ease with which reaction products can be isolated from the activating agent; by enlarge, however, the transfer of a reaction from homogeneous catalysis to a heterogeneous environment leads to a profound increase in reaction time. Additional optimization can therefore be required in order to obtain acceptable yields on the desired time scale; a process that is usually achieved by the use of heat and/or excess catalytic material. In recent years, it has been demonstrated that by conducting polymer and silica-assisted reactions under continuous flow, small quantities of catalytic material can be employed for the efficient synthesis of compounds such as acetals,[20] carboxylic acids/aldehydes,[21] α,β-unsaturated compounds,[22] substituted biphenyls,[23] natural products such as (±)-oxomaritidine[24] and even the enantioselective synthesis of grossamide.[25] As small volumes of the reaction mixture (μL) are in contact with a relatively large volume of catalytic material (mg), the result is that excellent conversions can be obtained within short reaction times, typically in the range of sec to min. Using this approach, the reaction times attained compare more favorably with those employed in homogeneous systems, whilst the ease with which reaction products can be isolated from the solid-supported catalyst is retained.

With these factors in mind, we recently communicated our initial appraisal of a borosilicate glass micro reactor (Figure 1) capable of performing the multi-component Strecker reaction. Employing polymer-supported (ethylenediaminetetraacetic acid)ruthenium(III) chloride (**1**) (Figure 2, a) as the Lewis acid catalyst and trimethylsilyl cyanide (TMSCN) **2** as the cyanide source, with the aim of providing a simple and efficient methodology for the synthesis of α-aminonitriles.[26] As an extension to this, we report herein the use of an alternative solid-supported Lewis acid catalyst, the polymer-bound scandium(III) bis(trifluoromethanesulfonate) **3** (Figure 2, b), as a means of increasing the throughput of the system and subsequently demonstrate the synthesis of 50 α-aminonitriles ranging from aromatic to aliphatic derivatives. The report is then concluded with an investigation into the chemoselective nature of the

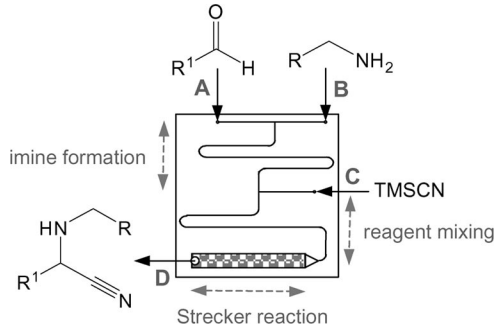


Figure 1. Diagrammatic representation of the reaction manifold used to evaluate the Strecker reaction conducted under continuous flow.

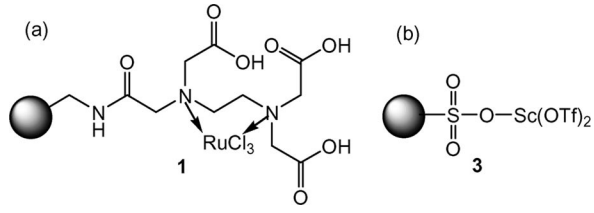


Figure 2. Illustration of the two immobilized Lewis acid catalysts investigated within the borosilicate glass micro reactor (a). Polymer-supported (ethylenediaminetetraacetic acid)ruthenium(III) chloride (PS-$RuCl_3$) (**1**) and (b). Polymer-bound scandium(III) bis(trifluoromethanesulfonate) [PS-$Sc(OTf)_2$] (**3**).

technique, employing 4-acetylbenzaldehyde (**4**) as a precursor to afford 2-(4-acetylphenyl)-2-(phenethylamino)acetonitrile (**5**) as the target molecule.

Results and Discussion

As Scheme 1 illustrates, initial investigations focused on the reaction of 4-bromobenzaldehyde (**6**) with 2-phenylethylamine (**7**) and TMSCN (**2**),[27] catalyzed by polymer-supported (ethylenediaminetetraacetic acid)ruthenium(III) chloride (PS-$RuCl_3$) (**1**). Prior to evaluating the model reaction under continuous flow, the reaction was conducted using the conventional one-pot approach, which consisted of the addition of TMSCN (**2**), to a stirred solution of 4-bromobenzaldehyde (**6**) and 2-phenylethylamine (**7**) in MeCN.[28] The resulting reaction mixture was stirred under N_2 at room temperature for 24 h prior to filtration and removal of solvent in vacuo, to afford a pale yellow oil. The crude reaction product was subsequently dissolved in $CDCl_3$ and analyzed by ^1H NMR spectroscopy. After 24 h, an appreciable quantity of the desired product 2-(4-bromophenyl)-2-(phenethylamino)acetonitrile (**8**) had formed; however, the reaction mixture also contained several by-products or intermediates including 2-(4-bromophenyl)-2-(trimethylsilyloxy)acetonitrile (**9**) and 2-(4-bromophenyl)-2-hydroxyacetonitrile (**10**).

Although the batch reaction served to illustrate the suitability of PS-$RuCl_3$ (**1**) as a catalyst for the transformation, it did highlight some of the drawbacks associated with the one-pot technique i.e. competing *O*-TMS cyanohydrin formation **9**, resulting in incomplete cyanation and the presence of residual amine within the reaction product. Consequently, where rapid *O*-TMS cyanohydrin formation is favored, the reaction conditions must ensure that the imine forms prior to the addition of the cyanide source. Therefore, rather than use a one-pot strategy, sequential reactant addition would enable the formation of the desired intermediate and subsequently ensure selective synthesis of the α-aminonitrile. In batch, however, this is difficult to achieve as the reaction conditions must be tailored to take into account the reactivity of the particular precursors and as such, the reaction was investigated within a borosilicate glass micro reactor under pressure-driven flow, whereby reaction conditions can be rapidly evaluated.

As depicted in Figure 3, the reaction manifold employed herein was a borosilicate glass micro reactor consisting of two etched layers, the first containing the reagent delivery inlets along with the mixing channels and the second comprised of a larger etched region and the reactor outlet, through which the reaction products are collected. Thermal annealing of the two etched layers afforded the integrated reactor, into which the solid-supported catalyst was dry-packed (Figure 1), with interconnections made by means of Microtight fittings and PEEK tubing, which as illustrated in Figure 4 is secured using epoxy resin. Solutions of reactants can then be delivered to the micro reactor via a series of gas-tight syringes and reaction products collected from the FEP tubing into a 2-mL glass sample vial at the outlet.

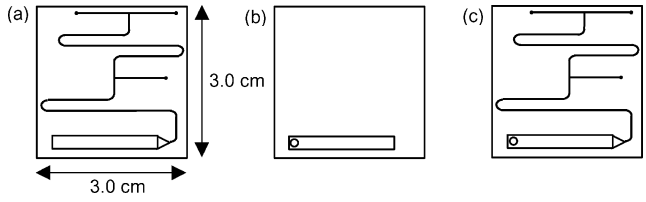


Figure 3. Schematic illustrating the components of the borosilicate glass reactor employed for the investigations described herein (a) top plate, (b) base plate and (c) bonded reactor.

Mechanistic Evaluation

To evaluate the synthesis of an α-aminonitrile under continuous flow, we must firstly consider the reaction mechanism, from which the order of reactant addition to the micro reactor can be determined. This not only ensures that reactants are delivered to the reaction channel in the correct spatial and temporal manner, but also enables us to identify the origin of side products, henceforth providing us with a means of preventing them. As Scheme 1 illustrates, there are several possible products that could arise from the combination of an amine **7**, aldehyde **6** and cyanide source **2** in a one-pot system, firstly the formation of the *O*-TMS cyanohydrin, 2-(4-bromophenyl)-2-(trimethylsilyloxy)acetonitrile (**9**), with subsequent hydrolysis affording the cyanohydrin, 2-(4-bromophenyl)-2-hydroxyacetonitrile (**10**), and secondly the formation of the imine intermediate, (*E*)-[1-(4-bromophenyl)methylidene]phenethylamine (**11**). As literature precedent exists for the Strecker reaction proceed-

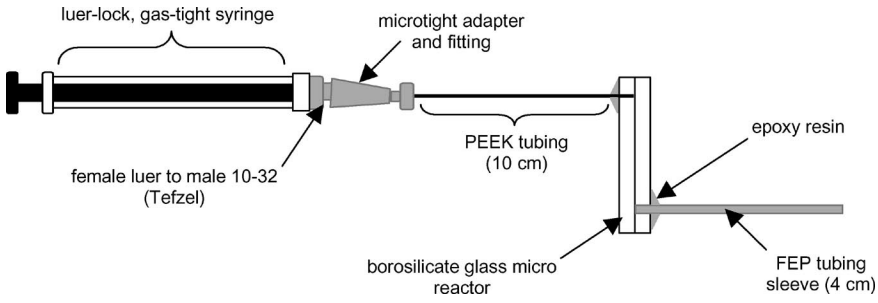


Figure 4. Schematic illustrating the technique employed for the connection of the micro reactor to a syringe driver.

ing via both of these intermediates, the mechanistic pathway followed by the model reaction, the synthesis of 2-(4-bromophenyl)-2-(phenylethylamino)acetonitrile (**8**), was evaluated firstly using a pre-formed *O*-TMS cyanohydrin **9** and then via the imine **11**.

The micro reactor was firstly charged with PS-$RuCl_3$ (**1**, 0.01 g, 0.26 mmol Ru g^{-1}) and the system purged with anhydrous MeCN, prior to performing a reaction. As depicted in Figure 5, a, a solution of *O*-TMS cyanohydrin **9** (0.2 M in MeCN) was introduced into the micro reactor from inlet A and 2-phenylethylamine (**7**, 0.2 M in MeCN) from inlet B, the reactants mixed in the central channel prior to passing through the catalyst bed and collection at outlet D (0.1 M). The reaction mixture was then analyzed by GC-MS, prior to concentrating in vacuo and subsequent analysis by ^1H NMR spectroscopy, whereby comparison of the integrals afforded the % conversion to be determined. Using this approach, the reaction was evaluated over a range of flow rates (5 to 100 μL min^{-1}) whereby no reaction to afford the desired α-aminonitrile **8** was observed, only recovery of the unreacted *O*-TMS cyanohydrin **9** and 2-phenylethylamine (**7**).

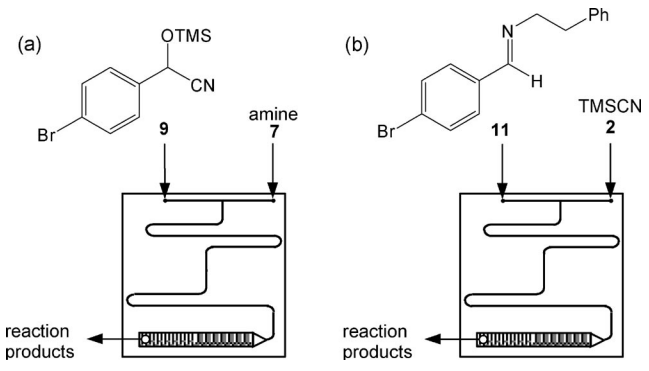


Figure 5. Reaction manifolds used to evaluate the order of addition for the synthesis of α-aminonitriles, catalyzed by PS-$RuCl_3$ (**1**), under continuous flow via (a). the *O*-TMS cyanohydrin **9** and (b). the imine **11**.

With this in mind, the investigation turned to the evaluation of the imine **11** as the reactive intermediate. As illustrated in Figure 5, b, (*E*)-[1-(4-bromophenyl)methylidene]-phenethylamine (**11**, 0.2 M in MeCN) was introduced from inlet A, a solution of TMSCN (**2**, 0.2 M in MeCN) from inlet B and the reactants mixed in the central channel, prior to reaction within the catalyst bed. The resulting reaction mixture was collected at outlet D (0.1 M) and concentrated in vacuo, prior to dissolution in $CDCl_3$ and analysis by ^1H NMR spectroscopy; whereby comparison of the integrals afforded quantification of the percentage conversion. Employing a flow rate of 100 μL min^{-1}, afforded 25.9% conversion to the desired α-aminonitrile **8**, which was subsequently improved upon by reduction of the flow rate to 20 μL min^{-1} and then to 10 μL min^{-1}, whereby the increased reactant residence time afforded 95.6% and 100.0% conversion, of the imine **11** to 2-(4-bromophenyl)-2-(phenylethylamino)acetonitrile (**8**), respectively.

From this example alone, it can be seen that when conducting reactions in a one-pot, multi-component manner the route of a reaction is not always apparent, consequently side reactions can be prevalent resulting in a complex reaction mixture. As such, these reactions often benefit from employing an excess of one reactant, in order to suppress side reactions; even so, the resulting reaction products require purification to remove any of the un-reacted material and/or by-products formed. Consequently, the use of a continuous flow approach, such as the micro reactor described herein, enables the user to perform rapid evaluation of a reaction, gaining a large amount of information from a small quantity of reactant, which is particularly useful if a starting material is scarce or expensive. The technique is also advantageous as the predictable nature of the mixing regime employed affords the ability to sequentially add reactants, enabling the chemist to ensure that one-step is complete prior to the addition of the next reactant; as such stoichiometric quantities of reactant can often be employed, increasing reaction efficiency and the purity of the resulting reaction product.

Multi-Component Synthesis of 2-(4-Bromophenyl)-2-(phenylethylamino)acetonitrile

Having determined the reactive intermediate of interest was the imine **11**, our attention turned to its in-situ preparation, making the technique suitable for those reactions where the reactive intermediate is hydrolytically unstable and hence not isolatable in a pure form. With this in mind, the synthesis of 2-(4-bromophenyl)-2-(phenylethylamino)-acetonitrile (**8**) was investigated using the following procedure; a solution of 4-bromobenzaldehyde (**6**, 0.4 M in MeCN[29]) was introduced from inlet A, followed by 2-phenylethylamine (**7**, 0.4 M in MeCN) from inlet B and finally TMSCN (**2**, 0.2 M in MeCN) from inlet C, affording a total flow rate of 20 μL min^{-1}, an overall reactant ratio of 1:1:1 and a final product concentration of 0.1 M. The reaction products were collected in a sample tube containing MeCN (250 μL) and after 2.5 h, the reaction products were concentrated in vacuo and the "crude" material **8** dissolved in $CDCl_3$ and analyzed by ^1H NMR spectroscopy. Through comparison of the integrals of the signals obtained for the intermediate imine **11** (δ = 8.1 ppm) and α-aminonitrile **8** (δ = 4.8 ppm),[30] the % conversion was found to be 95.9%, reduction of the flow rate to 10 μL min^{-1}, however, afforded quantitative conversion (see Figure 6) to the desired product **8** and an isolated yield of 99.5% was obtained. Further evaluation of the pale yellow solid **8** by ^{13}C NMR spectroscopy, IR spectroscopy, MS and elemental analysis confirmed the product was synthesized in analytical purity (Figure 7) and that no additional purification was found to be necessary, unlike a typical batch reaction performed under analogous conditions, over 24 h. In addition to the aforementioned analytical assessment of the flow-reaction product **8**, the material was also analyzed by ICP-MS, which confirmed that no detectable Ru was present within the reaction product. This demonstrates an improvement in

catalyst stability compared to the analogous batch reaction whereby 440 ppm of Ru was found to have been released from the supported catalyst **1**, an observation that is attributed to mechanical degradation of the catalyst, due to stirring of the material over the course of the reaction; leading to a dramatic reduction in the catalyst lifetime. Importantly, when the reaction was performed in the absence of the catalyst, achieved by simply replacing the PS-$RuCl_3$ (**1**) with PS-EDTA,[31] no background reaction was observed when operating the reactor at flow rates in the range of 1 to 100 μL min^{-1}, simply formation of the respective imine **11**, as would be expected.

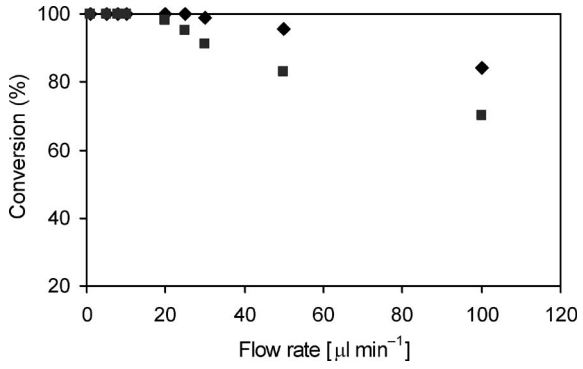


Figure 6. Illustration of the effect of flow rate on the synthesis of (♦) (*E*)-[1-(4-bromophenyl)methylidene]phenethyl-amine (**11**) and (■) 2-(4-bromophenyl)-2-(phenethylamino)acetonitrile (**8**) in a micro reactor.

Therefore not only does this example serve to illustrate the fact that under stoichiometric reaction conditions a product **8** of superior purity can be obtained in a continuous flow micro reactor via the use of sequential reactant addition, but reduced reaction times are also required in order to afford quantitative conversion of the starting materials **6** and **7** to the desired α-aminonitrile **8**, typically < 1 min cf. 24 h in batch. Furthermore, the notable reduction in catalyst degradation in the absence of mechanical stirring results in an extended catalyst lifetime and increased product purity.

Generality of the Technique

Having demonstrated that the Strecker reaction between 4-bromobenzaldehyde (**6**) and 2-phenylethylamine (**7**) could be conducted efficiently under continuous flow conditions, the scope of the technique was evaluated through the reaction of a further four amines with 4-bromobenzaldehyde (**6**). The amines were selected to illustrate a range of reactivities i.e. from aromatic to aliphatic and cyclic derivatives and as Table 1 illustrates, in the case of aniline (**12**), benzylamine (**13**) and phenylpropylamine (**14**), excellent yields were again obtained using analogous conditions to those employed for 2-phenylethylamine (**7**). However, in the case of pyrrolidine (**15**), which upon reaction with 4-bromobenzaldehyde (**6**) affords an iminium ion as the reactive intermediate, quantitative conversion of the aldehyde **6** to (4-bromophenyl)pyrrolidin-2-ylacetonitrile (**16**) was obtained at

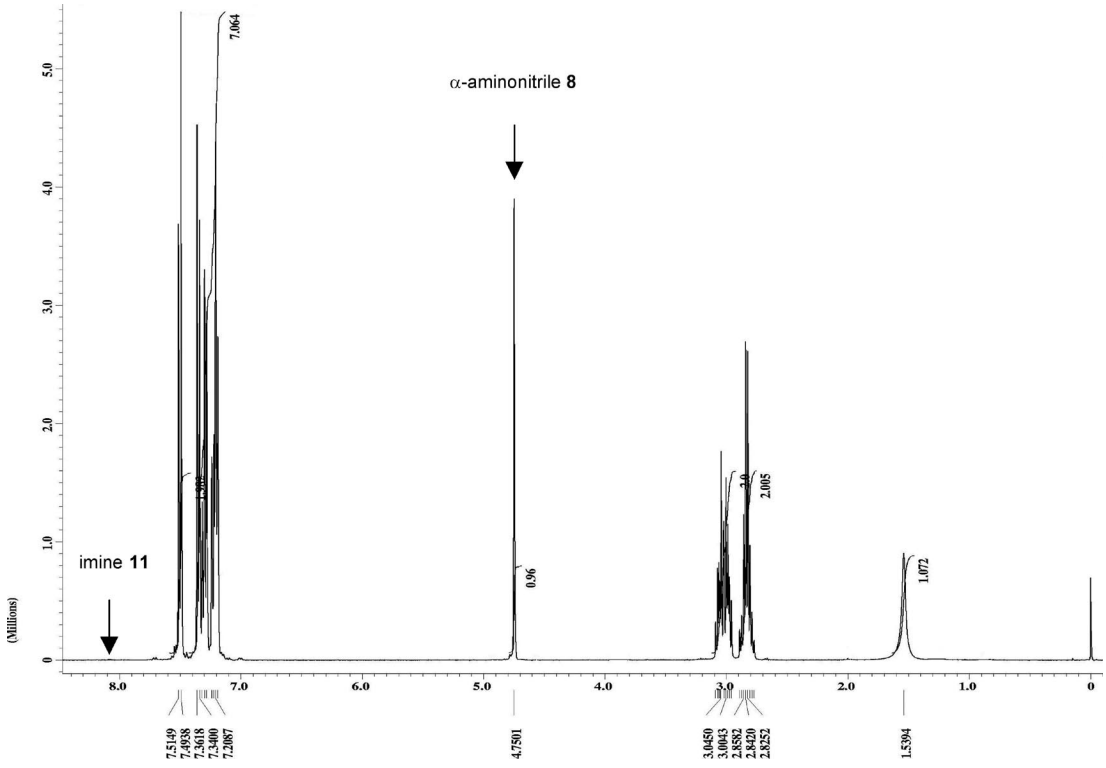
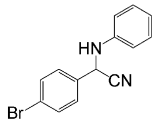
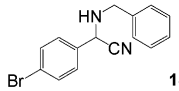
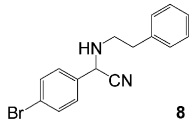
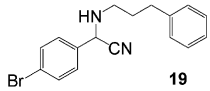
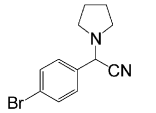


Figure 7. Typical ^1H NMR spectra obtained for 2-(4-bromophenyl)-2-(phenethylamino)acetonitrile (**8**) synthesized under continuous flow.

the higher flow rate of 20 μL min^{-1}, affording an increase in the reaction throughput compared to the primary amines investigated.

Table 1. Summary of the results obtained for the Strecker reaction between 4-bromobenzaldehyde (**6**) and an array of amines using PS-$RuCl_3$ (**1**) as the catalyst and a run time of 2.5 h.

Entry	Product	Flow rate, [μl min^{-1}][a]	Yield [g] (%)	Throughput [mg h^{-1}]
1	 **17**	10	0.043 (100)[b]	17.2
2	 **18**	10	0.045 (100)	18.1
3	 **8**	10	0.047 (100)	18.9
4	 **19**	10	0.049 (100)	19.7
5	 **16**	20	0.040 (100)	31.8[c]

[a] On the basis of the total flow obtained from 3 fluidic inputs. [b] % Conversion determined via comparison of the ^{1}H NMR integrals observed for the imine/α-aminonitrile. [c] Run time = 1.25 h.

From the examples discussed it can be seen that the use of a micro reactor, such as the one illustrated in Figure 1, has enabled us to validate the hypothesis that sequential reactant addition facilitates the efficient synthesis of α-aminonitriles, with Table 1 illustrating the excellent yields and purities attainable within such a system. It must also be noted that depending on the amine employed, the system affords a throughput of between 17.2 and 31.8 mg h^{-1} (equivalent to 0.06 and 0.12 mmol h^{-1}) and although batch reactions can be performed on larger scales, and hence afforded greater throughputs, they result in the formation of impure products that contain unreacted starting materials, along with being contaminated with significant quantities of trace metals, reducing the longevity of the catalysts employed and increasing the sophistication of purification techniques required post reaction.

Increased Reactor Throughput

Whilst a perceived disadvantage of micro-reaction technology is the relatively small quantity (mg h^{-1}) of material that can be prepared from a single reactor, techniques such as numbering-up and scale-out enable the user to increase throughput by employing multiple systems in parallel, an approach that does not incur the need to perform costly re-optimization steps usually associated with scale-up. This technique is particularly advantageous with respect to the production of pharmaceuticals and fine chemicals as it means that the reaction conditions employed at a development stage are those that are later employed on a production scale, all that changes is the number of reactors employed; consequently the risk associated with moving a product from development into production is removed. This in mind, it is still desirable for a single reactor unit to be as productive as possible and consequently, the next step of the investigation was to evaluate techniques that would afford a greater reaction throughput from a single micro reactor, namely the use of elevated reaction temperatures and alternative Lewis acid catalysts.

Elevated Reaction Temperatures

Employing the reaction conditions summarized in Table 1, the micro reactor was placed in a silicone oil bath and heated to 40 °C. Upon initial purging of the system with anhydrous MeCN, at a total flow rate of 10 μL min^{-1}, orange coloration of the solvent stream was noted at outlet D, an observation that was attributed to leaching of Ru from the catalyst **1**; as a result all further reactor evaluation was conducted at room temperature.

Increased Reactant Concentrations

One facile route often employed to increase the productivity of reactions conducted under continuous flow is to increase the concentration of the reactant feedstocks. As previously mentioned the use of MeCN as reaction solvent precludes the use of concentrations higher than 0.4 M owing to the precipitation of the imine **11** within the central reaction channel. Consequently, in an attempt to increase the throughput of the system, dichloromethane was evaluated as an alternative solvent system, selected for its inert nature, high volatility and its ability to solubilize large quantities of organic material. It was therefore proposed that through the increased solubilization of the imine intermediate, that the reaction could be operated at a higher concentration, to afford an increased reactor throughput i.e. double the concentration, double the quantity of product synthesized per unit time. Unfortunately, under analogous conditions to those employed with MeCN as the reaction solvent, the use of DCM led to swelling of the PS-$RuCl_3$ (**1**), attributed to the fact that the polymer used as a support was only crosslinked with 1% DVB, resulting in blockage of the reactor after only 20 min of operation. Clearly, this is unsuitable for a system that is required to operate unaided and over long periods; consequently, MeCN was retained as the reaction solvent and a final product stream concentration of 0.1 M employed throughout. Further to this, reactant stoichiometry is another variable i.e. where the proportion of a reactant is increased in order to drive the reaction to completion. This approach is, however, disadvantageous when attempting to improve the atom efficiency of a reaction and as such was not pursued as a solution herein.

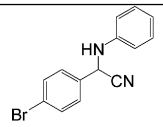
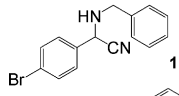
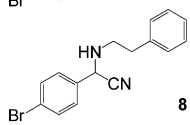
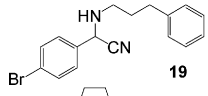
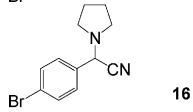
Alternative Lewis Acid Catalysts

As previously discussed, many Lewis acids have been reported within the literature to act as catalysts for the Strecker reaction, in particular rare earth (RE) metal triflates have found widespread application, with a microencapsulated (MC) $Sc(OTf)_3$ derivative reported by Kobayashi and co-workers.[32] The authors recently communicated the catalyst in a flow reactor, whereby MC-$Sc(OTf)_3$ containing ca. 0.12 g of catalytic material was packed into a circulating column and a mixture containing the imine and TMSCN (**2**, 0.5 mmol in MeCN) pumped through the reactor. Using this approach, the authors obtained 70% yield on the first run, 71% on the second and finally 75% on the third, illustrating the potential of the flow methodology. Owing to the use of a circulating column reactor, where reactants are added from a single inlet, the technique was only suitable for the use of pre-formed imines or precursors unlikely to result in by-product formation, when pre-mixed in the absence of the catalyst. This is in comparison to the technique described herein, whereby enhanced control and reaction flexibility can be obtained through the ability to introduce reactants from three separate inlets, prior to contact with the catalytic material. With this in mind, we investigated the incorporation of the commercially available polymer bound derivative PS-$Sc(OTf)_2$ (**3**) (Figure 2, b), within the aforementioned micro reactor and evaluated its performance against PS-$RuCl_3$ (**1**) and the MC-$Sc(OTf)_3$ reported by Kobayashi and co-workers.

The Continuous-Flow Evaluation of PS-$Sc(OTf)_2$

In order to compare the Lewis acid catalysts, PS-$Sc(OTf)_2$ (**3**, 0.01 g, 0.60 mmol Sc g^{-1}) was dry-packed into the catalyst bed and the micro reactor purged with anhydrous MeCN prior to performing a reaction. Again, 4-bromobenzaldehyde (**6**, 0.4 M in MeCN) was introduced from inlet A, 2-phenylethylamine (**7**, 0.4 M in MeCN) from inlet B and TMSCN (0.2 M in MeCN) from inlet C (1:1:1). The imine **11** and TMSCN (**2**) were subsequently pumped through the catalyst bed at a total flow rate of 10 μL min^{-1} and the reaction products collected at the outlet D in MeCN (250 μL). After 2.5 h, the reaction products were concentrated in vacuo to afford a pale yellow solid and the material dissolved in $CDCl_3$ prior to analysis by ^1H and ^{13}C NMR spectroscopy; whereby quantitative conversion to α-aminonitrile **8** was confirmed. As Table 2 illustrates, in contrast to the previous system (See Table 1), PS-$ScOTf_2$ (**3**) was found to be a more active catalyst, affording quantitative conversion to 2-(4-bromophenyl)-2-(phenethylamino) acetonitrile (**8**) at double the flow rate (20 μL min^{-1}) previously found to be optimal for PS-$RuCl_3$ (**1**), affording a throughput of 0.12 mmol h^{-1}. Again, no cyanohydrin formation was observed and the desired product **8** was obtained in analytical purity. In addition to the synthesis of α-aminonitrile **8**, the catalyst was found to activate the reaction between 4-bromobenzaldehyde **6** with aniline (**12**), benzylamine (**13**), phenylpropylamine (**14**) and pyrrolidine (**15**) to afford 2-(4-bromophenyl)-2-(phenylamino)acetonitrile (**17**), 2-(benzylamine)-2-(4-bromophenyl)acetonitrile (**18**), 2-(4-bromophenyl)-2-(3-phenylpropylamino)acetonitrile (**19**) and 2-(4-bromophenyl)-2-(pyrrolidin-2-yl)acetonitrile (**16**), with isolated yields ranging from 99.8 to 99.9%. Again it can be seen that in the case of the secondary amine pyrrolidine (**15**), an increased flow rate (40 μL min^{-1}) can be employed compared to the primary amines evaluated (20 μL min^{-1}), affording a throughput of 0.24 mmol h^{-1} cf. the previously obtained 0.12 mmol h^{-1}.

Table 2. Summary of the results obtained for the Strecker reaction between 4-bromobenzaldehyde **6** and an array of amines using PS-$Sc(OTf)_2$ **3** as the catalyst (run time = 1 h unless otherwise stated).

Entry	Product	Flow rate, [μl min^{-1}][a]	Yield [g] (%)	Throughput [mg h^{-1}]
1	 **17**	20	0.034 (100)[b]	34.4
2	 **18**	20	0.036 (100)	36.1
3	 **8**	20	0.038 (100)	38.0
4	 **19**	20	0.039 (100)	39.5
5	 **16**	40	0.032 (100)	63.6[c]

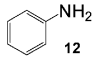
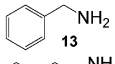
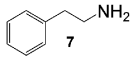
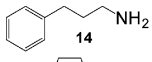
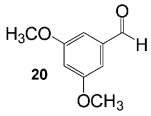
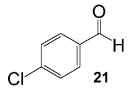
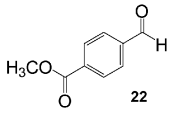
[a] On the basis of the total flow obtained from 3 fluidic inputs. [b]% Conversion determined via comparison of the ^1H NMR integrals observed for the imine/α-aminonitrile. [c] Run time = 0.5 h.

Evaluation of Aromatic Aldehydes

Having demonstrated the ability to increase reactor throughput by employing an alternative Lewis acid catalyst, the scope of the reaction was subsequently investigated. Again, the reactions were evaluated at room temperature employing stoichiometric quantities of all reactants, with the focus being on the evaluation of an array of aldehydes [3,5-dimethoxybenzaldehyde (**20**), 4-chlorobenzaldehyde (**21**) and methyl 4-formylbenzoate (**22**)], demonstrating any electronic substituent effects, with benzaldehyde (**23**) serving as a reference point (Table 3, Entries 1–5). To evaluate this effect, micro reactions were conducted for 0.5 h at 40 μL min^{-1} and 1.0 h at 20 μL min^{-1}, prior to removal of the reaction solvent and analysis of the "crude" reaction product. In the case of known compounds, ^1H NMR, ^{13}C NMR and MS were used to confirm the compounds structure and for previously unreported compounds, ^1H NMR, ^{13}C NMR, MS, IR and CHN analysis were performed (See Experimental Section for details). We were again pleased to report that this mode of operation afforded, in all cases,

analytically pure compounds with no sign of residual starting materials or the undesirable formation of the respective *O*-TMS cyanohydrin or cyanohydrin.

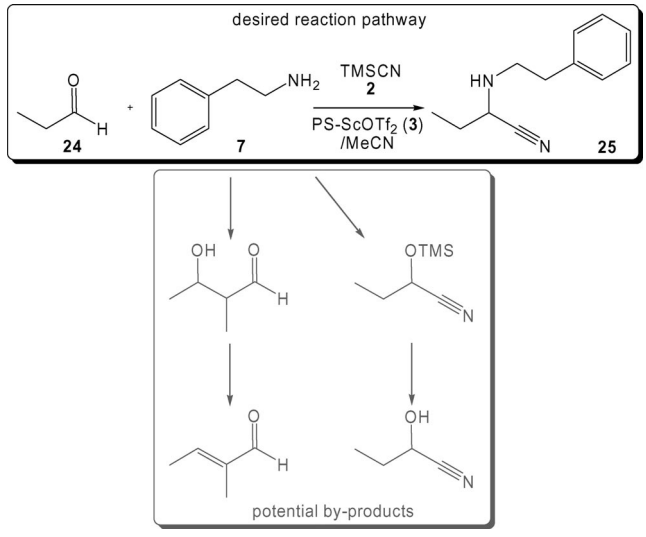
Table 3. Summary of the results obtained for the multi-component Strecker reaction of an array of aromatic aldehydes employing PS-Sc(OTf)$_2$ (**3**) as the catalyst.

Entry	Aldehyde	Amine	Flow rate, [μl min^{-1}][a]	Yield [%]	Throughput [mg h^{-1}]
1	 **23**	 **12**	20[c]	99.9	24.9
2	**23**	 **13**	20	100.0	26.6
3	**23**	 **7**	20	99.7	28.2
4	**23**	 **14**	20	99.9	30.0
5	**23**	**15** 	40[d]	99.9	44.6
6	 **20**	**12**	20	99.9	32.2
7	**20**	**13**	20	99.9	33.8
8	**20**	**7**	20	100.0	35.5
9	**20**	**14**	20	99.9	37.2
10	**20**	**15**	40[d]	100.0	59.0
11	 **21**	**12**	20	99.8	28.9
12	**21**	**13**	20	99.8	30.6
13	**21**	**7**	20	99.8	32.4
14	**21**	**14**	20	100.0	32.3
15	**21**	**15**	40[d]	100.0	52.8
16	 **22**	**12**	20	99.9	31.8
17	**22**	**13**	20	100.0	33.5
18	**22**	**7**	20	99.9	35.2
19	**22**	**14**	20	99.9	36.9
20	**22**	**15**	40	99.8	58.8

[a] On the baisis of the 3 fluidic i(nputs. [b] Isolated yield. [c] 1 h run time. [d] 0.5 h run time. [e] 1:1:1 Stoichiometry [aldehyde/amine/TMSCN (**2**)].

Investigation into the Reaction of Aliphatic Aldehydes

Having thoroughly evaluated the reaction of five aromatic aldehydes in the continuous flow reactor, the protocol was extended to the use of aliphatic aldehydes. Unlike their aromatic analogues, the use of aliphatic precursors adds another dimension of complexity due to the competing reaction pathway of the aldol reaction. Consequently, to further demonstrate the synthetic utility of continuous flow reactors, such as the micro reactor described herein, the reaction of propionaldehyde (**24**) and 2-phenylethylamine (**7**), to afford 2-phenethylamino-butyronitrile (**25**), was employed as a model reaction. As Scheme 2 illustrates, in addition to the previously encountered cyanohydrin formation, when conducted as a conventional one-pot transformation, the reaction can also yield the self-aldol product, 3-hydroxy-2-methylbutanal, which has the potential to eliminate water to afford (*E*)-2-methylbut-2-enal, further complicating the reaction mixture. In order to increase control over the reaction pathway followed, the synthesis of 2-(phenethylamino)butyronitrile (**25**) was subsequently investigated under continuous flow. To achieve this, propionaldehyde (**24**, 0.4 M in MeCN) and 2-phenylethylamine (**7**, 0.4 M in MeCN) were introduced into the reactor from inlets A and B respectively and a solution of TMSCN (**2**, 0.2 M in MeCN) from inlet C. Employing a total flow rate of 40 μL min^{-1}, the reaction mixture was pumped through the packed bed, containing PS-Sc(OTf)$_2$ (**3**), and the reaction products collected at outlet D, prior to concentrating in vacuo. Using this approach afforded 2-(phenethylamino)-butyronitrile (**25**) in excellent purity, confirming that enhanced reaction control can be obtained in microfluidic systems compared to the traditional one-pot approach where complex reaction mixtures resulted.

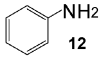
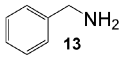
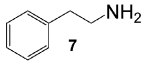
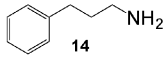


Scheme 2. Schematic illustrating a selection of the reaction products encountered when attempting to synthesize 2-(phenethylamino)butyronitrile (**25**) in a one-pot, batch reaction.

Having demonstrated that the aldol reaction could also be avoided through the use of sequential reactant addition, owing to the spatial control of reactive intermediates within the micro channel, the generality of the reaction was subsequently investigated, conducting the Strecker reaction of a further four aliphatic aldehydes, butyraldehyde (**26**), valeraldehyde (**27**), hexanal (**28**) and heptanal (**29**), with amines **7**, **12**–**15**. As Table 4 illustrates, owing to the increased reactivity of the aliphatic imines, to the nucleophilic attack of the CN anion, the reactions were successfully performed at higher flow rates (40 μL min^{-1}) compared to that previously employed for the aromatic derivatives (20 μL min^{-1}, Table 2 and Table 3). Although using this approach, high-throughputs were obtained; the main advantage of the technique undoubtedly is the suppression of competing reactions, which enables the desired α-aminonitrile to be synthesized

in excellent yield and purity, negating the need to perform post reaction product purification. It must, however, be noted that the investigation of aliphatic aldehydes was limited to the use of short chain aliphatic precursors due to the immiscibility of compounds $> C_8$ in MeCN. Compared to analogous batch reactions, however, this approach is not only rapid and facile, but also provides generic reaction conditions with which plethoras of derivatives are prepared with ease.

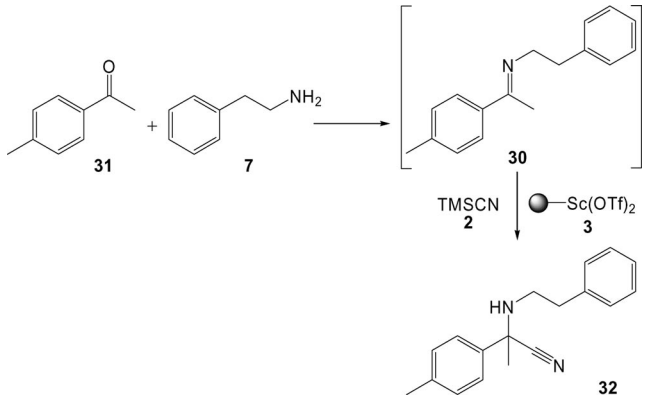
Table 4. Summary of the results obtained for the multi-component Strecker reaction of aliphatic aldehydes under continuous flow conditions, employing a run time of 0.5 h otherwise stated.

Entry	Aldehyde	Amine	Flow rate, [µl min^{-1}][a]	Yield [%]	Throughput [mg h^{-1}]
1	 **24**	 **12**	30[c]	100.0[d]	28.8
2	**24**	 **13**	40	99.6	41.8
3	**24**	 **7**	40	99.8	45.1
4	**24**	 **14**	40	99.9	48.5
5	**24**	 **15**	40	99.7	33.1
6	 **26**	**12**	30[c]	99.9	31.3
7	**26**	**13**	40	99.8	45.1
8	**26**	**7**	40	99.9	48.5
9	**26**	**14**	40	99.6	51.8
10	**26**	**15**	40	99.9	36.4
11	 **27**	**12**	30	99.9	33.8
12	**27**	**13**	40	99.9	48.5
13	**27**	**7**	40	100.0	51.8
14	**27**	**14**	40	99.9	55.2
15	**27**	**15**	40	100.0	39.8
16	 **28**	**12**	30[c]	99.9	36.3
17	**28**	**13**	40	99.9	51.8
18	**28**	**7**	40	99.9	55.2
19	**28**	**14**	40	99.9	58.6
20	**28**	**15**	40	99.9	43.2
21	 **29**	**12**	30[c]	99.9	38.9
22	**29**	**13**	40	99.9	55.7
23	**29**	**7**	40	99.9	58.6
24	**29**	**14**	40	99.9	61.9
25	**29**	**15**	40	100.0	46.6

[a] On the basis of the3 fluidic inputs. [b] Isolated yield. [c] Run time = 1 h. [d] 1:1:1 Stoichiometry [aldehyde/amine/TMSCN (**2**)].

Evaluation of Carbonyl Selectivity Under Continuous Flow

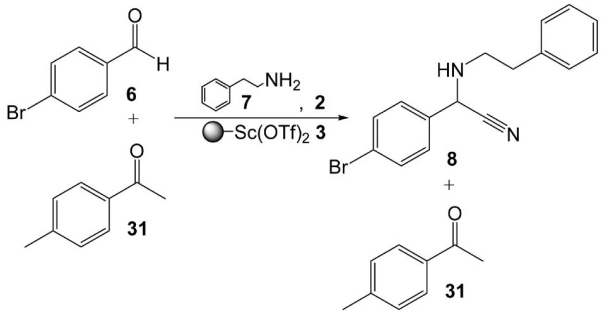
Having illustrated the efficient synthesis of fifty α-aminonitriles employing precursors ranging from aliphatic to aromatic aldehydes along with both primary and secondary amines, we subsequently investigated the feasibility of performing the ketonic Strecker reaction under continuous flow. As Scheme 3 illustrates the model reaction selected involved the preparation of the ketoimine **30**, formed via the reaction of 4-methylacetophenone (**31**) and 2-phenylethylamine (**7**), followed by the nucleophilic addition of the cyanide anion to afford 2-(phenylethylamino)-2-*p*-tolylpropanenitrile (**32**) as the desired product.



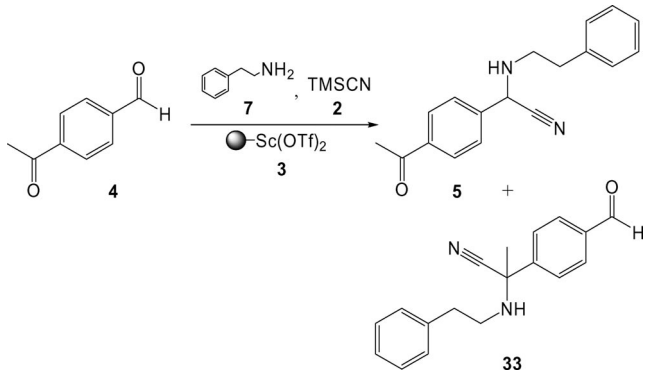
Scheme 3. Synthesis of 2-(phenylethylamino)-2-*p*-tolylpropanenitrile (**32**) investigated within a micro reactor.

To evaluate the reaction under continuous flow, the reaction manifold illustrated in Figure 1 was again employed along with working solutions of 4-methylacetophenone (**31**, 0.4 M in MeCN), 2-phenylethylamine (**7**, 0.4 M in MeCN) and TMSCN (**2**, 0.2 M in MeCN). Operating at the previously optimal flow rate of 20 µL min^{-1}, we were surprised to find that upon analysis of the resulting colorless oil that no reaction, to afford the desired α-aminonitrile **32**, had occurred. Fully expecting the reaction to take longer than the respective aldehydic Strecker reaction, the residence time was increased via reduction of the flow rate to 1 µL min^{-1} and again no reaction was observed, analysis of the reaction products simply confirmed recovery of the starting materials **31** and **7**. In a final attempt to optimize the reaction, the concentration of the TMSCN (**2**) solution was increased from 0.2 M (1 equiv.) to 0.6 M (3 equiv.) and again no conversion to 2-(phenylethylamino)-2-(*p*-tolyl)propanenitrile (**32**) was observed. This led us to conclude that the formation of the ketoimine **30** was the limiting step and being less favorable than the previously observed aldimine synthesis, would possibly require catalysis to afford the desired intermediate **30**. In accordance with this observation, it was postulated that due to the catalyst free conditions employed within the first portion of the micro reactor that it should be possible to perform the aldehydic Strecker reaction in the presence of the ketone moiety, due to the preferential formation of the aldimine, as depicted by Scheme 4.

With this in mind, a solution of 4-bromobenzaldehyde (**6**) and 4-methylacetophenone (**30**) (0.4 M respectively in MeCN) was introduced into the reactor at inlet A, a solution of 2-phenylethylamine **7** (0.4 M in MeCN) from inlet B and a solution of TMSCN (**2**, 0.2 M in MeCN) from inlet



Scheme 4. Illustration of the model reaction used to evaluate reaction selectivity under continuous flow and the potential reaction products.



Scheme 5. Schematic illustrating the potential reaction products obtained when employing 4-acetylbenzaldehyde (**4**) as a precursor.

C. In line with the optimization previously performed for the synthesis of 2-(4-bromophenyl)-2-(phenylamino)acetonitrile (**8**), a total flow rate of 20 μL min^{-1} was employed and the reaction products collected (1 h) and concentrated in vacuo to afford a pale yellow oil. Analysis of the crude reaction products by NMR confirming the quantitative synthesis of 2-(4-bromophenyl)-2-(phenylamino)acetonitrile (**8**), indicated by the appearance of the CH signal at 4.8 ppm, and the presence of the un-reacted 4-methylacetophenone (**31**), confirmed by the residual CH_3 signals at δ = 2.3 and 2.5 ppm, which is attributed to the reduced reactivity of the ketonic moiety.

Having demonstrated the ability to synthesize 2-(4-bromophenyl)-2-(phenylamino)acetonitrile (**8**) in the presence of a ketone **31**, the chemoselectivity of the reaction was further evaluated for the synthesis of 2-(4-acetylphenyl)-2-(phenethylamino)acetonitrile (**5**) (Scheme 5). Employing a bifunctional compound, such as 4-acetylbenzaldehyde (**4**), further increased the complexity of the reaction owing to the potential to synthesize the respective cyanohydrins, aldimine and ketoimine, along with the aldehydic **5** or ketonic Strecker product **33** and the bis-adduct **34** (Figure 8). It was therefore proposed that by conducting the reaction under continuous flow, that the cyanohydrin formation would again be suppressed as a result of sequential reagent addition and that the desired aldehydic Strecker product would be synthesized due to (i) the kinetically preferred formation of the aldimine (1-{4-[(*E*)-phenethyliminomethyl]-phenyl}ethanone), (ii) the short residence time employed within such as system, and(iii) the use of stoichiometric quantities of the cyanide source **2**.

To explore this hypothesis, 4-acetylbenzaldehyde (**4**, 0.4 M) was introduced into the reactor as a solution in MeCN from inlet A, 2-phenylethylamine (**7**, 0.4 M in MeCN) from inlet B and TMSCN (**2**, 0.2 M in MeCN) from inlet C. Operating at the previously optimized flow rate for aromatic aldehydes of 20 μL min^{-1}, quantitative formation of the aldehydic Strecker product was observed. Consequently, the reactor was operated for a period of 1 h, which upon concentrating in vacuo afforded 2-(4-acetylphenyl)-2-(phenylethylamino)acetonitrile (**5**) as a pale yellow oil in 99.8% yield (33 mg h^{-1}). Using this approach, the desired compound **5** was synthesized quantitatively, with no sign of

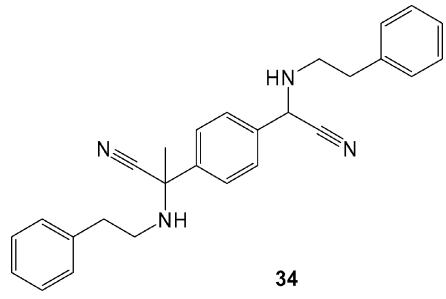


Figure 8. The bis-adduct **34** obtained when employing 4-acetylbenzaldehyde (**4**) in the Strecker reaction under batch conditions.

2-(4-formylphenyl)-2-(phenethylamino)propionitrile (**33**) or bis-adduct **34** formation, demonstrating excellent chemoselectivity compared to conventional methodology whereby *O*-TMS-cyanohydrin formation dominated.

Summary

In recent years the use of continuous flow reactors, and in particular micro reactors, has captured the attention of the modern day synthetic chemist, with uptake of the technology increasing as the systems have become commercially available. Some sectors of the scientific community, however, remain skeptical and as such our research focuses on comparing such emerging technologies with conventional batch-wise protocols, enabling any advantages and, potentially most importantly, disadvantages/limitations to be identified. Through this practice, the aim is to develop novel synthetic procedures using continuous flow processing as a means of improving the reproducibility of common synthetic transformations by providing operator independent reaction methodologies.

To increase the complexity of reactions evaluated in this way, the multi-component Strecker reaction was selected as a model reaction and enabled us to develop a single reactor capable of performing solution phase and polymer-assisted reactions in series. In contrast to conventional stirred reactor methodology, the development of an integrated micro fluidic system, such as the one described herein, is advan-

tageous as the predictable nature of diffusion based mixing enables a reaction manifold to be designed to afford complete mixing of two precursors and subsequent generation of an intermediate, prior to the addition of the third reactant, followed by contact with the catalyst. As such, this mode of operation offers a route to enhanced reaction selectivity as by-product formation is prevented. Coupled with the use of solid-supported catalysts and stoichiometric quantities of precursors, this approach yields a synthetic technique whereby post-reaction processing consists simply of solvent removal, affording the desired product in analytical purity; an advantage, which is highlighted throughout this report.

In conclusion, the integrated reactor reported herein offers significant operational advantages over batch-wise syntheses, ranging from shorter reaction times (< 1 min), increased atom efficiency [1 equiv. of TMSCN (**2**)] and enhanced yields/purities (>99.6%), to efficient catalyst recycle (turnover > 1050) and minimal exposure to hazardous reactants due to the use of a sealed reaction unit. The technique can also be scaled with ease through replication, as a means of increasing the system throughput from the current 0.12–0.24 mmol h^{-1}. Owing to the success of this investigation, further studies will be directed towards the development and evaluation of a solid-supported Lewis acid capable of catalyzing the ketonic Strecker reaction under continuous flow conditions.

Experimental Section

Materials: All solvents were purchased as puriss grade (>99.5%) over molecular sieves (H_2O < 0.005%) from Fluka and unless otherwise stated, reagents were purchased from Sigma–Aldrich and used as received. The polymer-bound scandium(III) bis(trifluoromethanesulfonate) [PS-ScOTf_2], **3**) (0.60 mmol Sc g^{-1}, 250–600 μm) was ground in a pestle and mortar to reduce the overall particle size and sieved to afford a particle size distribution of 38 to 75 μm (Endcotts, UK). The polymer-supported (ethylenediaminetetraacetic acid)ruthenium(III) chloride (PS-$RuCl_3$, **1**) (0.26 mmol Ru g^{-1}, 50–100 mesh) and polymer-bound ethylenediaminetetraacetamide (PS-EDTA) (3.62 mmol N g^{-1}) were also sieved to afford the narrow particle size distribution required (see PS-ScOTf_2, **3**) to enable the preparation of uniform packed beds.

Instrumentation: All ^1H and ^{13}C 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 reported in parts per million (ppm) with coupling constants given in Hertz (Hz). The following abbreviations are used to report NMR spectroscopic data; s = singlet, d = doublet, t = triplet, br. s = broad singlet, q = quartet, sext = sextet, dd = double doublet, dt = doublet of triplets, m = multiplet, ArH = aromatic proton and C_0 = quaternary carbon. Elemental analyses were performed using a Fisons Carlo–Erba CHN analyzer (EA1108) and infrared spectra (4000 to 600 cm^{-1}) were obtained in the solid state (KBr disks) using a Perkin–Elmer Optima 5300DV instrument, with peaks ($\tilde{\nu}_{max}$) reported in wavenumbers. Mass spectrometry data was obtained using a Shimadzu QP5050A instrument with an EI ionization source. Melting points were determined using a Gallenkamp melting point apparatus and are reported uncorrected. Delivery of reactants to the micro reactor was controlled using a displacement pump (MD-1001, Bioanalytical Systems Inc.), capable of delivering three solutions at flow rates of between 0.1 and 100 μL min^{-1} (calibrated for a 1 mL gastight syringe). Gas Chromatography-Mass Spectrometry (GC-MS) was performed using a Varian GC (CP-3800) coupled to a Varian MS (Saturn 2000) with a CP-Sil 8 column (30 m, Zebron ZB-5, Phenomenex, UK) and ultra high purity helium (99.999%, Energas, UK) carrier gas. Samples were analyzed using the following method; injector temperature 250 °C, 1.0 μL sample volume, helium flow rate 1.0 mL min^{-1}, oven temperature 50 °C for 4 min, then ramped to 250 °C at 30 °C min^{-1} and held at 250 °C for 10 min, with a 3 min filament delay.

With the exception of 2-(4-bromophenyl)-2-(trimethylsilyloxy)acetonitrile (**9**) and (*E*)-[1-(4-bromophenyl)methylidene]phenethylamine (**11**), all characterization data reported was obtained using compounds synthesized within the borosilicate glass micro reactors and in all cases, no additional product purification was performed.

Continuous-Flow Methodology: The borosilicate glass micro reactor was fabricated in-house using a series of photolithography, wet-etching and thermal annealing steps resulting in a reactor with an overall footprint of 3.0 cm (wide) × 3.0 cm (long) × 0.3 cm (deep). The first of the two etched layers had channel dimensions of 150 μm (wide) × 50 μm (deep) × 5.6 cm (long), with a catalyst bed of 3 mm (wide) × 50 μm (deep) and 2.0 cm (long) (Figure 3, a) and the second plate contained a catalyst bed of 3 mm (wide) × 150 μm (deep) × 2.1 cm (long) (Figure 3, b). Thermal annealing of the two etched layers afforded a catalyst bed with dimensions of 3 mm (wide) × 200 μm (deep) × 2.0 cm (long) (Figure 3, c) and an overall reactor dimension of 3.0 cm (wide) × 3.0 cm (long) × 0.6 cm (deep).

The borosilicate glass reactor was then packed with the polymer supported catalyst under evaluation and a series of PEEK (360 μm o.d. × 150 μm i.d. × 10 cm) and FEP tubes (1/16" o.d. × 380 μm i.d. × 4 cm), glued in place [using epoxy resin (Bondmaster, UK)] to enable the introduction and removal of reactants and products to and from the micro reactor. As Figure 4 illustrates, fluidic connections were made using a series of commercially available connectors (Supleco, UK), inlets A and B were fed with 500 μL syringes and inlet C with a 1000 μL syringe to afford a stoichiometric ratio of reactants.

Preparation of (*E*)-[1-(4-Bromophenyl)methylidene]phenethylamine (11) in Batch: 2-Phenylethylamine (**7**, 1.21 g, 10.0 mmol) was added to a solution of 4-bromobenzaldehyde (**6**, 1.85 g, 10.0 mmol) in anhydrous MeCN (10 mL) and stirred for 24 h. Over the course of the reaction a white crystalline solid precipitated from the reaction mixture, this was filtered under suction and recrystallized from DCM/hexane to afford the title compound **11** as a white, crystalline solid; (0.0361 g, 99.9%). $C_{15}H_{14}BrN$ (288.19): calcd. C 62.52, H 4.90, N 4.86; found C 62.31, H 4.92, N 4.64. IR: $\tilde{\nu}_{max}$ = 691.1, 738.2, 851.0, 1457.2, 1507.2, 1653.2, 2360.4 and 3350.1 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 3.03 (t, J = 7.4 Hz, 2 H, CH_2Ph), 3.89 (t, J = 7.4 Hz, 2 H, NCH_2CH_2), 7.21–7.39 (m, 5 H, 5× ArH), 7.57 (m, 4 H, 4× ArH) and 8.20 (s, 1 H, CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 37.5 (CH_2CH_2N), 63.2 (CH_2CH_2N), 125.1 (C_0Br), 126.3 (CH), 128.5 (2× CH), 129.2 (2× CH), 129.6 (2× CH), 131.9 (2× CH), 135.2 (C_0), 139.9 (C_0) and 160.3 (CH) ppm. MS (EI): m/z = 290 (35), 289 (15), 288 (60), 198 (90), 197 (10), 196 (100), 171 (5), 169 (5), 105 (20) and 76 (15). GC-MS R_T = 12.40 min.

Continuous-Flow Synthesis of 2-(4-Bromophenyl)-2-(phenethylamino)acetonitrile (8) via the Cyanohydrin Intermediate: Employing polymer-supported (ethylenediaminetetraacetic acid)ruthenium(III) chloride (**1**, 0.01 g, 0.26 mmol Ru g^{-1}) as the catalyst, solutions of 2-(4-bromophenyl)-2-(trimethylsilyloxy)acetonitrile (**9**, 0.2 M in MeCN) and 2-phenylethylamine (**7**, 0.2 M in MeCN) were introduced into the reactor from inlets A and B respectively, where they mixed in the central channel prior to passing through the catalyst bed in a 1:1 ratio and an overall concentration of 0.1 M. The reaction products were collected at outlet D, into a pre-weighed sample vial, over a period of 2.5 h and concentrated in vacuo prior to analysis by ^{1}H NMR spectroscopy. Comparison of the integrals obtained for the signals arising from the *O*-TMS cyanohydrin **9**, at δ = 5.38 ppm, and α-aminonitrile **8**, at δ = 4.8 ppm, enabled the % conversion to be quantified.

Continuous-Flow Synthesis of 2-(4-Bromophenyl)-2-(phenethylamino)acetonitrile (8) via the Imine Intermediate 11: Employing polymer-supported (ethylenediaminetetraacetic acid)ruthenium(III) chloride (0.01 g, 0.26 mmol Ru g^{-1}) as the catalyst, solutions of (*E*)-[1-(4-bromophenyl)methylidene]phenethylamine (**11**, 0.2 M in MeCN) and TMSCN (**2**, 0.2 M in MeCN) were introduced into the reactor from inlets A and B respectively, where they mixed in the central channel prior to passing through the packed bed at an overall concentration of 0.1 M (1:1). The reaction products were collected at outlet D, into a pre-weighed sample vial, over a period of 2.5 h and concentrated in vacuo prior to analysis by ^{1}H NMR spectroscopy. Comparison of the integrals obtained for the signals arising from the imine **11**, at δ = 8.20 ppm, and α-aminonitrile **8**, δ = 4.75 ppm, enabled quantification of the % conversion.

General Procedure for the Continuous-Flow Synthesis of α-Aminonitriles via an Imine Intermediate (Prepared in-Situ): Employing **1** (0.01 g, 0.26 mmol Ru g^{-1}) or **3** (0.010 g, 0.60 mmol Sc g^{-1}), solutions of the aldehyde (0.4 M in MeCN) and amine (0.4 M in MeCN) were introduced into the reactor from inlets A and B respectively, to afford the respective imine within the central channel at a concentration of 0.2 M. TMSCN (**2**, 0.2 M in MeCN) was subsequently introduced into the reactor, where it mixed with the in-situ generated imine, prior to passing through the catalyst bed at a total flow rate of 20 to 40 μL min^{-1}.[33] The reaction mixture was collected at outlet D, in a pre-weighed sample vial, and concentrated in vacuo, prior to dissolution in $CDCl_3$ and analysis by ^{1}H NMR spectroscopy. Comparison of the integrals from the residual CH signal of the imine and that of the CH from the desired α-aminonitrile enabled quantification of the% conversion and hence the relative success of the reaction. All known compounds were identified by comparison of their spectroscopic data and physical properties with those of authentic samples (See Supporting Information for further details) and for those compounds that were previously unknown, full characterization was performed on the compounds synthesized under continuous flow using PS-$ScOTf_2$ (**3**) as the catalyst; in all cases, no additional product purification was performed.

2-Benzylamino-2-(4-bromophenyl)acetonitrile (18): (Table 2, Entry 2) Employing 4-bromobenzaldehyde (**6**) and benzylamine (**13**) as reactants, the micro reaction was conducted at a total flow rate of 20 μL min^{-1} to afford **18** as a pale yellow oil (0.0361 g, 99.9%). $C_{15}H_{13}BrN_2$ (301.19): calcd. C 59.82, H 4.35, N 9.30; found C 60.10, H 4.56, N 9.06]. IR: $\tilde{\nu}_{max}$ = 701.0, 736.7, 788.2, 823.5, 1454.1, 1488.2, 1551.6, 1591.1, 2303.6, 2846.5, 3030.4, 3053.5 and 3322.5 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.85 (br. s, 1 H, NH), 3.82 (d, *J* = 12.9 Hz, 1 H, C*H*H), 3.94 (d, *J* = 12.9 Hz, 1 H, CH*H*), 4.81 (s, 1 H, CH), 7.28–7.41 (m, 5 H, 5× ArH), 7.44 (d, *J* = 8.4 Hz, 2 H, 2× ArH) and 7.54 (d, *J* = 8.4 Hz, 2 H, 2× ArH), 51.2 (CH_2), 52.9 (CH), 118.3 (CN), 123.3 (C_0Br), 127.8 (CH), 128.4 (2× CH), 128.7 (2× CH), 129.0 (2× CH), 132.1 (2× CH), 133.7 (C_0) and 137.8 (C_0) ppm. MS (EI): *m*/*z* = 303 (30), 302 (20), 301 (30), 274 (13), 272 (5), 195 (5), 194 (11), 106 (21), 92 (50), 91 (100) and 65 (20).

2-(4-Bromophenyl)-2-(phenethylamino)acetonitrile (8): (Table 2, Entry 3) Conducting the reaction at a total flow rate of 20 μL min^{-1} and employing 4-bromobenzaldehyde (**6**) and 2-phenylethylamine (**7**) as reactants, the title compound **8** was obtained as a pale yellow solid (0.038 g, 99.9%); mpt. 91–92 °C. $C_{16}H_{15}BrN_2$ (315.21): calcd. C 60.97, H 4.80, N 8.89; found C 61.06, H 4.96, N 8.69]. IR: $\tilde{\nu}_{max}$ = 701.2, 750.6, 770.8, 811.9, 1419.6, 1450.0, 1542.2, 1581.0, 2347.4, 2896.1, 3002.7, 3056.1 and 3315.8 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.54 (br. s, 1 H, NH), 2.62–2.86 (m, 2 H, CH_2), 2.95–3.10 (m, 2 H, 2× CH_2), 4.75 (s, 1 H, CH), 7.12 (m, 3 H, 3× ArH), 7.23 (m, 2 H, 2× ArH), 7.43 (d, *J* = 8.4 Hz, 2 H, ArH) and 7.50 (d, *J* = 8.4 Hz, 2 H, 2× ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 35.7 (CH_2), 47.8 (CH_2N), 53.6 (CH), 118.2 (CN), 122.9 (C_0Br), 128.2 (C_0), 128.5 (4× CH), 128.6 (2× CH), 131.8 (2× CH), 133.6 (CH) and 138.8 (C_0) ppm. MS (EI): *m*/*z* = 317 (80), 316 (50), 315 (82), 290 (10), 288 (8), 197 (75), 196 (100), 170 (44), 169 (48), 91 (34), 90 (31), 89 (34), 77 (19) and 65 (21).

2-(4-Bromophenyl)-2-(3-phenylpropylamino)acetonitrile (19): (Table 2, Entry 4) Employing **6** and **14** as reactants, the micro reaction was conducted at a total flow rate of 20 μL min^{-1}, to afford **19** as a pale yellow gum (0.0394 g, 99.9%). $C_{17}H_{17}BrN_2$ (329.24): calcd. C 62.02, H 5.20, N 8.51; found C 61.95, H 5.29, N 8.48]. IR: $\tilde{\nu}_{max}$ = 699.7, 746.6, 817.7, 1453.0, 1487.2, 1573.3, 1589.1, 2226.6, 2855.9, 2935.0, 3025.1 and 3316.0 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.48 (br. s, 1 H, NH), 1.76 (m, 2 H, CH_2), 2.61–2.74 (m, 4 H, 2× CH_2), 4.61 (s, 1 H, CH), 7.12–7.30 (m, 5 H, 5× ArH), 7.32 (d, *J* = 8.5 Hz, 2 H, 2× ArH) and 7.46 (d, *J* = 8.5 Hz, 2 H, 2× ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 30.8 (CH_2), 32.9 (CH_2), 46.2 (CH_2), 53.5 (CH), 118.2 (CN), 122.6 (C_0), 125.6 (CH), 128.0 (2× CH), 128.1 (4× CH), 131.1 (2× CH), 133.7 (C_0) and 141.8 (C_0) ppm. MS (EI): *m*/*z* = 329 (1), 328 (15), 304 (8), 303 (4), 301 (10), 199 (93), 198 (90), 197 (100), 196 (99), 169 (20), 118 (65), 91 (85), 77 (17) and 65 (25).

2-Phenyl-2-(3-phenylpropylamino)acetonitrile: (Table 3, Entry 4) Employing benzaldehyde **23** and phenylpropylamine (**14**) as reactants, the micro reactor was operated at a total flow rate of 20 μL min^{-1}, to afford 2-phenyl-2-(3-phenylpropylamino)acetonitrile as a pale yellow gum (0.0300 g, 99.9%). $C_{17}H_{18}N_2$ (250.34): calcd. C 81.56, H 7.25, N 11.19; found C 81.50, H 7.23, N 11.10]. IR: $\tilde{\nu}_{max}$ = 689.9, 738.0, 1452.5, 1496.1, 1580.3, 1600.9, 1643.6, 202.6, 2856.0, 2937.6, 3027.3 and 3317.8 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.89 (m, 2 H, CH_2), 2.67–2.86 (m, 4 H, 2× CH_2), 4.76 (s, 1 H, CH), 7.26–7.38 (m, 10 H, 10× ArH) ppm and NH not observed. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 31.1 (CH_2), 33.2 (CH_2), 46.7 (CH_2), 54.4 (CH), 118.8 (CN), 125.8 (CH), 128.2 (2× CH), 128.3 (CH), 128.4 (4× CH), 128.8 (2× CH), 132.3 (C_0) and 141.6 (C_0) ppm. MS (EI): *m*/*z* = 251 (4), 250 (8), 224 (7), 145 (14), 131 (20), 119 (48), 118 (100), 116 (70), 105 (14), 91 (47), 90 (10), 77 (12) and 65 (11).

2-(Benzylamino)-2-(3,5-dimethoxyphenyl)acetonitrile: (Table 3, Entry 7) Employing 3,5-dimethoxybenzaldehyde (**20**) and benzylamine (**13**) as reactants, the micro reactor was operated at a total flow rate of 20 μL min^{-1}, affording 2-(benzylamino)-2-(3,5-dimethoxyphenyl)acetonitrile as a white crystalline solid (0.0338 g, 99.9%). $C_{17}H_{18}N_2O_2$ (282.34): calcd. C 72.30, H 6.43, N 8.51; found C 72.23, H 6.62, N 9.69]. IR: $\tilde{\nu}_{max}$ = 691.3, 720.4, 810.3, 1445.2, 2260.6, 2820.6, 2866.3, 2938.1 and 3029.4 cm^{-1}. ^{1}H NMR

(400 MHz, $CDCl_3$/TMS): δ = 1.93 (br. s, 1 H, NH), 3.76 (s, 6 H, 2× OCH_3), 3.90 (d, J = 12.9 Hz, 1 H, C*H*H), 4.00 (d, J = 12.9 Hz, 1 H, CH*H*), 4.79 (s, 1 H, CH), 6.42 (t, J = 2.2 Hz, 1 H, ArH), 6.67 (d, J = 2.2 Hz, 2 H, 2× ArH) and 7.32–7.36 (m, 5 H, 5× ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 50.9 (CH), 53.2 (CH_2), 55.3 (2× OCH_3), 100.6 (CH), 105.2 (2× CH), 118.6 (CN), 127.5 (CH), 128.3 (2× CH), 128.4 (2× CH), 130.8 (C_0), 138.0 (C_0) and 161.0 (2× C_0OCH_3) ppm. MS (EI): m/z = 283 (8), 282 (16), 281 (17), 255 (38), 240 (5), 224 (10), 106 (20), 91 (100), 77 (20) and 75 (5).

2-(3,5-Dimethoxyphenyl)-2-(phenethylamino)acetonitrile: (Table 3, Entry 8) Conducting the reaction at a total flow rate of 20 μL min^{-1} and employing 3,5-dimethoxybenzaldehyde (**20**) and 2-phenylethylamine (**7**) as reactants, title compound was obtained as a white crystalline solid (0.0355 g, 99.9%). $C_{18}H_{20}N_2O_2$ (296.37): calcd. C 72.95, H 6.80, N 9.45; found C 72.75, H 6.81, N 9.39]. IR: $\tilde{\nu}_{max}$ = 740.7, 1156.3, 1265.5, 1429.7, 1457.6, 1598.2, 2305.7, 2841.5, 2986.5 and 3054.5 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 2.62 (m, 2 H, CH_2), 2.91 (m, 2 H, CH_2), 3.73 (s, 6 H, 2× OCH_3), 5.39 (s, 1 H, CH), 6.40 (t, J = 2.2 Hz, 1 H, ArH), 6.59 (m, 2 H, 2× ArH), 7.12–7.29 (m, 5 H, 5× ArH) ppm. and NH not observed. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 37.1 (CH_2), 47.9 (CH_2N), 50.1 (CH), 56.3 (2× OCH_3), 99.2 (CH), 107.1 (2× CH), 114.7 (CN), 126.3 (CH), 127.6 (2× CH), 128.3 (2× CH), 132.2 (C_0), 139.5 (C_0) and 162.3 (2× C_0OCH_3) ppm. MS (EI): m/z = 297 (5), 296 (3), 234 (10), 208 (15), 178 (100), 163 (25), 147 (45), 116 (10), 105 (20), 91 (30) and 76 (25).

2-(3,5-Dimethoxyphenyl)-2-(3-phenylpropylamino)acetonitrile: (Table 3, Entry 9) Employing 3,5-dimethoxybenzaldehyde (**20**) and phenylpropylamine (**14**) as reactants, the micro reactor was operated at a total flow rate of 20 μL min^{-1}, affording the title compound as a colorless oil (0.0372 g, 100.0%). $C_{19}H_{22}N_2O_2$ (310.39): calcd. C 73.52, H 7.14, N 9.03; found C 73.50, H 7.16, N 9.10]. IR: $\tilde{\nu}_{max}$ = 650.2, 680.4, 720.5, 1360.1, 1450.2, 2255.3, 2815.5, 2850.2 and 2920.5 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.82 (m, 2 H, CH_2), 2.67–2.69 (m, 4 H, 2× CH_2), 3.76 (s, 6 H, 2× OCH_3), 4.65 (s, 1 H, CH), 6.43 (t, J = 2.2 Hz, 1 H, ArH), 6.65 (d, J = 2.2 Hz, 2 H, 2× ArH), 7.15–7.27 (m, 5 H, 5× ArH) ppm and NH not observed. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 31.1 (CH_2), 33.1 (CH_2), 46.6 (CH_2), 54.3 (CH), 55.3 (2× OCH_3), 100.6 (CH), 105.6 (2× CH), 118.7 (CN), 125.8 (CH), 128.2 (4× CH), 137.0 (C_0), 141.5 (C_0), 161.0 (2× C_0OCH_3) ppm. MS (EI): m/z = 311 (18), 310 (8), 284 (100), 253 (10), 222 (15), 179 (90), 178 (85), 148 (50), 119 (45), 91 (65), 77 (15) and 75 (10).

2-(3,5-Dimethoxyphenyl)-2-(pyrrolidin-1-yl)acetonitrile: (Table 3, Entry 10) Operating the micro reactor at a total flow rate of 40 μL min^{-1}, employing 3,5-dimethoxybenzaldehyde (**20**) and pyrrolidine (**15**) as reactants, 2-(3,5-dimethoxyphenyl)-2-(pyrrolidin-1-yl)acetonitrile was obtained as a pale yellow oil (0.0295 g, 100.0%). $C_{14}H_{18}N_2O_2$ (246.31): calcd. C 68.27, H 7.40, N 11.38; found C 68.27, H 7.60, N 11.64]. IR: $\tilde{\nu}_{max}$ = 650.2, 683.6, 720.1, 740.7, 896.0, 1429.3, 1508.0, 1598.3, 2240.1, 2820.3 and 3055.4 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.83 (m, 4 H, 2× CH_2), 2.66 (m, 4 H, 2× CH_2), 3.80 (s, 6 H, 2× OCH_3), 4.97 (s, 1 H, CH), 6.43 (t, J = 2.2 Hz, 1 H, ArH) and 6.89 (d, J = 2.2 Hz, 2 H, 2× ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 23.1 (2× CH_2), 48.2 (2× CH_2), 51.0 (CH), 55.3 (2× OCH_3), 100.6 (CH), 105.2 (2× CH), 118.6 (CN), 136.8 (C_0) and 161.1 (2× C_0OCH_3) ppm. MS (EI): m/z = 247 (20), 246 (10), 220 (40), 194 (20), 177 (65), 109 (40), 84 (35), 70 (100) and 49 (50).

2-(4-Chlorophenyl)-2-(phenethylamino)acetonitrile: (Table 3, Entry 13) Conducting the micro reaction at a total flow rate of 20 μL min^{-1} and employing 4-chlorobenzaldehyde (**21**) and 2-phenylethylamine (**7**) as reactants, afforded the title compound as a colorless oil (0.0323 g, 99.8%). $C_{16}H_{15}ClN_2$ (270.76): calcd. C 70.98, H 5.58, N 10.35; found C 70.95, H 5.62, N 10.42]. IR: $\tilde{\nu}_{max}$ = 743.4, 792.1, 853.2, 2254.5, 2870.6, 2925.7 and 2962.3 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.93 (br. s, 1 H, NH), 2.83 (m, 2 H, CH_2), 2.98 (m, 2 H, CH_2), 4.75 (s, 1 H, CH), 7.23 (m, 3 H, 3× ArH), 7.32 (m, 2 H, 2× ArH), 7.33 (d, J = 8.5 Hz, 2 H, 2× ArH) and 7.41 (d, J = 8.5 Hz, 2 H, 2× ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 35.8 (CH_2), 42.6 (CH_2N), 53.6 (CH), 118.3 (CN), 126.4 (C_0), 128.5 (4× CH), 128.6 (4× CH), 133.1 (CH), 134.8 (C_0) and 138.8 (C_0) ppm.

2-(4-Chlorophenyl)-2-(3-phenylpropylamino)acetonitrile: (Table 3, Entry 14) Employing 4-chlorobenzaldehyde (**21**) and phenylpropylamine (**14**) as reactants, the micro reaction was conducted at a total flow rate of 20 μL min^{-1}, affording the title compound as a colorless oil (0.0342 g, 100.0%). $C_{17}H_{17}ClN_2$ (284.91): calcd. C 71.70, H 6.02, N 9.84; found C 71.65, H 6.10, N 9.82]. IR: $\tilde{\nu}_{max}$ = 690.1, 736.2, 792.1, 1453.0, 1496.6, 1580.3, 1601.3, 1644.2, 2304.5, 2856.1, 2937.8, 3027.4 and 3317.9 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.85 (m, 2 H, CH_2), 2.69–2.84 (m, 4 H, 2× CH_2), 4.74 (s, 1 H, CH), 7.14–7.20 (m, 5 H, 5× ArH), 7.27 (d, J = 7.8 Hz, 2 H, 2× ArH), 7.48 (m, 2 H, 2× ArH) ppm and NH not observed. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 33.1 (CH_2), 33.4 (CH_2), 45.3 (CH_2N), 49.9 (CH), 117.6 (CN), 125.6 (CH), 128.1 (2× CH), 128.3 (2× CH), 128.8 (2× CH), 130.4 (2× CH), 131.8 (C_0), 134.2 (C_0Cl) and 142.0 (C_0) ppm. MS (EI): m/z = 285 (3), 284 (2), 283 (4), 273 (5), 271 (10), 154 (100), 152 (95), 127 (14), 125 (40), 105 (20), 91 (30) and 76 (10).

2-(4-Chlorophenyl)-2-(pyrrolidin-1-yl)acetonitrile: (Table 3, Entry 15) Operating the micro reactor at a total flow rate of 40 μL min^{-1} and employing 4-chlorobenzaldehyde (**21**) and pyrrolidine (**15**) as reactants, the title compound was obtained as a pale yellow oil (0.0264 g, 100.0%). $C_{12}H_{13}ClN_2$ (221.63): calcd. C 65.31, H 5.94, N 12.70; found C 65.65, H 6.23, N 12.57]. IR: $\tilde{\nu}_{max}$ = 720.1, 750.2, 860.2, 1540.5, 1616.4, 2302.6, 2801.3 and 2915.4 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.83 (m, 4 H, 2× CH_2), 2.61 (m, 4 H, 2× CH_2), 5.02 (s, 1 H, CH), 7.36 (d, J = 8.2 Hz, 2 H, 2× ArH) and 7.47 (d, J = 8.2 Hz, 2 H, 2× ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 23.2 (2× CH_2), 48.2 (2× CH_2N), 51.3 (CH), 115.4 (CN), 128.1 (2× CH), 128.2 (CH), 130.4 (2× CH) and 133.2 (C_0Cl) ppm. MS (EI): m/z = 222 (5), 221 (10), 220 (15), 219 (12), 194 (5), 85 (13), 84 (15), 83 (38), 70 (50) and 51 (25).

Methyl 4-[Cyano(phenylamino)methyl]benzoate: (Table 3, Entry 16) Employing methyl 4-formylbenzoate (**22**) and aniline (**12**) as reactants, the micro reaction was conducted at a total flow rate of 20 μL min^{-1}, to afford the title compound as a colorless oil (0.0318 g, 99.8%). $C_{16}H_{14}N_2O_2$ (266.42): calcd. C 72.17, H 5.30, N 10.52; found C 71.89, H 5.53, N 10.28]. IR: $\tilde{\nu}_{max}$ = 690.2, 745.0, 840.3, 1250.2, 1752.1, 2253.6, 2835.2 and 2905.3 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 3.95 (s, 3 H, OCH_3), 4.13 (d, J = 8.4 Hz, 1 H, NH), 5.52 (d, J = 8.4 Hz, 1 H, CH), 6.78 (m, 2 H, 2× ArH), 6.98 (m, 1 H, ArH), 7.26–7.30 (m, 2 H, 2× ArH), 7.71 (d, J = 8.3 Hz, 2 H, 2× ArH) and 8.11 (d, J = 8.3 Hz, 2 H, 2× ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 50.0 (CH), 52.4 (OCH_3), 114.3 (2× CH), 118.2 (CN), 120.6 (CH), 127.2 (2× CH), 129.6 (2× CH), 130.5 (2× CH), 139.2 (C_0), 144.3 (C_0) and 168.3 ($C_0CO_2CH_3$) ppm. MS (EI): m/z = 267 (5), 266 (15), 235 (15), 207 (25), 189 (20), 175 (75), 135 (100), 131 (10), 77 (15) and 76 (10).

Methyl 4-[Cyano(benzylamino)methyl]benzoate: (Table 3, Entry 17) Conducting the micro reaction at a total flow rate of 20 μL min^{-1} and employing methyl 4-formylbenzoate (**22**) and benzylamine **13**

as precursors, afforded the title compound as a colorless oil (0.0335 g, 99.9%). $C_{17}H_{16}N_2O_2$ (280.33): calcd. C 72.84, H 5.75, N 9.99; found C 72.63, H 5.65, N 5.65]. IR: $\tilde{\nu}_{max}$ = 720.3, 741.2, 841.2, 1252.3, 1457.0, 1719.6, 2254.1, 2987.0 and 3054.5 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.96 (br. s, 1 H, NH), 3.90 (s, 3 H, OCH_3), 3.90 (d, J = 12.9 Hz, 1 H, C*H*H), 4.02 (d, J = 12.9 Hz, 1 H, CH*H*), 4.77 (s, 1 H, CH), 7.28 (m, 5 H, 5× ArH), 7.60 (d, J = 8.4 Hz, 2 H, 2× ArH) and 8.05 (d, J = 8.4 Hz, 2 H, 2× ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 51.0 (CH), 52.1 (OCH_3) 52.9 (CH_2), 118.1 (CN), 127.2 (2× CH), 127.6 (CH), 128.3 (2× CH), 128.5 (2× CH), 129.9 (2× CH), 130.6 (C_0), 137.7 (C_0), 139.3 (C_0) and 166.2 (C_0COCH_3) ppm. MS (EI): m/z = 281 (5), 280 (10), 254 (25), 135 (75), 91 (100), 77 (15) and 76 (5).

Methyl 4-[Cyano(phenethylamino)methyl]benzoate: (Table 3, Entry 18) Conducting the micro reaction at a total flow rate of 20 μL min^{-1} and employing methyl 4-formylbenzoate (**22**) and 2-phenylethylamine (**7**) as reactants, afforded the title compound as a pale yellow oil (0.0352 g, 99.9%). $C_{18}H_{18}N_2O_2$ (294.35): calcd. C 73.45, H 6.16, N 9.52; found C 73.52, H 6.48, N 9.37]. IR: $\tilde{\nu}_{max}$ = 738.7, 908.9, 1262.9, 1437.6, 1456.0, 1543.3, 1718.1, 2254.1, 2986.9 and 3540.3 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 2.89 (m, 2 H, CH_2), 3.01 (m, 2 H, CH_2), 3.89 (s, 3 H, OCH_3), 4.21 (br. s, 1 H, NH), 4.83 (s, 1 H, CH), 7.19 (m, 2 H, 2× ArH), 7.52 (m, 3 H, 3× ArH), 7.55 (d, J = 8.4 Hz, 2 H, 2× ArH) and 8.02 (d, J = 8.4 Hz, 2 H, 2× ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 35.7 (CH_2), 47.9 (CH_2), 52.1 (CH), 53.8 (OCH_3), 118.1 (CN), 123.1 (CH), 127.1 (2× CH), 128.4 (4× CH), 129.4 (C_0), 129.7 (2× CH), 138.8 (C_0), 139.3 (C_0) and 166.2 ($C_0CO_2CH_3$) ppm. MS (EI): m/z = 295 (8), 294 (4), 268 (28), 236 (5), 203 (49), 179 (100), 174 (75), 117 (33), 105 (32), 91 (53) and 76 (25).

Methyl 4-[Cyano(3-phenylpropylamino)methyl]benzoate: (Table 3, Entry 19) Conducting the micro reaction at a total flow rate of 20 μL min^{-1} and employing methyl 4-formylbenzoate (**22**) and phenylpropylamine (**14**) as reactants, afforded the title compound as a colorless oil (0.0369 g, 99.9%). $C_{19}H_{20}N_2O_2$ (294.35): calcd. C 73.80, H 6.79, N 9.06; found C 74.01, H 6.54, N 9.09]. IR: $\tilde{\nu}_{max}$ = 738.7, 908.9, 1262.9, 1437.6, 1456.0, 1543.3, 1718.1, 2254.1, 2986.9 and 3054.3 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.89 (m, 2 H, CH_2), 2.21 (br. s, 1 H, NH), 2.65–2.70 (m, 4 H, 2× CH_2), 3.90 (s, 3 H, OCH_3), 4.79 (s, 1 H, CH), 7.16–7.25 (m, 5 H, 5× ArH), 7.59 (d, J = 8.7 Hz, 2 H, 2× ArH) and 8.03 (d, J = 8.7 Hz, 2 H, 2× ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 31.0 (CH_2), 32.1 (CH_2), 46.6 (CH_2), 52.1 (CH), 54.0 (OCH_3), 118.3 (CN), 126.5 (CH), 127.1 (2× CH), 128.2 (4× CH), 128.6 (2× CH), 129.6 (C_0), 139.4 (C_0), 141.4 (C_0) and 166.2 ($C_0CO_2CH_3$) ppm. MS (EI): m/z = 309 (5), 308 (8), 277 (10), 249 (25), 223 (28), 147 (50), 134 (25), 105 (35) and 91 (100).

2-(Benzylamino)butanenitrile: (Table 4, Entry 2) Employing propionaldehyde (**24**) and benzylamine (**13**) as reactants, the micro reaction was performed at a total flow rate of 40 μL min^{-1} to afford the title compound as a colorless oil (0.0208 g, 99.6%). $C_{11}H_{14}N_2$ (175.24): calcd. C 75.82, H 8.10, N 16.08; found C 75.80, H 8.11, N 16.07]. IR: $\tilde{\nu}_{max}$ = 720.2, 741.2, 863.2, 1395.2, 1502.3, 1523.4, 2245.3, 2853.1, 2936.1 and 3346.1 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.00 (t, J = 7.3 Hz, 3 H, CH_3), 1.58 (br. s, 1 H, NH), 1.67–1.76 (m, 2 H, CH_2), 3.35 (dt, J = 7.3 Hz, 1 H and 0.8, CH), 3.74 (d, J = 12.9 Hz, 1 H, C*H*H), 3.96 (d, J = 12.9 Hz, 1 H, CH*H*) and 7.15–7.62 (m, 5 H, 5× ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 10.1 (CH_3), 26.8 (CH_2), 51.1 (CH), 51.6 (CH_2), 120.1 (CN), 127.5 (CH), 128.3 (2× CH), 128.5 (2× CH) and 138.3 (C_0) ppm. MS (EI): m/z = 175 (10), 174 (15), 148 (25), 105 (75), 91 (100) and 77 (15).

2-(3-Phenylpropylamino)butanenitrile: (Table 4, Entry 4) Employing propionaldehyde (**24**) and phenylpropylamine (**14**) as reactants, the micro reaction was conduced at a total flow rate of 40 μL min^{-1}, affording the title compound as a colourless oil (0.0242 g, 99.9%). $C_{13}H_{18}N_2$ (202.30): calcd. C 77.18, H 8.97, N 13.85; found C 77.20, H 8.99, N 13.82]. IR: $\tilde{\nu}_{max}$ = 695.3, 720.6, 1565.2, 2232.1, 2801.5, 2865.1, 2886.1, 2905.6, 2986.1 and 3456.2 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 0.98 (t, J = 7.6 Hz, 3 H, CH_3), 1.67–1.74 (m, 2 H, CH_2), 2.50–2.76 (m, 4 H, 2× CH_2), 2.57 (t, J = 7.6 Hz, 2 H, CH_2), 2.78–2.84 (m, 1 H, NH), 3.34 (t, J = 7.6 Hz, 1 H, CH), 7.08–7.10 (m, 3 H, 3× ArH) and 7.41–7.52 (m, 2 H, 2× ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 10.1 (CH_3), 26.9 (CH_2), 31.3 (CH_2), 33.4 (CH_2), 47.2 (CH_2), 51.1 (CH), 120.3 (CN), 125.8 (CH), 128.3 (2× CH), 128.4 (2× CH) and 141.6 (C_0) ppm. MS (EI): m/z = 203 (5), 202 (6), 187 (15), 173 (100), 134 (20), 120 (15), 105 (75), 91 (65) and 77 (10).

2-(3-Phenylpropylamino)pentanenitrile: (Table 4, Entry 9) Employing butyraldehyde (**26**) and phenylpropylamine (**14**) as precursors, the micro reactor was operated at a total flow rate of 40 μL min^{-1} to afford the title compound as a colorless oil (0.0258 g, 99.6%). $C_{14}H_{20}N_2$ (216.33): calcd. C 77.73, H 9.32, N 12.95; found C 77.62, H 9.38, N 12.83]. IR: $\tilde{\nu}_{max}$ = 692.6, 719.9, 740.3, 1543.2, 2234.1, 2840.6, 2885.6, 2921.3, 2956.1 and 3467.2 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 0.89 (t, J = 7.3 Hz, 3 H, CH_3), 1.41–1.48 (2 H, m CH_2), 1.64 (q, J = 7.3 Hz, 2 H, CH_2), 1.70–1.80 (m, 2 H, CH_2), 2.53–2.56 (m, 1 H, CH), 2.60 (t, J = 7.6 Hz, 2 H, CH_2), 2.82–2.86 (m, 1 H, CH), 3.42 (m, 1 H, CH), 7.12 (m, 3 H, 3× ArH), 7.19–7.24 (m, 2 H, 2× ArH) ppm and NH not observed. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 13.9 (CH_3), 19.4 (CH_2), 31.7 (CH_2), 33.8 (CH_2), 36.0 (CH_2), 47.6 (CH_2), 50.8 (CH), 120.8 (CN), 126.3 (CH), 128.8 (2× CH), 128.8 (2× CH) and 142.1 (C_0) ppm. MS (EI): m/z = 217 (5), 216 (10), 175 (15), 161 (15), 147 (20), 134 (15), 105 (100), 91 (75) and 77 (20).

2-(Phenylamino)hexanenitrile: (Table 4, Entry 11) Conducting the micro reaction at a total flow rate of 30 μL min^{-1} and employing valeraldehyde (**27**) and aniline (**12**) as reactants, 2-(phenylamino)-hexanenitrile was obtained as a pale yellow oil (0.0338 g, 99.9%). $C_{12}H_{16}N_2$ (188.27): calcd. C 76.55, H 8.57, N 14.88; found C 76.35, H 8.49, N 14.72]. IR: $\tilde{\nu}_{max}$ = 650.5, 732.7, 908.0, 1469.8, 1506.6, 1603.1, 2254.5, 2870.6, 2925.8, 2962.6 and 3431.6 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 0.89 (t, J = 7.3 Hz, 3 H, CH_3), 1.24–1.37 (m, 4 H, 2× CH_2), 1.72–1.93 (m, 2 H, CH_2), 3.52 (m, 1 H, CH), 4.31 (br. s, 1 H, NH), 6.63–6.81 (m, 3 H, 3× ArH) and 7.34–7.43 (m, 2 H, 2× ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 14.0 (CH_3), 21.9 (CH_2), 31.0 (CH_2), 33.2 (CH_2), 52.6 (CH), 112.5 (2× CH), 118.5 (CN), 119.2 (CH), 129.2 (2× CH) and 146.3 (C_0) ppm. MS (EI): m/z = 189 (5), 188 (100), 172 (17), 143 (13), 131 (18), 118 (30), 105 (20), 93 (58) and 77 (15).

2-(Benzylamino)hexanenitrile: (Table 4, Entry 12) Conducting the micro reaction at a total flow rate of 40 μL min^{-1} and employing valeraldehyde (**27**) and benzylamine (**13**) afforded 2-(benzylamino)-hexanenitrile as a colorless oil (0.0242 g, 99.9%). $C_{13}H_{18}N_2$ (202.30): calcd. C 77.18, H 8.97, N 13.85; found C 77.25, H 9.01, N 13.72]. IR: $\tilde{\nu}_{max}$ = 720.2, 741.2, 863.2, 1395.2, 1502.3, 1523.4, 2245.3, 2853.1 and 3346.1 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 0.90 (t, J = 7.0 Hz, 3 H, CH_3), 1.30–1.47 (m, 5 H, 2× CH_2 and NH), 1.74–1.78 (m, 2 H, CH_2), 3.49 (dt, J = 7.0 Hz, 1 H and 0.8, CH), 3.80 (d, J = 12.9 Hz, 1 H, C*H*H), 4.05 (d, J = 12.9 Hz, 1 H, CH*H*) and 7.22–7.74 (m, 5 H, 5× ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 13.8 (CH_3), 22.1 (CH_2), 27.7 (CH_2), 33.2 (CH_2), 49.8 (CH), 51.6 (CH_2), 120.3 (CN), 127.5 (CH),

128.5 (2× CH), 128.6 (2× CH) and 138.4 (C_0) ppm. MS (EI): *m*/*z* = 203 (5), 202 (15), 187 (30), 173 (75), 159 (30), 120 (16), 106 (5), 91 (100) and 77 (12).

2-(Phenethylamino)hexanenitrile: (Table 4, Entry 13) Employing valeraldehyde (**27**) and 2-phenylethylamine (**7**) as precursors, the micro reaction was conducted at a total flow rate of 40 μL min^{-1}, to afford 2-phenethylamino-hexanenitrile as a pale yellow oil (0.0259 g, 100.0%). $C_{14}H_{20}N_2$ (216.33): calcd. C 77.73, H 9.32, N 12.95; found C 77.69, H 9.31, N 12.97]. IR: $\tilde{\nu}_{max}$ = 704.2, 743.4, 1268.3, 1459.6, 2302.6, 2861.7, 2930.6, 2959.5 and 3649.5 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 0.85 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.23–1.43 (m, 2 H, CH_2), 1.56 (br. s, 1 H, NH), 1.65 (q, *J* = 7.3 Hz, 2 H, CH_2), 1.71–1.81 (m, 2 H, CH_2), 2.52–2.57 (dq, *J* = 7.3 Hz, 1 H and 1.4, C*H*H), 2.59 (t, *J* = 7.3 Hz, 2 H, CH_2), 2.81–2.86 (dq, 1 H, 7.3 and 1.4, CH*H*), 3.41 (dt, *J* = 7.3 Hz, 1 H and 0.8, CH), 7.12 (m, 2 H, 2× ArH) and 7.18 –7.25 (m, 3 H, 3× ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 14.2 (CH_3), 22.6 (CH_2), 28.1 (CH_2), 31.7 (CH_2), 33.7 (CH_2), 47.6 (CH_2N), 51.1 (CH), 120.9 (CN), 126.3 (CH), 128.7 (2× CH), 128.8 (2× CH) and 142.1 (C_0) ppm. MS (EI): *m*/*z* = 217 (6), 216 (10), 201 (30), 187 (80), 173 (60), 159 (20), 145 (5), 133 (20), 120 (10), 105 (100), 91 (75) and 77 (20).

2-(3-Phenylpropylamino)hexanenitrile: (Table 4, Entry 14) Operating the micro reactor at a total flow rate of 40 μL min^{-1} and employing valeraldehyde (**27**) and phenylpropylamine (**14**) as reactants afforded the title compound as a pale yellow oil (0.0276 g, 99.9%. $C_{15}H_{22}N_2$ (230.35): calcd. C 78.21, H 9.63, N 12.16; found C 78.27, H 9.83, N 12.25]. IR: $\tilde{\nu}_{max}$ = 695.1, 745.2, 1565.3, 2255.6, 2880.6, 2885.6, 2915.3, 2976.1 and 3469.2 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 0.85 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.25–1.36 (sext, *J* = 7.3 Hz, 2 H, CH_2), 1.37–1.41 (m, 2 H, CH_2), 1.65 (q, *J* = 7.3 Hz, 2 H, CH_2), 1.71–1.79 (m, 2 H, 7.3, CH_2), 2.55–2.57 (dq, *J* = 7.3 Hz, 1 H and 1.4, CH), 2.59 (t, *J* = 7.3 Hz, 2 H, CH_2), 2.81–2.86 (dq, *J* = 7.3 Hz, 1 H and 1.4, CH), 3.41 (dt, *J* = 7.3 Hz, 2 H and 1.4, CH_2) and 7.10–7.12 (m, 5 H, 5× ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 14.2 (CH_3), 22.6 (CH_2), 28.1 (CH_2), 31.7 (CH_2), 33.7 (CH_2), 33.8 (CH_2), 47.6 (CH_2), 51.1 (CH), 120.9 (CN), 126.3 (CH), 128.8 (4× CH) and 142.1 (C_0) ppm. MS (EI): *m*/*z* = 231 (6), 230 (10), 215 (20), 201 (15), 187 (65), 173 (100), 135 (25), 105 (75), 91 (45) and 77 (20).

2-(Pyrrolidin-1-yl)hexanenitrile: (Table 4, Entry 15) Conducting the micro reaction at a total flow rate of 40 μL min^{-1} and employing valeraldehyde (**27**) and pyrrolidine (**15**) as reactants, afforded a colorless oil 40 μL min^{-1} afforded 2-(benzylamino)hexanenitrile as a colorless oil (0.0199 g, 100.0%). $C_{10}H_{18}N_2$ (166.27): calcd. C 72.24, H 10.91, N 16.85; found C 72.14, H 10.87, N 16.81]. IR: $\tilde{\nu}_{max}$ = 1375.6, 2245.3, 2795.6, 2880.6, 2885.3 and 2960.7 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 0.82 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.19–1.40 (m, 4 H, 2× CH_2), 1.61–1.66 (m, 2 H, CH_2), 1.68–1.72 (m, 4 H, 2× CH_2), 2.51–2.59 (m, 4 H, 2× CH_2N) and 3.61 (t, *J* = 7.3 Hz, 1 H, CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 14.2 (CH_3), 22.5 (CH_2), 23.8 (2× CH_2), 28.1 (CH_2), 32.8 (CH_2), 50.4 (2× CH_2), 55.8 (CH) and 118.1 (CN) ppm. MS (EI): *m*/*z* = 167 (5), 166 (10), 151 (5), 123 (20), 109 (25), 96 (25) and 70 (100).

2-(Phenethylamino)heptanenitrile: (Table 4, Entry 18) Employing hexanal (**28**) and 2-phenylethylamine (**7**) as reactants, the micro reaction was performed at a total flow rate of 40 μL min^{-1}, to afford the title compound as a pale yellow oil (0.0276 g, 99.9%). $C_{15}H_{22}N_2$ (230.35): calcd. C 78.21, H 9.63, N 12.16; found C 78.23, H 9.65, N 12.14]. IR: $\tilde{\nu}_{max}$ = 695.2, 765.3, 1376.6, 1495.6, 2245.3, 2869.3, 2889.6, 2920.3 and 3467.1 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 0.80 (t, *J* = 7.0 Hz, 3 H, CH_3), 1.19–1.24 (m, 5 H, 2× CH_2 and CH), 1.32–1.43 (m, 1 H, CH), 1.55 (br. s, 1 H, NH), 1.63 (q, *J* = 7.0 Hz, 2 H, CH_2), 2.69–2.83 (m, 3 H, CH_2 and NCH), 3.04–3.10 (m, 1 H, NCH), 3.43 (t, *J* = 7.0 Hz, 1 H, CH), 7.09–7.18 (m, 3 H, 3× ArH) and 7.20–7.24 (m, 2 H, 2× ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 14.0 (CH_3), 22.5 (CH_2), 25.4 (CH_2), 31.3 (CH_2), 33.5 (CH_2), 36.1 (CH_2), 48.8 (CH_2), 50.8 (CH), 120.4 (CN), 126.6 (CH), 128.7 (2× CH), 128.8 (2× CH) and 139.2 (C_0) ppm. MS (EI): *m*/*z* = 231 (6), 230 (10), 215 (7), 201 (10), 187 (15), 173 (100), 159 (30), 145 (45), 105 (100) and 77 (45).

2-(3-Phenylpropylamino)heptanenitrile: (Table 4, Entry 19) Employing hexanal (**28**) and phenylpropylamine (**14**) as reactants, the micro reaction was performed at a total flow rate of 40 μL min^{-1}, to afford 2-(3-phenylpropylamino)heptanenitrile as a pale yellow oil (0.0293 g, 99.9%). $C_{16}H_{24}N_2$ (244.38): calcd. C 78.64, H 9.90, N 11.46; found C 78.61, H 9.92, N 11.43]. IR: $\tilde{\nu}_{max}$ = 695.1, 723.1, 1382.6, 1542.1, 2245.6, 2854.6, 2891.6, 910.7, 2986.1 and 3461.3 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 0.77 (t, *J* = 7.4 Hz, 3 H, CH_3), 1.16–1.24 (m, 5 H, 2× CH_2 and C*H*H), 1.35–1.39 (m, 1 H, CH*H*), 1.63 (q, *J* = 7.4 Hz, 2 H, CH_2), 1.65–1.76 (m, 2 H, CH_2), 2.49–2.53 (m, 1 H, C*H*H), 2.56 (t, *J* = 7.9 Hz, 2 H, CH_2), 2.77–2.84 (m, 1 H, CH*H*), 3.37 (dt, *J* = 7.4 Hz, 1 H and 1.4, CH), 7.04–7.22 (m, 5 H, 5× ArH) ppm and NH not observed. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 13.9 (CH_3), 22.4 (CH_2), 25.3 (CH_2), 31.2 (CH_2), 31.3 (CH_2), 33.4 (CH_2), 33.5 (CH_2), 47.2 (CH), 50.7 (CH_2N), 120.4 (CN), 125.9 (CH), 128.3 (2× CH), 128.4 (2× CH) and 141.6 (C_0) ppm. MS (EI): *m*/*z* = 245 (5), 244 (15), 215 (20), 187 (15), 173 (100), 159 (75), 135 (50), 105 (20), 91 (45) and 76 (10).

2-(Benzylamino)octanenitrile: (Table 4, Entry 22) Conducting the micro reaction at a total flow rate of 40 μL min^{-1} and employing heptanal (**29**) and benzylamine (**13**) as reactants, the title compound was obtained as a pale yellow oil (0.0278 g, 99.9%). $C_{15}H_{22}N_2$ (230.35): calcd. C 77.53, H 10.41, N 12.06; found C 77.55, H 10.45, N 12.01]. IR: $\tilde{\nu}_{max}$ = 680.6, 725.2, 1454.3, 1488.6, 1552.1, 1590.6, 2304.7, 2843.2, 3030.6, 3054.2 and 3324.0 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 0.79 (t, *J* = 7.0 Hz, 3 H, CH_3), 1.23 (m, 8 H, 4× CH_2), 1.51 (br. s, 1 H, NH), 1.69 (q, *J* = 7.0 Hz, 2 H, CH_2), 3.41 (d, *J* = 12.9 Hz, 1 H, C*H*H), 3.62 (m, 1 H, CH), 3.99 (d, *J* = 12.9 Hz, 1 H, CH*H*) and 7.26–7.28 (m, 5 H, 5× ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 14.0 (CH_3), 22.4 (CH_2), 25.5 (CH_2), 28.6 (CH_2), 31.5 (CH_2), 33.5 (CH_2), 49.7 (CH), 51.6 (CH_2), 120.3 (CN), 127.5 (CH), 128.3 (2× CH), 128.5 (2× CH) and 138.4 (C_0) ppm. MS (EI): *m*/*z* = 231 (3), 230 (17), 201 (15), 187 (20), 173 (75), 145 (10), 106 (25), 91 (100) and 76 (15).

2-(Phenylethylamino)octanenitrile: (Table 4, Entry 23) Employing heptanal (**29**) and 2-phenylethylamine (**7**) as reactants, the micro reaction was conducted at a total flow rate of 40 μL min^{-1}, to afford the title compound as a pale yellow oil (0.0293 g, 99.9%). $C_{16}H_{24}N_2$ (244.38): calcd. C 78.64, H 9.90, N 11.46; found C 78.65, H 9.72, N 11.35]. IR: $\tilde{\nu}_{max}$ = 620.5, 760.1, 1375.2, 1435.1, 1561.2, 2246.7, 2801.6, 2880.2, 2906.1, 3101.6 and 3401.2 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 0.83 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.22 (m, 8 H, 4× CH_2), 1.66 (m, 2 H, CH_2), 2.69–2.86 (m, 4 H, 2× CH_2), 3.09 (dt, *J* = 7.2 Hz, 1 H and 1.2, CH), 7.16–7.70 (m, 3 H, 3× ArH), 7.70–7.23 (m, 2 H, 2× CH) ppm and NH not observed. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 14.0 (CH_3), 22.4 (CH_2), 25.5 (CH_2), 28.6 (CH_2), 31.4 (CH_2), 33.4 (CH_2), 35.9 (CH_2), 48.6 (CH), 50.7 (CH_2N), 120.2 (CN), 126.4 (CH), 128.5 (2× CH), 128.6 (2× CH) and 139.0 (C_0) ppm. MS (EI): *m*/*z* = 245 (8), 244 (4), 218 (9), 153 (51), 139 (2), 126 (13), 105 (22), 91 (19), 77 (9), 69 (100) and 56 (28).

2-(3-Phenylpropylamino)octanenitrile: (Table 4, Entry 24) Employing heptanal (**29**) and phenylpropylamine (**14**) as reactants, the

micro reactor was operated at a total flow rate of 40 μL min^{-1}, affording the title compound as a pale yellow oil (0.0310 g, 99.9%). $C_{17}H_{26}N_2$ (258.41): calcd. C 79.02, H 10.14, N 10.84; found C 78.78, H 10.38, N 10.59]. IR: $\tilde{\nu}_{max}$ = 720.1, 750.3, 1365.2, 1440.6, 2251.6, 2890.3, 2922.6, 2980.5 and 3100.2 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 0.83 (t, J = 7.0 Hz, 3 H, CH_3), 1.20–1.36 (m, 6 H, 3× CH_2), 1.40–1.45 (m, 1 H, CH), 1.67 (q, J = 7.0 Hz, 2 H, CH_2), 1.72–1.83 (m, 2 H, CH_2), 2.55 (m, 1 H, CH), 2.63 (m, 2 H, CH_2), 2.55 (m, 2 H, CH_2), 3.42 (m, 1 H, CH), 7.27 (m, 2 H, 2× ArH), 7.13 (m, 3 H, 3× ArH) ppm and NH not observed. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 14.4 (CH_3), 22.9 (CH_2) 26.0 (CH_2), 29.1 (CH_2), 31.7 (CH_2), 31.9 (CH_2), 33.8 (CH_2), 34.0 (CH_2), 47.7 (CH_2), 51.1 (CH), 120.9 (CN), 126.3 (CH), 128.8 (4× CH) and 142.1 (C_0) ppm. MS (EI): m/z = 259 (6), 258 (20), 243 (5), 229 (6), 215 (10), 201 (5), 187 (16), 173 (100), 159 (16), 147 (5), 105 (45), 91 (65) and 77 (21).

2-(Pyrrolidin-1-yl)octanenitrile: (Table 4, Entry 25) Conducting the micro reaction at a total flow rate of 40 μL min^{-1} and employing heptanal (**29**) and pyrrolidine (**15**) as precursors, afforded 2-(pyrrolidin-1-yl)octanenitrile as a pale yellow oil (0.0233 g, 100.0%). $C_{12}H_{22}N_2$ (194.32): calcd. C 74.17, H 11.41, N 14.42; found C 74.21, H 11.40, N 14.20]. IR: $\tilde{\nu}_{max}$ = 1385.6, 2259.1, 2803.2, 2889.6 and 2915.4 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 0.75 (t, 3 H, CH_3), 1.15–1.23 (m, 6 H, 3× CH_2), 1.25–1.46 (m, 2 H, CH_2), 1.52–1.75 (m, 6 H, 3× CH_2), 2.45–2.50 (m, 2 H, CH_2N), 2.55–2.60 (m, 2 H, CH_2) and 3.56 (dt, J = 7.8 Hz, 1 H and 1.4, CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 13.9 (CH_3), 22.4 (CH_2), 23.2 (2× CH_2), 25.9 (CH_2), 28.5 (CH_2), 31.4 (CH_2), 32.6 (CH_2), 49.9 (2× CH_2N), 55.3 (CH) and 117.6 (CN) ppm. MS (EI): m/z = 195 (2), 194 (6), 193 (10), 168 (10), 152 (2), 109 (100), 96 (20), 84 (30), 67 (10) and 55 (25).

2-(4-Acetylphenyl)-2-(phenethylamino)acetonitrile (5): Employing 4-acetylbenzaldehyde (**4**) and 2-phenylethylamine (**7**) as precursors, the micro reaction was performed at a total flow rate of 20 μL min^{-1} to afford **5** as a pale yellow oil (0.0333 g, 99.8%). $C_{18}H_{18}N_2O$ (278.35): calcd. C 77.67, H 6.52, N 10.06; found C 77.62, H 6.53, N 10.10]. IR: $\tilde{\nu}_{max}$ = 610.5, 721.2, 842.6, 1001.3, 1246.1, 1561.3, 1600.2, 1690.3, 2245.3, 2880.5, 2890.6, 2961.2, 3031.2 and 3461.2 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 2.63 (s, 3 H, CH_3), 2.84–2.93 (m, 2 H, CH_2), 3.04–3.12 (m, 2 H, CH_2N), 4.89 (s, 1 H, CH), 7.22–7.35 (m, 5 H, 5× ArH), 7.63 (d, J = 8.7 Hz, 2 H, 2× ArH), 8.00 (d, J = 8.7 Hz, 2 H, 2× ArH) ppm and NH not observed. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 26.7 (CH_3), 35.8 (CH_2), 48.0 (CH_2), 54.0 (CH), 118.1 (CN), 126.5 (CH), 127.5 (2× CH), 128.6 (2× CH), 128.7 (2× CH), 128.9 (2× CH), 137.5 (C_0), 138.8 (C_0), 139.4 (C_0) and 197.3 (CO) ppm. MS (EI): m/z = 279 (5), 278 (20), 264 (5), 252 (10), 235 (25), 159 (45), 145 (20), 131 (15), 120 (10), 105 (100), 91 (45) and 76 (5).

Supporting Information (see also the footnote on the first page of this article): Additional experimental details such as the spectroscopic data obtained for known compounds (NMR and MS).

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[27] The hydrolytic instability of TMSCN **2** makes it an ideal candidate for use within a sealed reaction unit such as a micro reactor.
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[29] A starting concentration of 0.4 M was selected as this afforded an imine concentration of 0.2 M which was found to be soluble within MeCN, any attempts to increase this concentration were met with precipitation, and with time blockages, within the central reaction channel. Consequently, for completeness, all investigations were conducted at a total concentration of 0.1 M, however, for specific aldimines, it may be possible to increase this concentration further.

[30] No residual amine or aldehyde was detected, and as such the percent conversion was calculated based on residual imine, with the cyanation being the rate-limiting step.
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[33] Unless otherwise stated, where the total flow rate equals 20 to 30 μL min^{-1}, a run time of 1 h was employed and in cases where an optimal flow rate of 40 μL min^{-1} was employed, reaction products were collected over 0.5 h.

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