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# Solid-Supported Gallium Triflate: An Efficient Catalyst for the Three-Component Ketonic Strecker Reaction

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In light of the growing interest in the use of rare earth metal triflates as water-tolerant Lewis acid catalysts, we embarked upon the development of a solid-supported gallium triflate (PS-Ga(OTf)$_2$) derivative as a means of increasing the cleanliness and cost effectiveness of using these increasingly expensive catalytic materials in synthetic processes. Having previously highlighted the advantages associated with coupling solid-supported catalysis and the emerging area of micro-reaction technology, we screened PS-Ga(OTf)$_2$ for activity towards the ketonic Strecker reaction, in which the target $\alpha$-aminonitriles were obtained in higher yield and purity compared to reactions reported in literature, in which the analogous homogeneous catalyst was used.

## Introduction

Micro reaction technology (MRT) offers the synthetic chemist a new method of executing chemical reactions, which in addition to obtaining enhanced reaction control, affords the user a means of transferring methodology developed within the laboratory to production without the need for lengthy re-optimization.[1] This approach enables the conditions identified within the R&D laboratory to be harnessed within a production environment. This not only reduces the time taken to scale up a process, but also removes the risks conventionally associated with increasing production volume.

Based on the findings of initial research programs, which served to illustrate the practical advantages associated with MRT, the field of continuous-flow synthesis has grown, with many research groups now involved in the exploration of this methodology. Recent examples include the synthesis of biologically relevant molecules, such as efaproxiral,[2] pristane,[3] and ibuprofen,[4] with DSM demonstrating the use of glass reactors for the large-scale production of pharmaceutically relevant materials, such as naproxcinod.[5]

Several interesting molecules have been prepared by using this technology; however, to continue to increase product complexity generated in this way, it is imperative that multiple reaction steps are combined in single continuous processes, rather than the recent trend, where the vast majority of reactions are conducted via a series of single steps, with the reaction products from each step purified off-line.[6] To enable realization of this, researchers have developed methodologies that allow processes, such as in-line separations[7] and micro-distillations,[8] to be performed in series. The use of solid-supported reagents, catalysts, and scavengers is another approach that affords a facile method of increasing the number of transformations possible within microreactors and enables the synthesis of analytically pure materials without the need to perform formal purifications between reaction steps.[9]

### Solid-supported catalysis under flow

Compared to solution-phase catalysis, the immobilization of catalysts onto inert supports can be advantageous, affording ease of product isolation and recycling, which leads to increased efficiency, cost effectiveness, and reduced waste generation. Immobilization of catalysts can, however, lead to extended reaction times compared to their homogeneous counterparts, a feature that is frequently overcome by the use of increased reactant stoichiometries, which drives the reactions to completion. Stirring or shaking the catalytic material can also lead to mechanical degradation of the support, which makes recovery and re-use inefficient especially on small scales.

Based on our experience of continuous-flow reactors[1,10] we proposed that the disadvantages could be overcome by coupling heterogeneous catalysis with micro-reaction technology (Figure 1), whereby the catalytic material is retained within a small packed bed (Labtrix device 3026). Using this approach, the issue of mechanical degradation is removed, which leads to increased catalyst lifetimes and reaction efficiency compared to batch reactions, thus affording a more sustainable process. In addition, recycling is easier as filtration of the reaction product is no longer required and, therefore, no loss of material arises between reactions; reduced leaching of the catalyst is also observed, which can be problematic in batch reactions.[11] Furthermore, reaction times are reduced owing to the high surface-to-volume ratio obtained within such systems; a high catalyst-to-substrate ratio is obtained whilst only milligram

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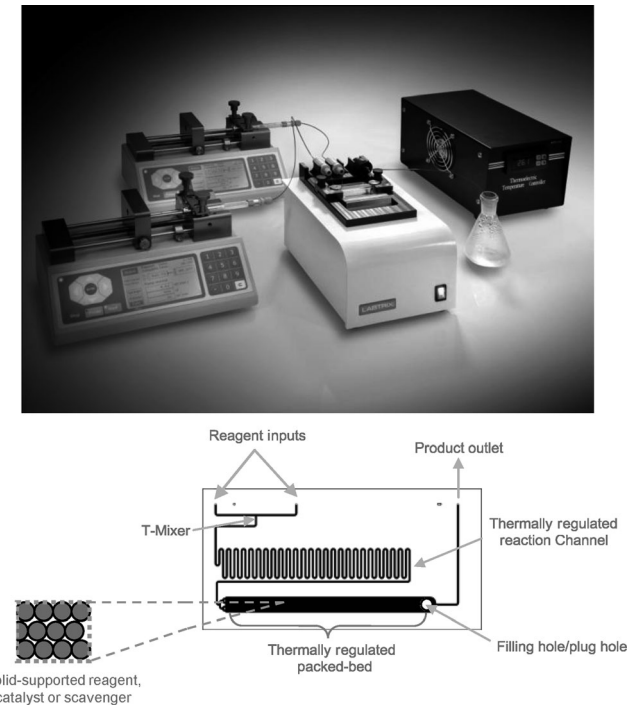



**Figure 1.** The Labtrix Start equipment (top) and the glass microreactor used for the evaluation of PS-Ga(OTf)$_2$ under continuous flow (bottom).

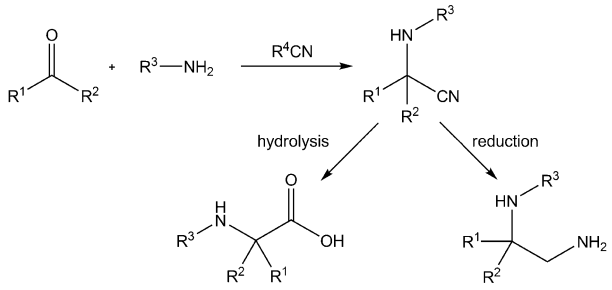
quantities of catalytic material are used. The inherently high level of reaction control obtained also enables the user to obtain previously inaccessible reaction selectivities, as demonstrated in the oxidation of alcohols[12] and the thioacetalisation of 4-acetylbenzaldehyde.[13]

Incorporating such materials into multi-step flow processes has to-date been limited. This often consists of solution-phase reactions that are performed in separate modules to polymer-assisted reaction steps, and although techniques exist to perform reactions in series, the use of multiple interconnections result in regions of large dead volume.[14]

### Strecker reaction

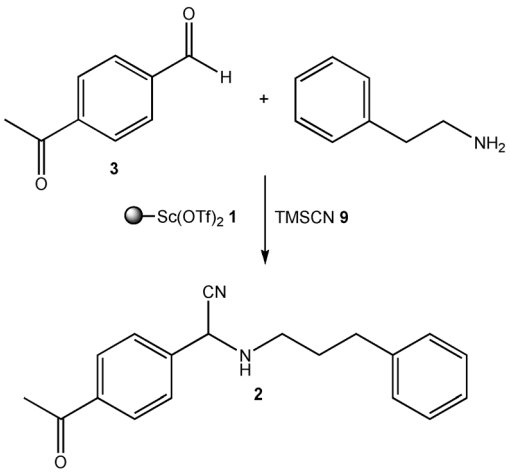
Building on our experience within the field of MRT, we recently developed and evaluated an integrated borosilicate-glass micro-reactor in which liquid–liquid and liquid–solid reaction steps were performed in series in a single integrated reactor, which reduced the dead volume between reaction steps dramatically and increased reaction complexity.

Using this approach, more than 50 analytically pure α-aminonitriles were synthesized, using the aldehydic Strecker reaction (Scheme 1), with isolated yields in excess of 99.6% obtained by using polymer-supported scandium triflate [PS-Sc(OTf)$_2$] (**1**) as the catalyst. In addition, the unique reaction environment obtained within such micro-channel networks enabled us to rapidly evaluate the reaction mechanism by controlling the order of reactant addition, preventing the formation of byproducts commonly associated with the Strecker reaction (typically cyanohydrins and tetramethylsilane cyanohydrins).[15]




**Scheme 1.** Generalization of the multi-component Strecker reaction and the synthetic versatility of the resulting α-aminonitrile.

We found the technique to be chemoselective, which enabled the synthesis of aldehydic Strecker products in the presence of ketonic functionalities. The investigation culminated in the chemoselective synthesis of 2-(4-acetylphenyl)-2-(phenethylamino)acetonitrile (**2**) obtained in 99.8% yield and quantitative purity (Scheme 2). During this investigation, we were




**Scheme 2.** The sole reaction product obtained from the Strecker reaction of 4-acetylbenzaldehyde (**3**).

surprised by the lack of reaction observed for ketonic substrates, with the starting materials recovered quantitatively even at elevated reaction temperatures (50 °C) and prolonged reaction times (2 h).

After this work was performed, the microreactor was commercialized, which enabled the evaluation of solid-supported reagents and catalysts at high temperature (−15–195 °C) and pressure (2 MPa, Figure 1). With this equipment in hand, we tried to identify a solid-supported Lewis acid catalyst capable of performing the ketonic Strecker reaction under continuous flow.

### Ketonic Strecker reaction

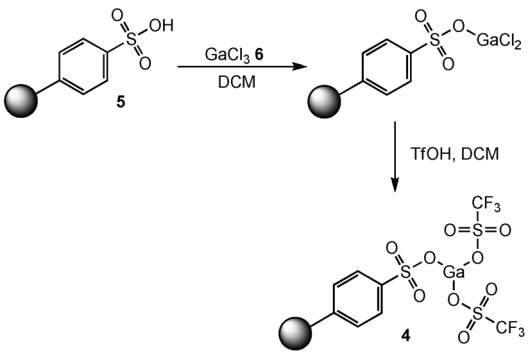
The Strecker reaction is often referred to as one of the most important multi-component reactions[16,17] owing to the ease with which the reaction products can be converted into synthetically useful diamines, α-amino acids (Scheme 1),[18] den-



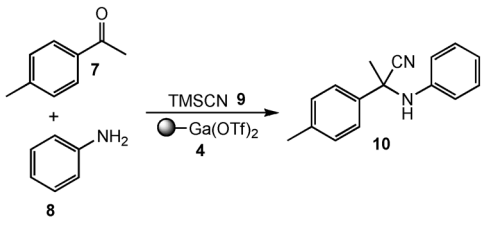
drimers,[19] and substituted hydantoins.[20] Utilizing conventional batch reaction methodology, the ketonic Strecker reaction has been performed by using catalysts such as bis(dialkylamino)cyanoborane,[21] palladium(II) complexes,[22] $Fe(Cp)_2PF_6$,[23] rare earth metal triflates ($RE(OTf)_3$),[24] and zinc halides.[25] However, as reaction times are long (24–72 h), large quantities of the cyanide source are used to drive the reaction, thus making work-up and isolation of the α-aminonitrile tedious, with some examples even found to require high pressures to complete the transformation.[26] In all cases, efficient recovery and re-use of the catalytic material is difficult and, therefore, this catalysts are not suitable to be used on a large scale and, unlike its aldehydic counterpart, no examples of the aromatic ketonic Strecker reaction have been reported to be promoted by a solid-supported catalyst.

As a means of improving catalyst recovery and reducing the reaction time required, we investigated the preparation of a solid-supported Lewis acid catalyst capable of performing the ketonic Strecker reaction. Based on our previous success with (**1**)[15b,c] and the homogeneous investigation of Olah and coworkers,[24] we evaluated the preparation of polymer-supported gallium(III) bis(trifluoromethanesulfonate) [PS-Ga(OTf)$_2$, **4**, Scheme 3], affording a loading of 1.10 $mmol_{Ga}\,g^{-1}$ [determined




**Scheme 3.** Reaction protocol used to prepare polymer-supported gallium(III) bis(trifluoromethanesulfonate) (**4**) through the reaction of Amberlyst-15 (**5**) with gallium(III)chloride (**6**).

by using acid digestion and inductively coupled plasma mass spectrometry (ICP–MS) analysis of the filtrate]. The activity of the materials towards the ketonic Strecker reaction was subsequently evaluated under continuous flow, utilizing the microreactor depicted in Figure 1 and the model reaction illustrated in Scheme 4.




**Scheme 4.** Model reaction used to evaluate the activity of polymer-supported gallium(III) bis(trifluoromethanesulfonate) (**4**) towards the ketonic Strecker reaction.

## Results and Discussion

To investigate the activity of **4** towards the ketonic Strecker reaction, a D263T glass microreactor (Chemtrix BV, The Netherlands) was fabricated (Footprint = 22.5 mm × 45.0 mm × 2.0 mm), which consisted of a T-intersection, where two solutions could be mixed [300 μm (wide) × 60 μm (deep); volume = 5 μL] prior to entering the packed bed [2.5 mm (wide) × 3.3 cm (long) × 600 μm (deep)].

Dichloromethane (DCM) was selected as the reaction solvent, due to increased substrate solubility, ease of solvent removal upon completion of the reaction, and a literature precedent with respect to rare-earth-metal-triflate catalysis.

By using the reaction manifold previously described, **4** (0.01 g, $1.1 \times 10^{-2}$ mmol Ga) was packed into the reactor and a pre-mixed solution of 4-methylacetophenone (**7,** 0.4 M) and aniline (**8**, 0.4 M) in DCM was introduced into the reactor from inlet A, and a solution of trimethylsilylcyanide (TMSCN, **9**, 0.4 M in DCM) was introduced into the reactor from inlet B. The reactants were mixed, but did not react, prior to entering the packed bed, upon which the ketoimine intermediate formed and subsequently underwent nucleophilic addition of the cyanide anion to afford the respective α-aminonitrile, 2-(phenylamino)-2-*p*-tolylpropanenitrile (**10**). The reaction products were collected over a period of 1 h prior to evaporation of the reaction solvent and dissolved in $CDCl_3$. The reaction products were subsequently analyzed by using $^1H$ and $^{13}C$ NMR spectroscopy, with the product conversion determined by comparison of the integrals obtained for the methyl signals in the starting material **7** ($\delta = 2.31$ ppm) and product **10** ($\delta =$ 1.95 ppm) respectively.

The effect of reactant flow rate was initially evaluated, with a total flow rate of 20 μL $min^{-1}$, affording 25.6% conversion to the target α-aminonitrile, with the residual being unreacted starting materials **7** and **8** (Table 1). Reducing the flow rate,

**Table 1.** Results obtained for the optimization of 2-(phenylamino)-2-*p*-tolylpropane-nitrile (**10**) under continuous flow.

| Flow rate [μL $min^{-1}$] | *T* [°C] | Conversion [%] | Throughput [mg $h^{-1}$][a] | Flow rate [μL $min^{-1}$] |
|---|---|---|---|---|
| 20[b] | RT | 25.6 | 13.6 | 20[b] |
| 10 | RT | 40.8 | 10.8 | 10 |
| 5 | RT | 52.3 | 7.0 | 5 |
| 1 | RT | 89.1 | 2.4 | 1 |
| 20[b] | 30 | 76.2 | 43.1 | 20[b] |
| 20[b] | 40 | 100.0 | 56.6 | 20[b] |
| 20[b] | 50 | 100.0 | 56.6 | 20[b] |

[a] After product purification. [b] Residence time = 1 min.

and hence increasing the reactant residence time, was found to increase the conversion of **7** to **10** (89.1%); however, this resulted in a reduction in reactor productivity, affording only 2.4 mg $h^{-1}$ after purification.

To increase conversion and productivity, the effect of reactor temperature was investigated by placing the microreactor onto the Labtrix Start thermal control unit (Figure 1). To keep



the reactants and solvent in the liquid phase, a backpressure regulator (2 MPa) was fitted to the reactor holder outlet, which enabled controlled liquid handling within the microreactor above the boiling point of the solvent (38 °C). By using this approach, a reactor temperature of 30 °C and a flow rate of 20 μL $min^{-1}$ resulted in an increase of conversion to 76.2%, which corresponds to a throughput of 43.1 mg $h^{-1}$. Increasing the reactor temperature (40–50 °C) afforded quantitative conversion of **7** to **10** and a 23.6 fold increase in productivity (56.6 mg $h^{-1}$) compared with reactions performed at room temperature. In addition, complete conversion of starting materials **7** and **8** was observed, implying that upon evaporation of the reaction solvent, **10** was obtained in analytical purity with no need for subsequent purification.

Having confirmed the ability to efficiently transform an aromatic ketone into the respective α-aminonitrile **10** by using the Lewis acid catalyst **4**, the reaction products were assessed by using ICP–MS to quantify the proportion of Ga within **10**. As with previous flow reactions, no Ga was detected above the instruments detection limit [the limit of detection (LOD) was determined to be 8.8 ppb for Ga], which confirmed the long-term mechanical stability of catalyst **4** compared to the batch reaction, for which 400 ppm of Ga was detected. With regard to catalyst activity, the same aliquot of material **4** remained active over a one-month period of use without showing any signs of degradation.

To confirm that the transformation could be attributed to **4**, the flow reaction was performed in the presence of Amberlyst-15, (**5**), the material used as the solid support, and subsequently 2% cross-linked polystyrene beads; in all cases, no reaction was observed, and recovery of the starting materials **7** and **8** monitored by using $^1$H NMR spectroscopy. In addition, the stability of the pre-mixed ketone **7** and amine **8** stock solution was validated by using $^1$H NMR spectroscopy after 1 and 24 h, whereby no ketoimine formation was observed.

Having demonstrated the ability to synthesize **10** within a packed-bed reactor, affording increased product purity compared to batch, we evaluated the reactivity of a series of ketones with **8**. As is illustrated in Table 2, high yields were obtained under the optimized reaction conditions for a range of electron-withdrawing and donating aromatic ketones along with aliphatic precursors. Interestingly, compared to the homogeneous-batch investigation performed by Olah and co-workers,[24] we were able to obtain the target α-aminonitriles in higher yield and increased purity by using this combined approach, whilst reducing the proportion of **9** used from 3 to 1 equivalents.

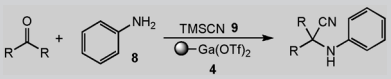
### Aldehydic Strecker reaction

In an extension to our initial investigation, we subsequently evaluated the activity of **4** towards the aldehydic Strecker reaction. DCM was used as the reaction solvent and in contrast to previous investigations utilizing **1**, the effect of reactor temperature was investigated (25–40 °C). By using the same aliquot of **4** (0.01 g, $1.1\times10^{-2}$ mmol Ga), a solution of 4-bromobenzaldehyde (**11** 0.2 M) and **8** (0.2 M) was introduced into the reactor from inlet A, and a solution of **9** (0.2 M) was then introduced into the reactor from inlet B, where it was mixed with the aldimine prior to reaction in the presence of catalyst **4**. Again, the reaction progress was determined by removal of the reaction solvent and dissolution of the reaction products in $CDCl_3$ prior to using $^1$H and $^{13}$C NMR spectroscopy.

By using this approach, quantitative conversion to 2-(4-bromophenyl)-2-(phenylamino)acetonitrile was obtained at a total flow rate of 20 μL $min^{-1}$ (34.4 mg $h^{-1}$) when the reaction was performed at room temperature. Increasing the reactor temperature to 40 °C enabled the reaction time to be reduced to 30 s, affording an increase in throughput to 68.9 mg $h^{-1}$. By using sequential reactant addition, cyanohydrin formation was again suppressed, and 2-(4-bromophenyl)-2-(phenylamino)acetonitrile was obtained in analytical purity (99.9% yield). Based on this observation, a library of five compounds was prepared to illustrate the increased throughput obtained by using **4**.

As illustrated in Table 3, increased yields were obtained in all cases as a result of using a solid-supported Lewis acid within a microreactor compared to batch reactions, with throughputs doubled for **4** compared to **1**.

**Table 2.** Results obtained for the evaluation of PS-Ga(OTf)$_2$ (**4**) as a Lewis acid catalyst for the ketonic Strecker reaction performed under flow conditions.




| Ketone | Yield [%] | Throughput [mg $h^{-1}$][a] |
|---|---|---|
| 4-methylacetophenone (**7**) | 99.6 (78)[b] | 56.6 |
| acetophenone (**12**) | 99.8 (98)[b] | 53.3 |
| 4-bromoacetophenone (**13**) | 99.5 (95)[b] | 72.3 |
| 4-nitroacetophenone (**14**) | 99.7 | 67.4 |
| cyclohexanone (**15**) | 99.8 (85)[b] | 48.0 |

[a] Flow Rate = 20 μL $min^{-1}$ and temperature = 40 °C. [b] The number in parentheses represents the isolated yield obtained by Olah et al.[24] in 4–6 h.

**Table 3.** Results obtained for the evaluation of PS-Ga(OTf)$_2$ (**4**) as a Lewis-acid catalyst for the aldehydic Strecker reaction performed under continuous flow conditions.


| Aldehyde[a] | Yield [%] | Throughput [mg $h^{-1}$][a] |
|---|---|---|
| benzaldehyde (**16**) | 99.7 (90)[b] | 49.9 (24.9)[c] |
| 4-bromobenzaldehyde (**11**) | 99.9 | 68.9 (34.4)[c] |
| 4-chlorobenzaldehyde (**17**) | 99.8 (90)[b] | 58.3 (28.9)[c] |
| 4-fluorobenzaldehyde (**18**) | 99.8 (88)[b] | 54.3 |
| methyl-4-formylbenzoate (**19**) | 99.9 | 63.9 (31.8)[c] |

[a] Flow Rate = 20 μL $min^{-1}$ and temperature = 40 °C. [b] The number in parentheses represents the isolated yield obtained by Olah et al.[24] in 4–6 h. [c] Throughput obtained by using PS-Sc(OTf)$_2$ (**1**).



## Conclusions

Through the preparation of a novel, non-hydrolysable solid-supported analogue of $Ga(OTf)_3$, we were able to develop a versatile and efficient continuous-flow technique for the synthesis of α-aminonitriles by utilizing stoichiometric quantities of the cyanide source. Incorporation of catalyst **4** into a flow reactor enabled a dramatic reduction in reaction time from 8 h to 1 min for ketones and 30 sec for aldehydes, with yields in excess of 99% for all substrates evaluated (0.24 $mmol\,g^{-1}\,h^{-1}$). As the catalytic material **4** is confined within a micro channel, no loss of catalyst occurs between reactions, and ICP–MS analysis of the reaction products confirmed no detectable leaching of Ga from catalyst **4** over the course of the investigation. This represents a significant advantage over conventional homogeneous systems (400 ppm in a standard batch reaction).

We have, therefore, developed a continuous-flow method suitable for the preparation of α-aminonitriles, derived from both aromatic and aliphatic aldehydes and ketones, by utilizing mild reaction conditions.

In addition to improvements in catalyst recyclability and stability, the use of a micro-flow reactor is advantageous, as it enables the detailed screening of small quantities of catalytic material when compared to conventional macro packed-bed reactors. It is, however, acknowledged that should novel reactions be identified by using a microreactor, efficient and predictable scale-up techniques are required to realize the synthesis of larger quantities of products. Future work will focus on the development of meso-reactors suitable for the performance of heterogeneously-catalyzed reactions, initially at the gram to kilogram scale and subsequently aimed at industrial production volumes.

## Experimental Section

### Materials

All solvents were purchased as puriss grade (>99.5%) over molecular sieves ($H_2O$ < 0.005%) from Fluka (Gillingham, UK) and, unless otherwise stated, chemicals were purchased from Sigma–Aldrich (Gillingham, UK) and used as-received. Prior to use, Amberlyst-15 (**5**) was ground and sieved to afford a particle size distribution of 45–75 μm (Endcotts, UK).

### Instrumentation

$^1H$ and $^{13}C$ NMR spectra were obtained at room temperature as solutions in deuteriochloroform ($CDCl_3$), using tetramethylsilane (TMS) as an internal standard, or deuterated acetonitrile ($CD_3CN$). The spectra were recorded by using a Jeol GX400 spectrometer, and all spectral data of previously reported compounds were consistent with the literature. Inductively coupled plasma mass spectrometry (ICP–MS) measurements were performed by using a Perkin–Elmer Optima 5300DV instrument.

Micro reactions were performed by using the Labtrix Start microreactor development apparatus (Chemtrix BV, The Netherlands) illustrated in Figure 1. Fluidic connections to the microreactor (3026, Figure 1, bottom) were made by using polyether ether ketone (PEEK) tubing (1/32" o.d.×90 μm i.d.×10 cm) for the inlets and outlet, secured with 6–32 PEEK nuts (Upchurch Scientific, USA); previously, epoxy resin was used for prototyping purposes.[15a,b] Reagents were delivered to the reactor by using displacement pumps (F-200, Chemyx, USA), capable of delivering three solutions at flow rates between 0.1–100 μL $min^{-1}$. A maximum flow rate of 25 $\mu L\,min^{-1}$ per feed is recommended to keep the pressure drop generated in the system low. Inlets A and B were fed by using 1000 μL gas-tight syringes (SGE, USA), and the reaction products collected at the outlet of the ultra-low, dead-volume, back pressure regulator (Upchurch Scientific, USA), which was set to 2 MPa by using a hand-held pressure gauge (Omega, DPG 120). Prior to use, the catalyst was graded by using metal sieves to remove particulates that were <45 μm and >75 μm to enable efficient and controlled packing of the microreactor.

### Preparation of polymer-supported gallium(III) bis(trifluoromethanesulfonate) (4)

By using Amberlyst-15 (**5**) as the solid-support (Scheme 3) was prepared by using the following procedure. A-15 (1.00 g, 4.2 mmol $SO_3H\ g^{-1}$) was added to a stirred solution of $GaCl_3$ (1.85 g, 10.5 mmol) in DCM (10 mL). After 24 h at room temperature, the solid-supported material was isolated under vacuum filtration and was washed with DCM (3×50 mL), EtOH (1×50 mL), deionized $H_2O$ (1×50 mL), EtOH (1×50 mL), and DCM (1×50 mL). The solid-supported gallium(III) chloride (**6**, 1.00 g) was subsequently wetted with DCM (10 mL) prior to the addition of trifluoromethanesulfonic acid (6 equiv) under $N_2$. The reaction mixture was stirred at room temperature for 48 h prior to isolation of **4** under filtration. The material **4** was washed with DCM (1×50 mL), EtOH (1×50 mL), deionized $H_2O$ (1×50 mL), EtOH (1×50 mL), and DCM (1×50 mL), which was followed by oven drying at 90 °C. By using a pestle and mortar, the catalyst was ground into a fine powder and sieved (Endcotts, UK) to afford a particle size distribution of 45–75 μm. The resulting **4** was characterized by using ICP–MS; by using acid digestion of the solid-supported catalyst **4** and analysis of the filtrate, a loading of 1.10 $mmol_{Ga}\,g^{-1}$ was confirmed. Catalyst **4** was stored in a screw-top amber vessel and found to remain active for 3 years (to-date).

### Filling the microreactor

Prior to filling, the device was cleaned with acetone and oven dried (90 °C) to remove any residual solvent. Catalyst **4** was sieved, and the graded material packed into the reactor through the filling hole (Figure 1, bottom). The reactor was inverted and tapped to settle the material and to ensure no voids were present. The reactor was then laid flat on a bench and tapped to settle the catalyst around the filling hole. Before placing the plug into the filling hole, the surface of the reactor was wiped with a piece of tissue wetted with DCM to remove any particulates. As the outlet channel is shallow (60 μm) compared to the packed-bed (600 μm) the catalyst is physically retained in the device once the plug is installed. Care must be taken not to overfill the hole, leaving space for the plug to be fitted. The cover plate was then fitted, and the thumbscrews tightened evenly to afford a liquid tight seal.

### Emptying the microreactor

To remove catalyst **4** from the reactor, the system was flushed with DCM (2 mL). The reactor was removed from the holder, and the solvent was allowed to evaporate. Once the catalyst was dry, the



reactor was inverted, and the catalyst tapped gently out of the filling hole. The reactor was then returned to the reactor holder, without the plug and DCM pumped through the packed-bed to remove any remaining particulates. The reactor was removed from the holder, the solvent allowed to evaporate in a fume cupboard, and then the reactor was stored for subsequent investigations.

### General ketonic Strecker flow procedure

Gallium(III) bis(trifluoromethanesulfonate) (PS-Ga(OTf)$_2$, **4**) was dry packed into the packed-bed of a 3026 microreactor (0.01 g, $1.1\times10^{-2}$ mmol Ga, Figure 2) and a solution of ketone (0.4 M); amine

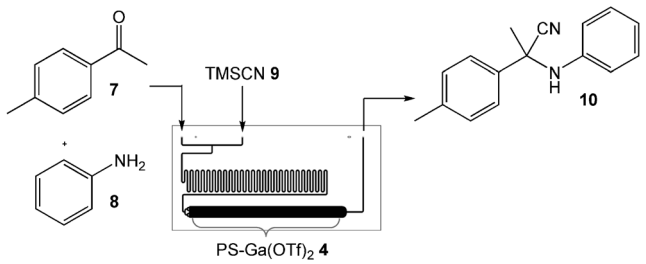



**Figure 2.** The reaction manifold (Labtrix 3026) used to investigate the ketonic Strecker reaction under continuous flow.

(0.4 M in DCM) was pumped into the reactor from inlet A and a solution of trimethylsilylcyanide (**9**, 0.4 M in DCM) from inlet B to afford a 1:1:1 ratio and a final concentration of 0.2 M. The microreactor was placed onto the Labtrix Start thermal control unit, where it was heated to 40 °C by using a Peltier element and the reaction products collected into a pre-weighed sample tube for a period of 1 h. The reaction products were concentrated in vacuo prior to analysis as solutions in $CDCl_3$ or $CD_3CN$ by $^1$H and $^{13}$C NMR spectroscopy. The synthesis of the following compounds was described in Ref. [24].

2-(Phenylamino)-2-*p*-tolylpropanenitrile (Entry 1, Table 2): By using 4-methylacetophenone (**7**) and aniline (**8**) as reactants, along with a total flow rate of 20 μL min$^{-1}$ and a reactor temperature of 40 °C, the compound was obtained as a colorless, crystalline solid (56.6 mg, 99.6%). $^1$H NMR (400 MHz, $CD_3CN$): $\delta=1.84$ (3H, s, $CH_3$), 1.91 (s, 3H; $CH_3$), 4.22 (s, 1H; NH), 6.46 (d, $J=7.8$ Hz, 2H; 2ArH), 6.70 (t, $J=7.8$ Hz, 1H; ArH), 7.01–7.13 (m, 4H; ArH), 7.42 ppm (d, $J=7.8$ Hz, 2H; ArH); $^{13}$C NMR (100 MHz, $CDCl_3$/TMS): $\delta=21.1$ ($CH_3$), 33.0 ($CH_3$), 56.8 ($C_0$), 115.4 (2CH), 119.6 (CN), 119.7 (CH), 124.7 (2CH), 128.9 (2CH), 129.8 (2CH), 136.9 ($C_0$), 138.2 ($C_0$), 146.9 ppm ($C_0$N).

2-Phenyl-2-(phenylamino)propanenitrile (Entry 2, Table 2): By using acetophenone (**12**) and **8** as reactants, along with a total flow rate of 20 μL min$^{-1}$ and a reactor temperature of 40 °C, the compound was obtained as a colorless oil (53.3 mg, 99.8%). $^1$H NMR (400 MHz, $CDCl_3$/TMS): $\delta=1.95$ (s, 3H; $CH_3$), 6.49–6.57 (m, 2H; ArH), 6.71–6.89 (m, 1H; ArH), 7.05–7.18 (m, 2H; ArH), 7.35–7.45 (m, 3H; ArH), 7.61 ppm (d, $J=7.9$ Hz, 2H; ArH), NH not observed; $^{13}$C NMR (100 MHz, $CDCl_3$/TMS): $\delta=33.0$ ($CH_3$), 57.1 ($C_0$), 105.7 (2CH), 120.2 (CH), 121.1 (CN), 125.1 (2CH), 128.3 (CH), 128.7 (2CH), 128.9 (2CH), 130.1 ($C_0$), 147.3 ppm ($C_0$N).

2-(4-Bromophenyl)-2-(phenylamino)propanenitrile (Entry 3, Table 2): By using 4-bromoacetophenone (**13**) and **8** as reactants, along with a total flow rate of 20 μL min$^{-1}$ and a reactor temperature of 40 °C, the compound was obtained as a colorless crystalline solid (72.3 mg, 99.5%). $^1$H NMR (400 MHz, $CDCl_3$/TMS): $\delta=1.93$ (s, 3H; $CH_3$), 4.27 (s, 1H; NH), 6.52 (d, $J=7.8$ Hz, 2H; ArH), 6.83 (t, $J=7.8$ Hz, 1H; ArH), 7.13 (d, $J=7.8$ Hz, 2H; ArH), 7.51–7.55 ppm (m, 4H; ArH); $^{13}$C NMR (100 MHz, $CDCl_3$/TMS): $\delta=33.4$ ($CH_3$), 56.8 ($C_0$), 115.9 (2CH), 120.3 (CN), 120.4 (CH), 122.7 ($C_0$), 126.8 (2CH), 129.2 (2CH), 132.5 (2CH), 139.2 ($C_0$), 143.2 ppm ($C_0$).

2-(4-Nitrophenyl)-2-(phenylamino)propanenitrile (Entry 4, Table 2): By using 4-nitroacetophenone (**14**) and **8** as reactants, along with a total flow rate of 20 μL min$^{-1}$ and a reactor temperature of 40 °C, the compound was obtained as a pale yellow solid (67.4 mg, 99.7%). $^1$H NMR (400 MHz, $CDCl_3$/TMS): $\delta=1.98$ (s, 3H; $CH_3$), 4.38 (s, 1H; NH), 6.49 (d, $J=7.8$ Hz, 2H; ArH), 6.83–6.87 (m, 1H; ArH), 7.14 (t, $J=7.8$ Hz, 2H; ArH), 7.83 (d, $J=8.8$ Hz, 2H; ArH), 8.27 ppm (d, $J=8.8$ Hz, 2H; ArH); $^{13}$C NMR (100 MHz, $CDCl_3$/TMS): $\delta=33.2$ ($CH_3$), 56.8 ($C_0$), 115.8 (2CH), 119.7 (CN), 120.8 (CH), 124.7 (2CH), 126.3 (2CH), 129.3 (2CH), 142.7 ($C_0$), 147.1 ($C_0$), 148.2 ppm ($C_0NO_2$).

1-(Phenylamino)cyclohexanecarbonitrile (Entry 5, Table 2): By using cyclohexanone (**15**) and **8** as reactants, along with a total flow rate of 20 μL min$^{-1}$ and a reactor temperature of 40 °C, the compound was obtained as a colorless oil (48.0 mg, 99.8%). $^1$H NMR (400 MHz, $CDCl_3$/TMS): $\delta=1.27$–1.38 (m, 3H; $CH_2$ and CH), 1.59–1.83 (m, 7H; 3$CH_2$ and CH), 4.01 (s, 1H; NH), 6.91–7.10 (m, 3H; ArH), 7.21–7.40 ppm (m, 2H; CH); $^{13}$C NMR (100 MHz, $CDCl_3$/TMS): $\delta=22.1$ (2$CH_2$), 24.9 ($CH_2$), 35.9 (2$CH_2$), 53.1 ($C_0$), 113.7 (2CH), 118.2 (CN), 120.2 (CH), 129.8 (2CH), 147.3 ppm ($C_0$N).

### General aldehydic Strecker flow procedure

Catalyst **4** was dry-packed into a packed-bed reactor (0.01 g, $1.1\times10^{-2}$ mmol Ga, (Figure 2); a solution of aldehyde and amine (0.2 M) was introduced from inlet A and a solution of **9** (0.2 M in DCM) from inlet B to afford a 1:1:1 ratio and a final concentration of 0.1 M. The microreactor was placed within the Labtrix Start unit and heated to 40 °C. The reaction products were collected into a pre-weighed sample tube for a period of 1 h prior to concentrating in vacuo. Dissolution of the product in $CDCl_3$ enabled analysis of the crude reaction product by using $^1$H and $^{13}$C NMR spectroscopy. The synthesis of the following compounds (unless marked otherwise) was described in Ref. [15b].

2-Phenyl-2-(phenylamino)acetonitrile (Entry 1, Table 3): By using benzaldehyde (**16**) and **8** as reactants, along with a total flow rate of 40 μL min$^{-1}$ and a reactor temperature of 40 °C, the compound was obtained as a colorless crystalline solid (49.9 mg, 99.7%). $^1$H NMR (400 MHz, $CDCl_3$/TMS): $\delta=4.38$ (s, 1H; NH), 5.36 (s, 1H; CH), 6.73 (dd, $J=7.6$ and 1.2 Hz, 2H; ArH), 6.86 (t, $J=7.6$ Hz, 1H; ArH), 7.23 (dd, $J=7.6$ and 1.2 Hz, 2H; ArH), 7.40–7.52 (m, 3H; ArH), 7.54–7.58 ppm (m, 2H; ArH); $^{13}$C NMR (100 MHz, $CDCl_3$/TMS): $\delta=$ 50.0 (CH), 114.1 (2CH), 115.2 (CN), 120.1 (CH), 127.1 (2CH), 128.3 (CH), 129.2 (2CH), 129.5 (2CH), 133.8 ($C_0$) and 144.6 ppm ($C_0$N).

2-(4-Bromophenyl)-2-(phenylamino)acetonitrile (Entry 2, Table 3): By using 4-bromobenzaldehyde (**11**) and **8** as precursors, the microreaction was performed at a total flow rate of 40 μL min$^{-1}$ and a reaction temperature of 40 °C to afford the compound as a colorless crystalline solid (68.9 mg, 99.9% yield). $^1$H NMR (400 MHz, $CDCl_3$/TMS): $\delta=3.65$ (s, 1H; NH), 5.32 (d, $J=3.7$ Hz, 1H; CH), 6.66 (d, $J=$ 8.4 Hz, 2H; ArH), 6.85 (t, $J=7.7$ Hz, 1H; ArH), 7.20 (t, $J=7.7$ Hz, 2H; ArH), 7.36 (d, $J=7.7$ Hz, 2H; ArH), 7.47 ppm (d, $J=8.4$ Hz, 2H; ArH); $^{13}$C NMR (100 MHz, $CDCl_3$/TMS): $\delta=49.8$ (CH), 112.3 (2CH), 114.9 (CN), 116.9 (CH), 122.6 ($C_0$Br), 128.3 (2CH), 129.1 ($C_0$), 131.3 (2CH), 131.4 (2CH), 143.7 ppm ($C_0$).



2-(4-Chlorophenyl)-2-(phenylamino)acetonitrile (Entry 3, Table 3): By using 4-chlorobenzaldehyde (**17**) and **8** as precursors, the microreaction was conducted at a total flow rate of 40 μL min$^{-1}$ and a reactor temperature of 40 °C to afford the compound as a colorless crystalline solid (58.3 mg, 99.8%). $^1$H NMR (400 MHz, $CDCl_3$/TMS): $\delta$ = 4.04 (s, 1H; NH), 5.42 (s, 1H; CH), 6.75 (dd, $J$ = 7.6 and 1.1 Hz, 2H; ArH), 6.92 (dd, $J$ = 7.6 and 1.1 Hz, 1H; ArH), 7.27 (dt, $J$ = 7.6 and 1.1 Hz, 2H; ArH), 7.42 (d, $J$ = 7.2 Hz, 2H; ArH), 7.54 ppm (d, $J$ = 7.2 Hz, 2H; ArH); $^{13}$C NMR (100 MHz, $CDCl_3$/TMS): $\delta$ = 49.6 (CH), 114.3 (2CH), 117.8 (CN), 120.6 (CH), 128.5 (4CH), 129.6 (2CH), 132.4 ($C_0$), 135.6 ($C_0$Cl), 144.3 ppm ($C_0$N).

2-(4-Fluorophenyl)-2-(phenylamino)acetonitrile (Entry 4, Table 3):[23] By using 4-fluorobenzaldeyde (**18**) and **8** as reactants, the microreaction was conducted at a total flow rate of 40 μL min$^{-1}$ and a reactor temperature of 40 °C to afford the compound as a colorless oil (54.3 mg, 99.9%). $^1$H NMR (400 MHz, $CDCl_3$/TMS): $\delta$ = 4.03 (d, $J$ = 8.4 Hz, 1H; NH), 5.40 (d, $J$ = 8.4 Hz, 1H; CH), 6.77–6.82 (m, 2H; ArH), 6.91–7.14 (m, 1H; ArH), 7.12–7.18 (m, 2H; ArH), 7.24–7.31 (m, 2H; ArH), 7.52–7.63 ppm (m, 2H; ArH); $^{13}$C NMR (100 MHz, $CDCl_3$/TMS): $\delta$ = 49.7 (CH), 114.3 (2CH), 116.3 (d, J 21.4, 2CH), 118.6 (CN), 120.4 (CH), 126.7 (CH), 126.9 (d, $J$ = 3.1 Hz, CH), 129.1 (d, $J$ = 8.4 Hz, 2CH), 144.5 ($C_0$), 163.4 ppm (d, $J$ = 248.5 Hz, $C_0$F).

Methyl-4-[cyano(phenylamino)methyl]benzoate (Entry 5, Table 3): By using methyl-4-formyl benzoate (**19**) and **8** as reactants, the microreaction was conducted at a total flow rate of 40 μL min$^{-1}$ and a reactor temperature of 40 °C to afford the compound as a colorless oil (63.9 mg, 99.9%). $^1$H NMR (400 MHz, $CDCl_3$/TMS): $\delta$ = 3.95 (s, 3H; $OCH_3$), 4.13 (d, $J$ = 8.4 Hz, 1H; NH), 5.52 (d, $J$ = 8.4 Hz, 1H; CH), 6.71–7.12 (m, 3H; ArH), 7.26–7.30 (m, 2H; ArH), 7.71 (d, $J$ = 8.3 Hz, 2H; ArH), 8.11 ppm (d, $J$ = 8.3 Hz, 2H; ArH); $^{13}$C NMR (100 MHz, $CDCl_3$/TMS): $\delta$ = 50.0 (CH), 52.4 ($OCH_3$), 114.3 (2CH), 118.2 (CN), 120.6 (CH), 127.2 (2CH), 129.6 (2CH), 130.5 (2CH), 139.2 ($C_0$), 144.3 ($C_0$), 150.1 ($C_0CO_2CH_3$), 168.3 ppm (CO).

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