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FULL PAPER

Divergent multistep continuous synthetic transformations of allylic alcohol enabled by catalysts immobilised in IL-phases.

Edgar Peris[a], Raúl Porcar[a], Joaquín García-Álvarez[b], María Isabel Burguete[a], Eduardo García-Verdugo*[a] and Santiago V. Luis*[a]

Abstract: Two individual catalytic platforms (metal- and organo-catalysed) based on the use of ILs have been successfully integrated and the right combination of continuous flow processes has enabled access to the divergent preparation of two alternative interesting intermediate compounds from the same starting material.

Introduction

Sustainability is not only a challenge, but also an opportunity to radically transform synthetic processes to new emerging technologies.[1] In this context, there is a need to develop alternative approaches mimicking natural processes that integrate multiple and consecutive catalytic sequences.[2,3,4,5] These transformations can be performed, to reduce their environmental impact, under alternative reaction conditions using neoteric solvents such as water, dimethyl carbonate, ionic liquids (ILs) or supercritical fluids.[6] Indeed, these solvents can contribute to not only reducing human health problems and the environment footprint of the synthetic process, but in some cases, to the modification of the catalytic system enhancing its activity, recyclability, stability and / or selectivity. At the same time, these new synthetic methodologies should also face challenges related to the paradigm shifts chemical industry is experiencing. These include replacing discontinuous processes requiring multiple unit operations by highly flexible and integrated continuous flow catalytic processes.[7,8,9,10,11] In this regard, the development of multicatalytic platforms allowing sequential and controllable processes is highly desirable. This can lead to complex syntheses through reduced external intervention and minimal environmental impact,.[12,13,14,15,16] These platforms facilitate: i) greater reproducibility of reactions; ii) easy scaling, which facilitates the direct transfer of laboratory results to production; iii) reduction in environmental impact; iv) improved safety; v) synthesis of new high-value chemical entities; vi) intensification of the process. Thus, smaller size systems can be used offering cost reduction and higher productivity. Furthermore, the assembly of these synthetic platforms in a divergent telescopic sequential fashion can lead to systems able to produce molecules with wide structural diversity.[17,18]

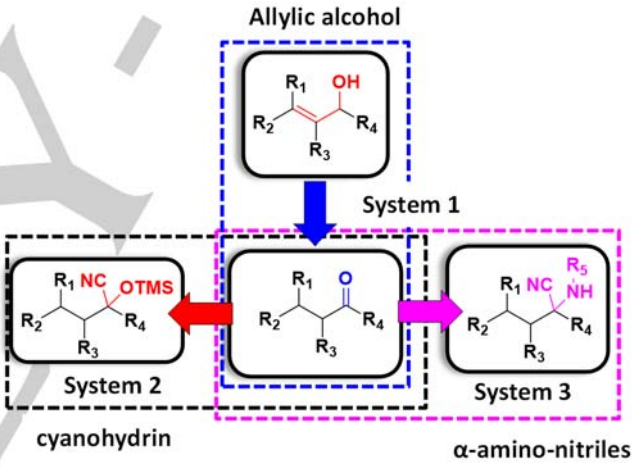

Figure 1. Divergent synthesis based on continuous flow catalytic platforms.

In this context, the main aim of the work has focused on the divergent synthesis of α-cyano-amines and cyanohydrin trimethylsilyl ethers as depicted in Figure 1. Both families of compounds are very useful synthetic intermediates for the preparation of a wide variety of organic molecules with relevant pharmacological properties.[19,20] α-Cyano-amines can be obtained by the three-component Strecker reaction using an aldehyde or ketone, an amine and a cyanide source. In the absence of the amine and with the selection of the proper catalyst the same reactants can alternatively be transformed in cyanohydrin trimethylsilyl ethers, which can easily be converted into functionalized α-hydroxy acids, α-hydroxy aldehydes, β-amino alcohols or other polyfunctional compounds.[21] These two reactions generally require HCN or alkali metal cyanides such as KCN or NaCN as cyanide sources, which represents a serious concern in terms of chemical hazards and waste treatment. To overcome these problems TMSCN (trimethylsilyl cyanide) has proven to be an effective, relatively safe, and easily handled cyanide anion source.[20] Both reagents use ketones or aldehydes

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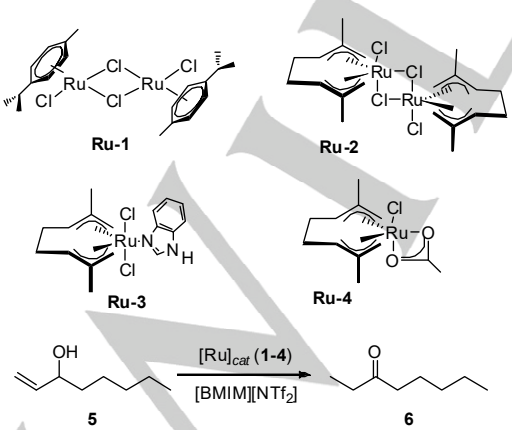
as starting materials that can be obtained from the isomerisation of readily accessible allylic alcohols in a ruthenium-catalysed process.[22-25]

In the search for such divergent platforms, here we report our efforts to develop IL-based catalytic systems that can be combined in a single continuous flow process to provide alternatively two different families of intermediate compounds. Such platforms allow the reduction in environmental impact and enable the simple separation and reuse of the catalysts, providing products not contaminated by traces of either catalyst or solvent.

Results and Discussion

Catalytic Platform 1. Ruthenium-catalysed isomerisation of allylic alcohols into ketones: Ru-complexes are highly efficient catalysts for the isomerisation of different allylic alcohols under mild conditions and using neoteric solvents such as water,[22] deep eutectic solvents,[23] or ILs like [BMIM][BF_4].[24,25] With this IL the catalysts can be recovered during at least five consecutives batches, using hexane as the extraction solvent, alothough the catalyst showed a certain degree of deactivation upon recycling. In order to develop a catalytic platform based on a Ru-catalyst able to efficiently work for multiple cycles and allowing a simple recycling, the combination of ILs with supercritical CO_2 ($scCO_2$) provides a relatively simple and straightforward technological solution.[26] Generally, the IL-phase is used for the homogeneous immobilisation of the catalyst (metal complexes, enzymes, nanoparticles, etc), while the $scCO_2$ phase is intended to favour the delivery of substrates to the catalytic sites in the IL phase and to facilitate the extraction and separation of the final products. Very often, this combination allows optimised yields and productivities by the fine tuning of the contact time of the $scCO_2$/IL-phases using either the pressure or the flow rates. These catalytic platforms exclude the need for other additional solvents and facilitate the isolation and separation of the products from the catalyst, being able to work 24/7, requiring less work force for operation, reducing the equipment size and maximising productivity.



Scheme 1. Model isomerisation reaction and Ru catalysts used.

In order to develop such a catalytic platform, four different Ru-complexes were initially screened for the batch isomerisation of 1-octen-3-ol in an IL phase (Scheme 1). The reaction was performed using a solution of the Ru-complexes in [BMIM][NTf_2] (0.5% weight) and employing a 1% mol loading of the catalyst with respect to the alcohol. The reaction was monitored at 1 and 17 hours. Results obtained are summarised in Table 1. The Ru(IV)-acetate complex **Ru-4** was the organometallic catalyst showing the highest activity, reaching > 99% of isomerisation yield (scheme 1) in only one hour (TOF 100 h^{-1}). The other Ru(IV)-catalysts (**Ru-2** and **Ru-3**) led to lower yields in one hour (67% and 73%, respectively, Table 1), while the Ru(II)-complex (**Ru-1**) showed almost no activity (< 10%) during the same period. The three Ru-complexes afforded good to excellent isomerisation yields after 17 hours. These results are in agreement with previous results showing that **Ru-4** was an efficient catalyst for this reaction in both water (0.2 mol%, > 99%, 5 min, TOF 6000 h^{-1}) and [BMIM][BF_4] (1 mol%, > 99%, 5 min, TOF 1200 h^{-1}).[25] The lower activity observed here is most likely associated with the less polar nature of [BMIM][NTf_2].

Table 1. Isomerisation of 1-octen-3-ol (**5**) in [BMIM][NTf_2] with 1% mol of Ru catalysts.[a]

Entry	Catalyst	Yield (%)[b]	
		1 h	17 h
1	**Ru-1**	< 7	> 99
2	**Ru-2**	67	> 99
3	**Ru-3**	73	87
4	**Ru-4**	> 99	--

[a] 2 mmol of **5**. 1 gram of IL per mmol of reagent. 1% mol catalyst. Room temperature. [b] Determined by GC.

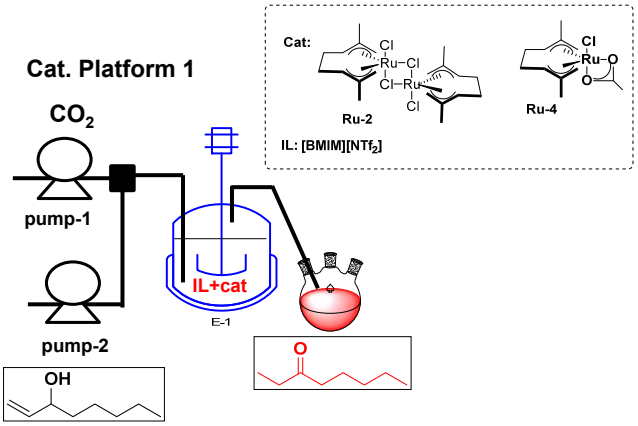


Figure 2. Schematic representation of the IL/$scCO_2$ set-up used for the isomerisation of **5** catalysed by **Ru-2** and **Ru-4**.

Based on these results, the reaction was studied using an IL/$scCO_2$ system, enabling the semi-continuous production of the ketone without the use of any additional organic solvent (Fig. 2). The IL-phase was used simultaneously as reaction solvent and homogenous media for catalyst immobilisation.[27] In spite of the higher activity of **Ru-4**, initial experiments were performed with the dimeric complex **Ru-2**, which displayed a reasonable activity and is commercially available. The schematic reactor set-up is depicted in Fig. 2. The allylic alcohol was delivered by a HPLC pump, while a refrigerated head $scCO_2$ pump was used to feed the CO_2. Initially the flow rates were set to 0.1 mL/min of 1-octen-3-ol (**5**) and 1.5 mL/min of CO_2 at 75 °C and 10 MPa (Fig. 3). The reaction was performed by first feeding 3 mL of **5** to the reactor at a flow rate of 0.1 mL/min. After this, the system was filled with CO_2 until reaching 10 MPa pressure and then, maintaining a constant flow rate of 1.5 mL/min, samples were collected at different times and analysed by GC. The initial samples showed a low degree of isomerisation due to the short contact time of the allylic alcohol with the complex. The degree of isomerisation increased with time, reaching *ca.* 50% and 70% after 3 and 4 hours, respectively (Cycle I, Fig. 3).

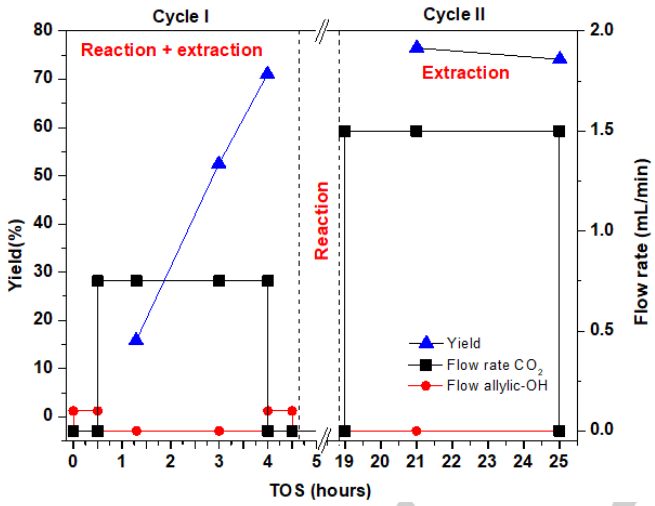


Figure 3. Results obtained for the isomerisation of **5** catalysed by **Ru-2** in a [BMIM][NTf_2]/$scCO_2$ system at 75 °C and 10 MPa, (TOS: Time on stream, measured since the feed of the allylic alcohol **5** starts). Ru(IV)-complex **Ru-2** (154 mg) was dissolved in 10.5 g of [BMIM][NTf_2] (1.5% by weight).

These results, demonstrated the feasibility of the isomerisation using the Ru complex immobilised in the homogenous liquid IL-phase and the need for longer reaction times. Thus, the reactor was charged again in a second cycle with 3 mL of **5** and the reaction was left to proceed during 15 h before restarting the CO_2 pumping an collecting the product for an additional 7 hours period, achieving a 95% of conversion of the allylic alcohol into the corresponding ketone (Cycle II; Fig. 3). An additional cycle was repeated under the same conditions leading to comparable results (93% of the product was ketone). However, the overall mass balance indicated a relatively low extraction efficiency of the product from the IL-phase. To evaluate this, the catalyst/IL-phase in the reactor was further extracted with Et_2O confirming the presence of an appreciable residual mass of the ketone (718 mg). However, it is important to note that the product extracted with $scCO_2$ was a clear uncoloured oil without any trace of IL or catalyst, while the product obtained by ether extraction showed traces of the catalyst (coloured solution) and IL-phase (Fig. S.1).

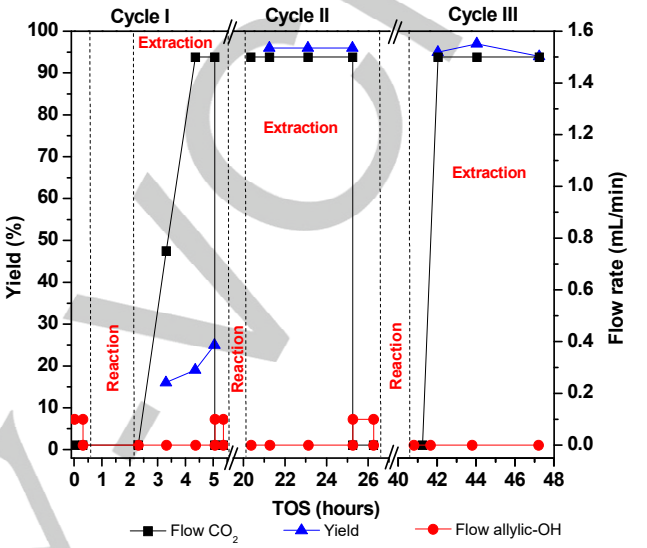


Figure 4. Results obtained for the isomerisation of **5** catalysed by **Ru-4** in a [BMIM][NTf2]/$scCO_2$ system at 75 °C and 10 MPa (TOS: Time on stream).

Encouraged by these results, the catalyst **Ru-4** was assayed under similar conditions (0.27% mol catalyst loading, Fig. 4). When the reactor was loaded with 2 mL of **5** and left to react overnight, the extract obtained under these conditions (1.5 mL/min flow rate of CO_2) showed full conversion of the allylic alcohol into the corresponding ketone (Cycle II). In Cycle III, 6 mL of **5**, were fed (0.09% mol catalyst loading) for an overnight reaction and again the extract showed > 95% conversion. Noteworthy, cycles II and III altogether provided a TON of 1425 moles of **6** per mol of **Ru-4**.

Catalytic Platforms 1 + 2. From allylic alcohols to cyanohydrins: Once established that the **Ru-4** / IL / $scCO_2$ combination can efficiently transform the allylic alcohol **5** into ketone **6**, the further transformation of **6** into its cyanohydrin trimethylsilyl ether (**7**) by reaction with TMSCN was evaluated using an organocatalytic system (catalytic platform 2) using the efficient catalytic system reported for us for this transformation and based on supported ionic liquid-like phases.[28] Thus, the conversion of **6** into **7** was evaluated by directly pumping **6** through a fixed-bed reactor containing the catalyst **8** (Fig. 5).

Figure 6 summarises the results obtained using a flow rate of 0.1 mL/min of a mixture of one equivalent of ketone **6** and 1.2 equivalents of TMSCN at room temperature and under solvent free conditions. Under this experimental set-up, 6 mL of the ketone **6** (from platform 1) were transformed into the corresponding cyanohydrin **7** with an excellent yield (99%). Hence, the combination of these two systems can be used for the

efficient synthesis of cyanohydrins starting from allylic alcohols with productivities for both synthetic transformations of 1.08 Kg of **6**·g^{-1} hour^{-1}·L^{-1} and 3.8 Kg of **7**·g^{-1} cat **8**·hour^{-1} L^{-1} in terms of mass of product obtained per gram of catalyst and per reactor volume in one hour.

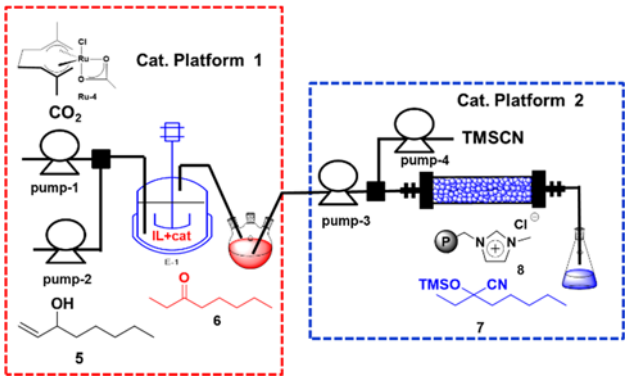


Figure 5. Schematic representation of the set-up combining the catalytic platforms 1 + 2 for the conversion of **5** into **7** catalysed by **Ru-4** and **8**.

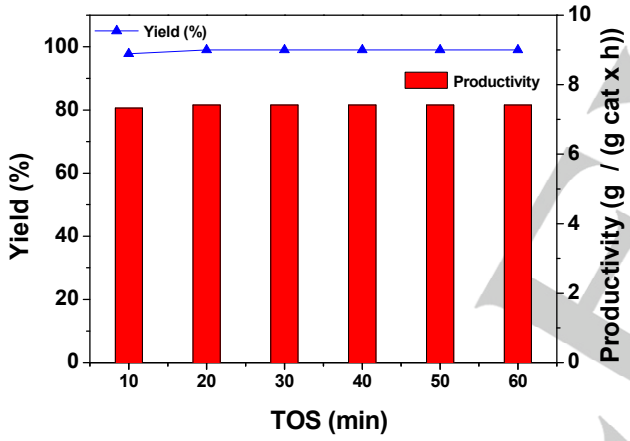


Figure 6. Catalytic platform 2. Solventless conversion of the ketone **6** obtained with the catalytic platform 1 into **7**. Flow rate: 0.1 mL/min. **6**:TMSCN 1:1.2 mol ratio. Residence time: 20 min. 600 mg of catalyst **8** (TOS: Time on stream).

Catalytic Platforms 1 + 3. From allylic alcohols to α-amino-nitriles: The classical Strecker reaction is one of the simplest and most economical methods for the synthesis of racemic α-aminonitriles.[29] Polystyrene-immobilised catalysts, with either Ru or Sc as the Lewis acid site, have been reported to promote this three-component reaction of aldehydes, amines and TMSCN with excellent conversions.[30] However, analogous reactions with ketones required significantly more reactive catalysts like the polystyrene-supported gallium triflate (PS-Ga(OTf)$_2$) reported to provide the targeted α-aminonitriles in high yield and purity.[31]
Task-specific supported ionic liquid-like phases modified with sulfonic groups (**9a**, Fig. 7) can be used to complex lanthanide triflates, in particular scandium triflate (Sc(OTf)$_3$).[32,33] In this regard, the presence in **9a** of the imidazolium fragments can contribute to improve the catalytic activity provided by the Lewis acid units.[34,35,36,37] Such contribution is absent in the analogous Sc-supported catalyst **9b**, prepared from a commercially available sulfonic polystyrene-divinylbenzene polymer (Amberlyst® 15).[38]

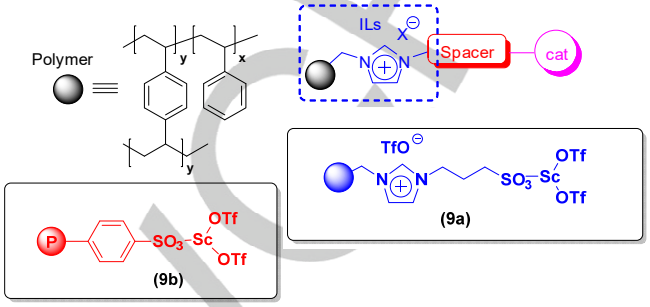
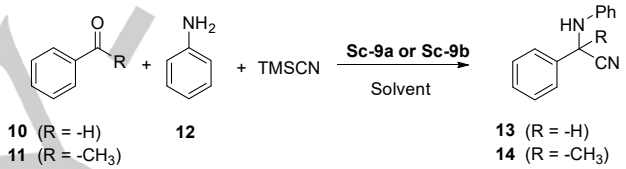


Figure 7. PS-DVB supported Sc catalysts **9a** and **9b**.



10 (R = -H) **12** **13** (R = -H)
11 (R = -CH$_3$) **14** (R = -CH$_3$)

Scheme 2. Three-component benchmark Strecker reaction catalysed by **9a** and **9b**.

Both catalysts, **9a** and **9b**, were evaluated for the Strecker reaction between benzaldehyde (**10**), aniline (**12**) and trimethylsilyl cyanide (TMSCN) (Scheme 2).[39] Under solvent free conditions, benzaldehyde was smoothly converted in to the corresponding α-aminonitrile in the presence of **9a** (Entry 1, Table 2). Near quantitative yields were achieved when the reaction was performed in the presence of an additional solvent (Entries 2-4, Table 2) including the use of benign solvents like 2-methyl-tetrahydrofuran (2-Me-THF) and dimethylcarbonate (DMC). When the reaction was carried out in the presence of **9b** using either CH$_3$CN or 2-Me-THF as solvents, yields (Entries 5 and 6, Table 2) were significantly lower than those observed for **9a**. This difference was lower for the reactions carried out in CH$_3$CN (99 *vs.* 84%, entries 2 and 5, Table 2). When the less reactive acetophenone (**11**) was used instead of benzaldehyde the differences were even more pronounced. While **9a** afforded moderate yields of **14** in 2-Me-THF (69%, Entry 8, Table 2) and a 20% yield in CH$_3$CN (Entry 7, Table 2), the catalyst **9b** was not active for this reaction in none of the solvents evaluated (Entries 9 and 10, Table 2).
The different behaviour of catalysts **9a** and **9b** highlights the key role played by the presence of IL-like fragments in **9a**. A cooperative effect seems to exist between the scandium sites and the IL-like units leading to a more efficient catalyst. The substrates can be activated through hydrogen bonding with both the imidazolium cation and the OTf$^-$ anion, which is not feasible in **9b**. As could be expected, this effect is more important in 2-Me-THF as CH$_3$CN can compete with TMSCN minimising the

"*electrophile–nucleophile dual activation*" of the reactants with the IL-like units.

Table 2. Three-component Strecker reaction of benzaldehyde (**10**) or acetophenone (**11**) with aniline (**12**) and TMSCN catalysed by **9a** or **9b** (r.t).[a]

Entry	Catalyst	Substrate	Solvent	R	Yield
1	**9a**	**10**	Solvent free	-H	89
2	**9a**	**10**	CH_3CN	-H	99
3	**9a**	**10**	2-Me-THF	-H	98
4	**9a**	**10**	DMC	-H	95
5	**9b**	**10**	CH_3CN	-H	84
6	**9b**	**10**	2-Me-THF	-H	17
7	**9a**	**10**	CH_3CN	$-CH_3$	20
8	**9a**	**10**	2-Me-THF	$-CH_3$	69
9	**9b**	**11**	CH_3CN	$-CH_3$	< 5
10	**9b**	**11**	2-Me-THF	$-CH_3$	< 5

[a] 1 eq benzaldehyde (**10**) or acetophenone (**11**) (5 mmol), 1 eq aniline (**12**) (5 mmol), 1.2 eq TMSCN (6 mmol); 50 mg cat. **9a** or **9b** per mmol of **10**/**11**; 1 mL of solvent per mmol of **10**/**11**. Room temperature.

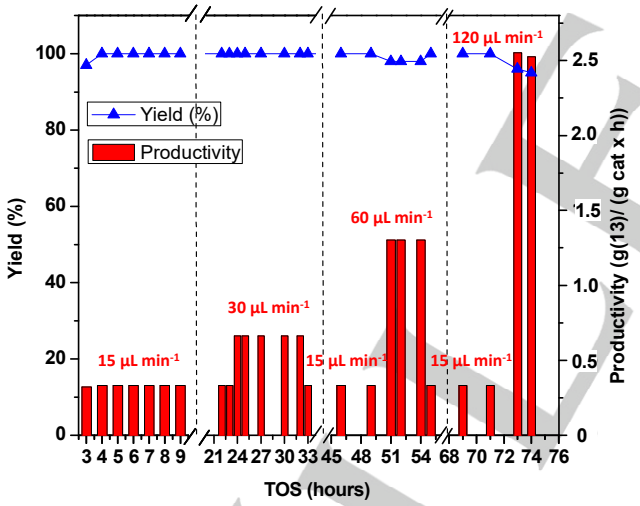


Figure 8. Yield of **13** *vs*. time on stream (TOS) for the three-component Strecker reaction of benzaldehyde (**10**), aniline (**12**) and TMSCN catalysed by **9a** under continuous flow. 1.5 M in 2-Me-THF, 0.850 g of catalyst **9a**, 2.4 mL reactor volume.

The long-term stability of the catalyst **9a** was studied for the continuous flow reaction between benzaldehyde, aniline and TMSCN in 2-Me-THF. Flow conditions allow evaluating catalyst stability in the absence of any physical abrasion of the polymeric beads associated with their extensive use under batch conditions.[40] As shown in Fig. 8, when the reactants were initially pumped through a reactor packed with 0.85 g of **9a** at 15 µL/min the yield obtained was > 99% without any apparent activity decay during more than 24 hours. Thereafter, the flow rate was increased to 30 µL/min, 60 µL/min and 120 µL/min, still achieving a very good activity (yield > 95%). Intermediate flow rate reductions to 15 µL/min provided again yields > 99%. No leaching of scandium was detected in the liquid phase by ICP-MS. These results confirmed the stability of the catalyst **9a** for the Strecker reaction under flow conditions, with no detectable indication of deactivation for more than 75 hours of continuous use. It is worth mentioning that increasing the flow rate provided important improvements in productivity. Thus, for the higher flow rate used (120 µL/min) *ca*. 2.5 g of **13** per hour and gram of catalyst were produced, keeping a 95% conversion of the reactants. Accordingly, with a small lab reactor loaded with *ca*. 2 g of catalyst and using a flow rate of 0.12 mL/min, *ca*. 121 g of **13** could be obtained in only 24 hours.

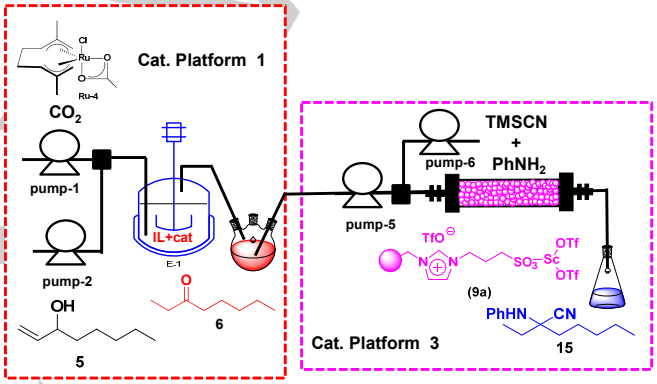


Figure 9. Schematic representation of the reactor set-up combining catalytic platforms 1 and 3 for the conversion of **5** into **15** catalysed by **Ru-4** and **9a**.

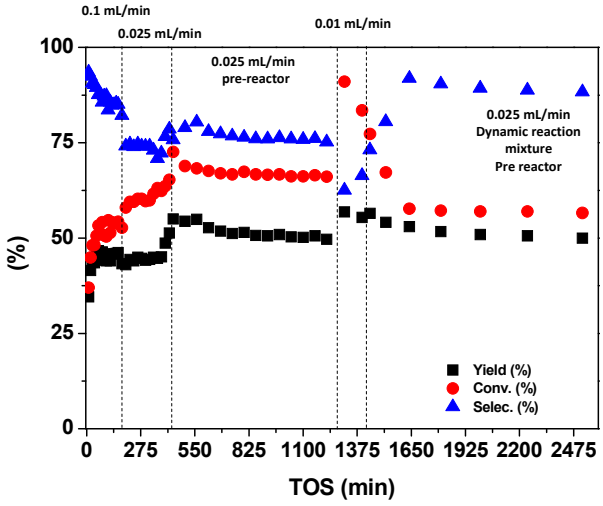


Figure 10. Results obtained combining the catalytic platforms 1 and 3. Conversion, yield and selectivity of **15** *vs.* time on stream (TOS) for the Strecker reaction of ketone **6**, aniline (**12**) and TMSCN catalysed by **9a**. 0.6 g of catalyst **9a**, 1.9 mL reactor volume.

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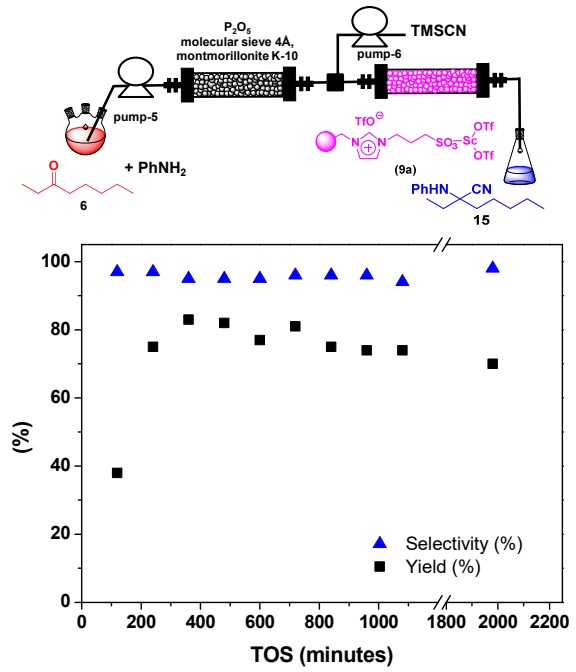

Figure 11. Yield and selectivity for **15** *vs.* time on stream (TOS) for the Strecker reaction of ketone **6**, aniline (**12**) and TMSCN catalysed by **9a** and set-up used for the reaction. Reactor I: 1.2 g of 4Å molecular sieves, 1.2 g P_2O_5 and 1.2 g of MMK10, 3.9 mL reactor volume. Reactor II: 0.6 g of catalyst **9a**, 1.9 mL reactor volume.

The reaction of **6** with **11** and TMSCN was also evaluated under solvent free batch conditions with catalyst **9a**, affording the corresponding α-aminonitrile **15** in 99% yield (no traces of **7** were observed). This allowed to study the telescoped transformation of the allylic alcohol **5** into the ketone **6** and this into the α-aminonitrile **15** by combining catalyst **9a** (catalytic platform 3) and the **Ru-4**/IL/$scCO_2$ system (catalytic platform 1) (Fig. 9). Thus, the product extracted from the system 1 was pumped through a catalytic fixed-bed reactor containing 0.6 g of **9a** at 0.1 mL/min. Results summarised in Fig. 10 show that initially modest yields (*ca.* 40-45%) of product **15** were achieved, along with low selectivities (80-85%) due to the formation of the corresponding cyanohydrin (through direct reaction of **6** and TMSCN). An increase in conversion accompanied by decay in selectivity (*ca.* 70%) was observed by reducing the flow rate to 25 μL/min. Thus, ketimine formation seemed to be the limiting factor. It must be noted that the actual substrate/catalyst ratio in the flow system is much higher than under batch conditions, which can additionally promote the cyanosilylation of the unreacted aldehyde, reducing selectivity. To improve imine formation before contacting catalyst **9a**, the mixture of ketone and amine was pumped through a coil reactor (0.2 mL, 8 min residence time) located before the fixed-bed reactor loaded with **9a**. However, under these conditions (25 μL/min flow rate), only a slight improvement in selectivity (75-77%) and yield of **15** (50-55%) was observed (Fig. 10). A further increase of the residence time (10 μL/min flow rate) did not improve the results. When the ketone (**6**) and the aniline (**12**) were mixed together under solvent free conditions for 12 hours before pumping the mixture into the reactor (25 μL/min) similar results were obtained in terms of yield (50-55%) but the selectivity was clearly improved (*ca.* 90-92%).

Finally, a further improvement in the formation of the ketamine was achieved using a new fixed-bed reactor packed with equal amounts of two dehydrating agents P_2O_5 and 4Å molecular sieves along with an acid montmorillonite (MM K10), which have been reported to promote the preparation of imines under batch conditions (Fig. 11).[41,42] Thus, ketone (**6**) and aniline (**12**) were mixed together under solvent free conditions for 12 hours and then pumped through the first reactor heated at 60 °C (12 μL/min flow rate) and the solution at the outlet of this reactor was mixed with a flow of TMSCN (15 μL/min) before entering the second fixed-bed reactor maintained at room temperature and packed with **9a**. Under these conditions, the yield was higher than 70% and the selectivity excellent (> 95%). The final product (**15**) was obtained with productivities of 26.5 g of **15** day^{-1} with only 0.6 g of catalyst **9a**. Thus, the combination of the catalytic platform 1 (metal-catalysed) and 3 (organo-catalysed) demonstrated to be suitable for the telescoped preparation of α-cyanoamines from allylic alcohols.

Conclusions

By the right combination of three different catalytic continuous flow platforms, a divergent synthetic flow system for the preparation of both the protected cyanohydrin **8** and the α-amino nitrile **15** from the allylic alcohol **5** has been achieved. The long term stability and the activity of each catalytic platform has been evaluated and optimised. In all of the catalytic platforms ILs-related species, as reaction media and / or as supported catalysts (SILLPs) played a key role. The results obtained for the Strecker reaction highlight the potential for catalytic applications of task specific supported ionic liquid-like phases containing specific functionalities (imidazolium-sulfonic acid in this case). The three component Strecker reaction of a non-reactive aliphatic ketone (**6**) has been achieved using a combination of dehydrating agents and supported catalysts in telescoped consecutive flow mini-reactors. Thus, the combination of allylic alcohol isomerisation with the cyanosilylation and Strecker reactions, both for aldehydes and ketones, gives access to a broad scope of valuable synthetic building blocks as protected cyanohydrins and α-amino nitriles with good yields in long-term stable continuous flow procedures. It is worth mentioning that catalytic platforms 2 and 3 work under solventless conditions and that the neoteric solvents $scCO_2$ and [BMIM][NTf_2] used in platform 1 are the only solvents employed. Moreover, no purification step is needed between catalytic platforms and therefore a waste minimisation is reached in the whole process reported. Reasonable productivities can be obtained for the different catalytic and multicatalytic systems developed at the multigram scale (g^{-1} cat h^{-1}).

Experimental Section

Ruthenium complexes (**Ru-1** to **Ru-4**) were obtained as previously described,[24] as well as SILLPs **8** and **9a-b**.[28,32]

Batch isomerisation of 1-octen-3-ol (5) into 3-octanone (6). 0.315 mL (2 mmol) of 1-octen-3-ol (**5**) were dissolved in 2 g of [BMIM][NTf_2]. 0.02 mmol (1% mol) of the ruthenium catalyst (**Ru-1** to **Ru-4**) were added and the mixture was left at 80 ºC under orbitalic stirring (220 rpm) for 1 hour. Samples were periodically analysed by GC.

Batch three-component Strecker reaction of benzaldehyde (10) or acetophenone (11), aniline (12) and TMSCN catalysed by 9a or 9b. 0.515 mL (5 mmol) of benzaldehyde (**10**) or 0.590 mL (5 mmol) of acetophenone (**11**), 0.456 mL (5 mmol) of aniline (**12**) and 0.758 mL (6 mmol) of TMSCN were mixed. 5 mL of solvent (except solvent free cases) and 250 mg of catalysts **9a** or **9b** were added (50 mg/mmol **10** or **11**). The mixture was stirred for 24 hours at room temperature. The samples were analysed by ^{1}H-NMR.

Continuous flow three-component Strecker reaction of benzaldehyde (10), aniline (12) and TMSCN catalysed by 9a. The reactor was set-up by introducing the SILLP-**9a** (850 mg) in a glass Omnifit® column 006RG-10-10 (0.7854 cm x 10 cm), which was connected at its head to a KdScientifics model of syringe pump. A 25 mL Hamilton syringe filled with benzaldehyde (**10**), aniline (**12**) and TMSCN (1:1:1.2) was used. The mixture of reagents was pumped through the catalytic bed at different flow rates going from 0.015 to 0.12 mL/min. Aliquots were taken at constant time intervals and analysed by ^{1}H-NMR.

Continuous flow cyanosilylation reaction of 3-octanone (6). The reactor was set-up by introducing the SILLP-**8** (600 mg) in a glass Omnifit® column 006RG-10-10 (0.7854 cm x 10 cm), which was connected at its head to a KdScientifics model of syringe pump. A 25 mL Hamilton syringe filled with 3-octanone (**6**) and TMSCN (1:1.2) was used. The mixture of reagents was pumped through the catalytic bed at 0.1 mL/min. Aliquots were taken at constant time intervals and analysed by GC.

Continuous flow three-component Strecker reaction of 3-octanone (6), aniline (12) and TMSCN catalysed by 9a The reactor was set-up by introducing the SILLP-**9a** (600 mg) in a glass Omnifit® column 006RG-10-10 (0.7854 cm x 10 cm). The reagents mixture was pumped through the reactor using Hamilton syringes in KdScientifics syringe pumps. Several different strategies were used in order to favour the previous formation of the ketimine. Method i) a mixture of 3-octanone (**6**), aniline (**12**) and TMSCN (1:1:1.2) was pumped through a coil reactor at 0.025 mL/min (1 m, 0.2 mL, 8 min residence time) set-up before the fixed-bed reactor loaded with **9a.** Aliquots were taken at constant time intervals and analysed by GC. Method ii) a mixture of 3-octanone (**6**) and aniline (**12**) (1:1) was stirred at r.t. overnight (15 h). Then, TMSCN was added (1.2 molar eq.) and the mixture was pumped through the fixed bed reactor loaded with **9a** using a 25 mL Hamilton syringe and a KdScientifics model of syringe pump. Aliquots were taken at constant time intervals and analysed by GC. Method iii) a Omnifit® column 006RG-10-10 (0.7854 cm x 10 cm) was packed with 4Å molecular sieves (1.2 g), P_2O_5 (1.2 g) and montmorillonite K10 (1.2 g). The reactor was heated at 60 ºC using a *i*-PrOH reflux and was connected at the head to a KdScientifics model of syringe pump. A mixture of 3-octanone (**6**) and aniline (**12**) (1:1) was pumped through the reactor at 0.012 mL/min. After this reactor a T-piece was connected and TMSCN was pumped at 0.013 mL/min joining the previous reagents mixture before entering the reactor packed with **9a**. Aliquots were taken at the exit of the second reactor and analysed by ^{1}H-NMR.

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Keywords: Ionic liquid • Supported ionic liquid • supercritical CO_2 • catalysis • continuous flow

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FULL PAPER

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Electronic Supporting Information

Divergent multistep continuous synthesis enabled by immobilised catalysts on IL-phases

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Table of Contents

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1. $scCO_2$ vs Et_2O extraction

The product of the isomerisation of 1-octen-3-ol (**5**), 3-octanone (**6**), was extracted with $scCO_2$ in a continuous flow system. The catalytic ruthenium complex was dissolved in the IL [BMIM][NTf_2] inside the reactor where the reaction takes place. 1-octen-3-ol (**5**) was pumped inside the reactor and finally the product 3-octanone (**6**) was extracted using $scCO_2$. This allowed to extract only the product (colourless) remaining intact the IL+Ru catalyst for the next catalytic cycle. In order to compare and confirm the suitability of the choice of $scCO_2$, an extraction with diethyl ether was performed. As could be seen in Figure S.1, with diethyl ether not only the product was extracted, but also part of the ionic liquid and the Ru catalyst dissolved in it. The colouration of the colourless diethyl ether is a proof (see Figure S1). Moreover, ^{1}H-NMR studies were done (see Figure S2) confirming this hypothesis. The top spectrum only contains the signals from 3-octanone (**6**), but the spectrum on the bottom shows additional signals.

Figure S1. Et_2O (left) vs $scCO_2$ (right) extraction of the 3-octanone (6)

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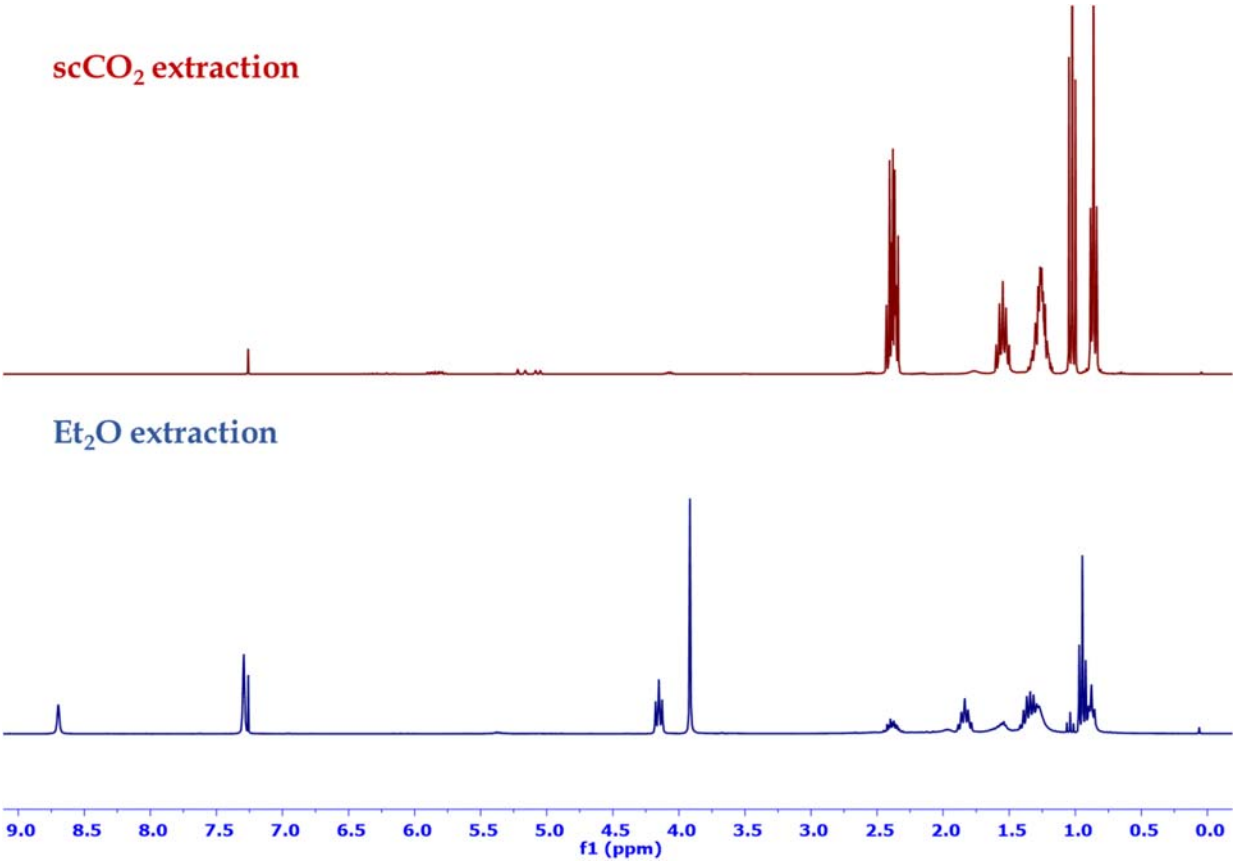

Figure S2. ^{1}H-NMR comparative study of the extraction of 3-octanone with $scCO_2$ or Et_2O

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2. Set-up used for 1-octen-3-ol (5) isomerisation in $scCO_2$.

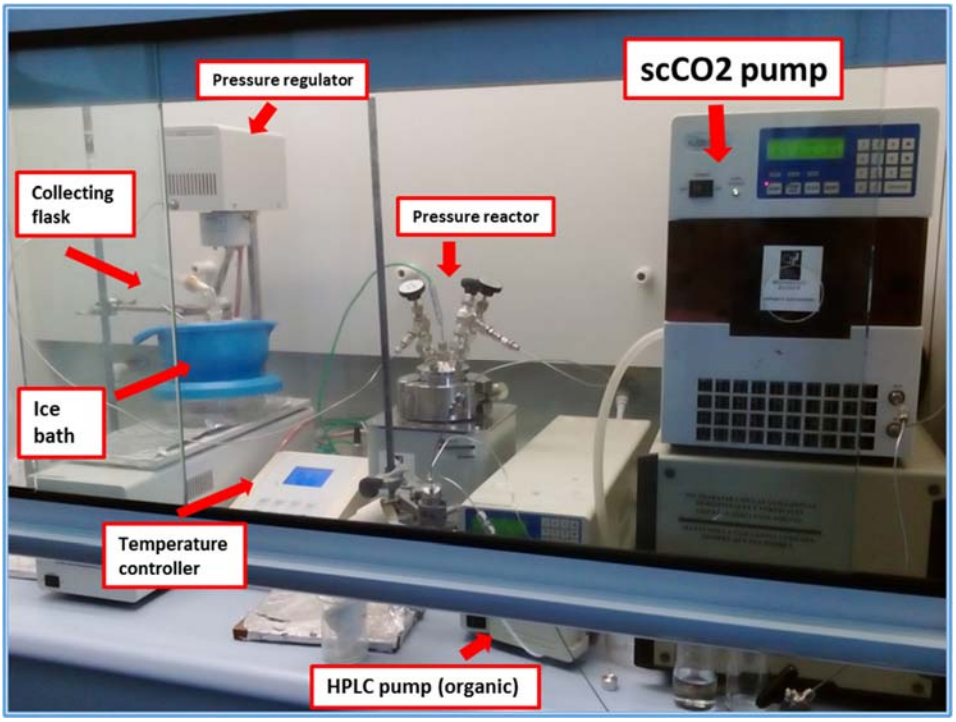

Figure S3. Set-up used for the continuous flow isomerisation of 1-octen-3-ol (5) into 3-octanone (6) using $scCO_2$

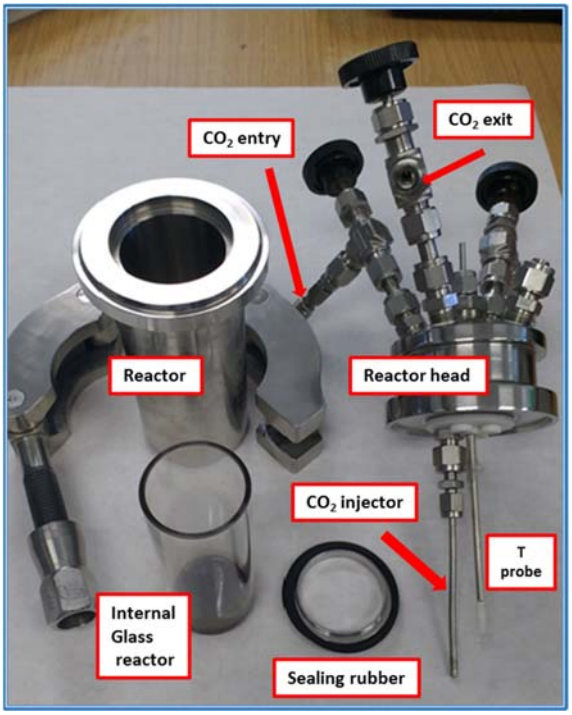

Figure S4. Parts of the pressure reactor used

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3. Kinetic study of the batch Strecker reaction of benzaldehyde (10), aniline (12) and TMSCN catalysed by 9a.

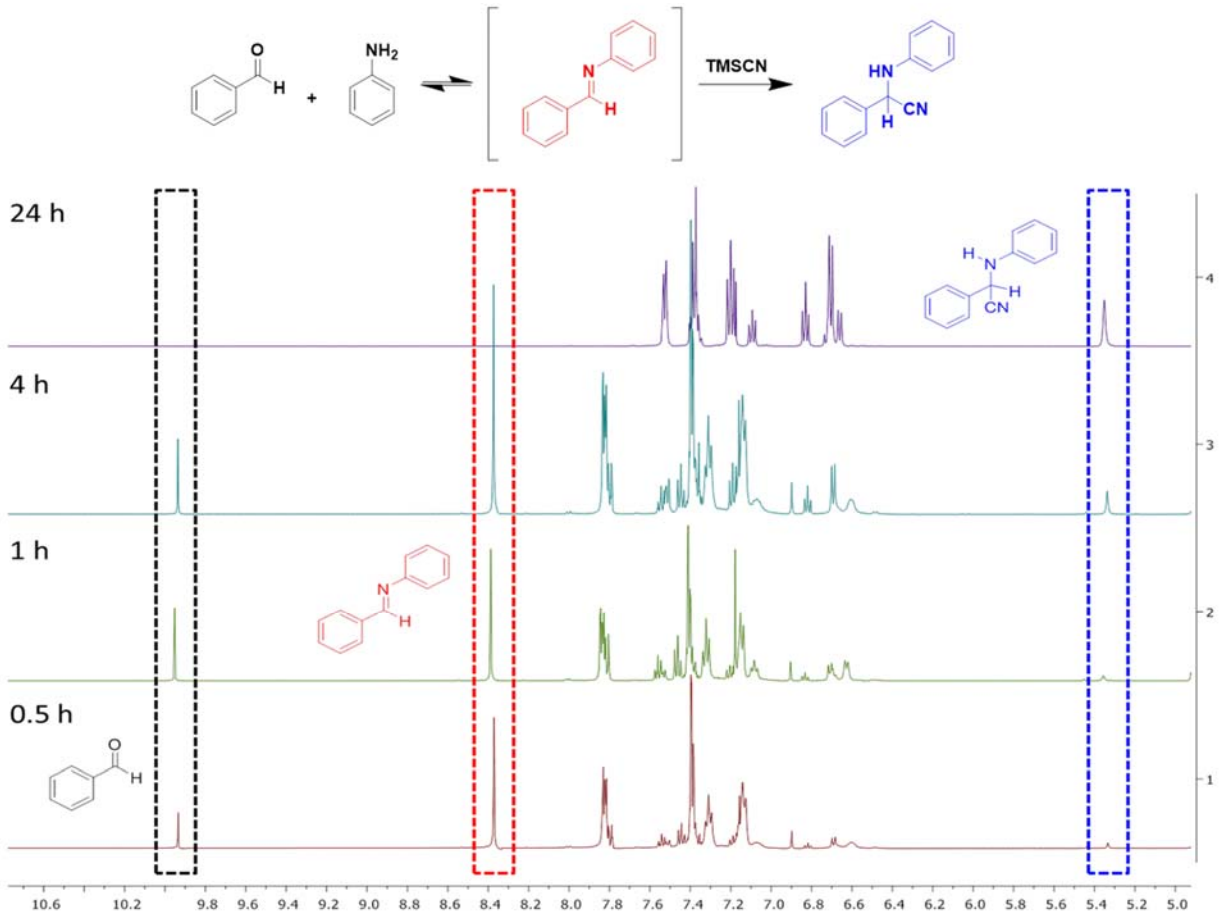

Figure S5. *Kinetic study by ^{1}H-NMR ($CDCl_3$) of the batch Strecker reaction of benzaldehyde (**10**), aniline (**12**) and TMSCN. Conditions: 1 eq benzaldehyde (**10**) (5 mmol), 1 eq aniline (**12**) (5 mmol), 1.2 eq TMSCN (6 mmol), 250 mg cat-**9a**, 5 mL 2-MeTHF, r.t. The benzaldehyde singlet proton signal is observed at 9.9 ppm. The imine intermediate singlet proton signal is observed at 8.4 ppm. The Strecker product singlet proton signal is observed at 5.3 ppm. The evolution of the reaction with the appearing of the imine intermediate and posterior disappearing could be observed.*

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4. Set-up used for the continuous flow three-component Strecker reaction of benzaldehyde (10), aniline (12) and TMSCN catalysed by 9a.

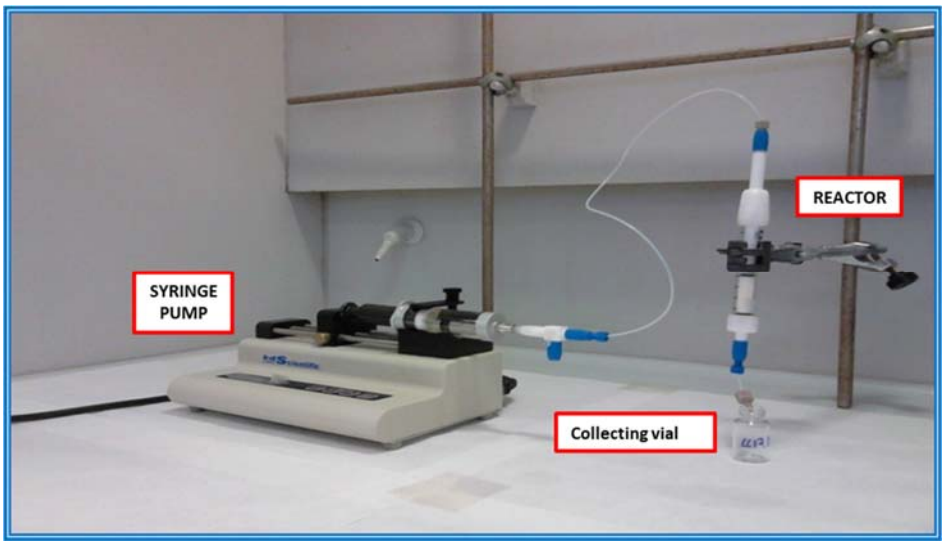

Figure S6. *Set-up used for the continuous flow Strecker reaction of benzaldehyde (**10**). Syringe pump from kdScientific and Hamilton 25 mL syringe were used. Glass Omnifit column 006RG-10-10 (0.7854 cm diameter x 10 cm length) was used as reactor. The syringe was filled with a mixture of benzaldehyde (**10**), aniline (**12**) and TMSCN (1:1:1.2) 1.5 M in 2-MeTHF. The reactor was packed with 850 mg of SILLP-**9a**. The samples were collected in 12 mL glass vials.*

5. Different set-ups/strategies used for the continuous flow three-component Strecker reaction of 3-octanone (6), aniline (12) and TMSCN catalysed by 9a.

Imine intermediate formation showed to be the yield limiting step in the continuous flow Strecker reaction of the 3-octanone (**6**). One strategy tested to improve imine formation was to pump the ketone and the amine together in a coil reactor (0.2 mL, 8 min residence time) set-up before the fixed bed reactor loaded with **9a** (see Figure S7). Increasing the contact time of ketone and aniline can favor the formation of the ketamine prior to the action of the catalyst **9a**.

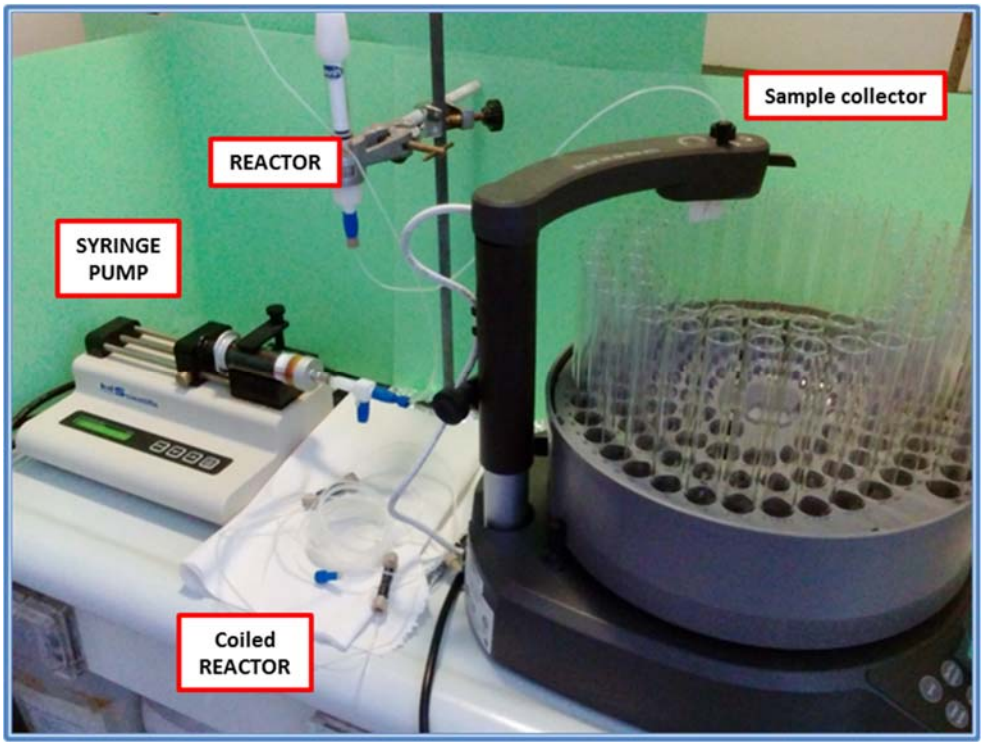

Figure S7. Set-up used to perform the Strecker reaction of 3-octanone (**6**) with a previous coil reactor to favor the imine intermediate formation. Syringe pump from kdScientific and Hamilton 25 mL syringe were used. Glass Omnifit column 006RG-10-10 (0.7854 cm diameter x 10 cm length) was used as reactor. Syringe was filled with a mixture of 3-octanone (**6**), aniline (**12**) and TMSCN (1:1:1.2). The coil reactor was 1 m length and 0.2 mL volume. Omnifit column reactor was filled with 600 mg of SILLP **9a**. Fractions were collected at the exit of the column reactor using a Collector "GE Healthcare Frac-920".

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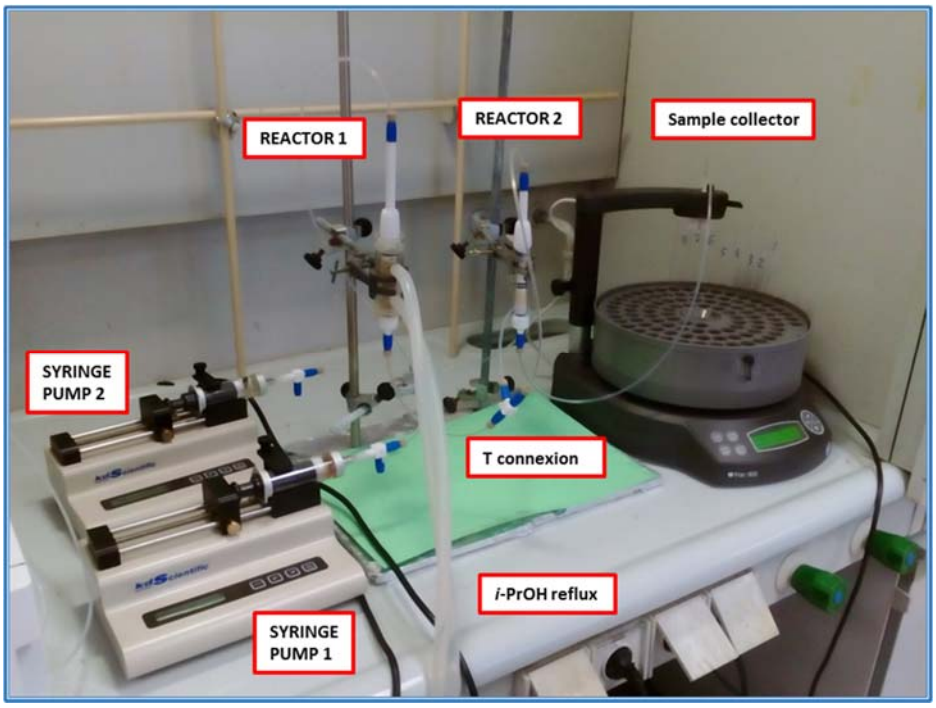

The second strategy used in order to push further the formation of the selectivity limiting ketamine, was to build a previous dehydrating catalytic reactor to favour the formation of the imine (see Figure S8).

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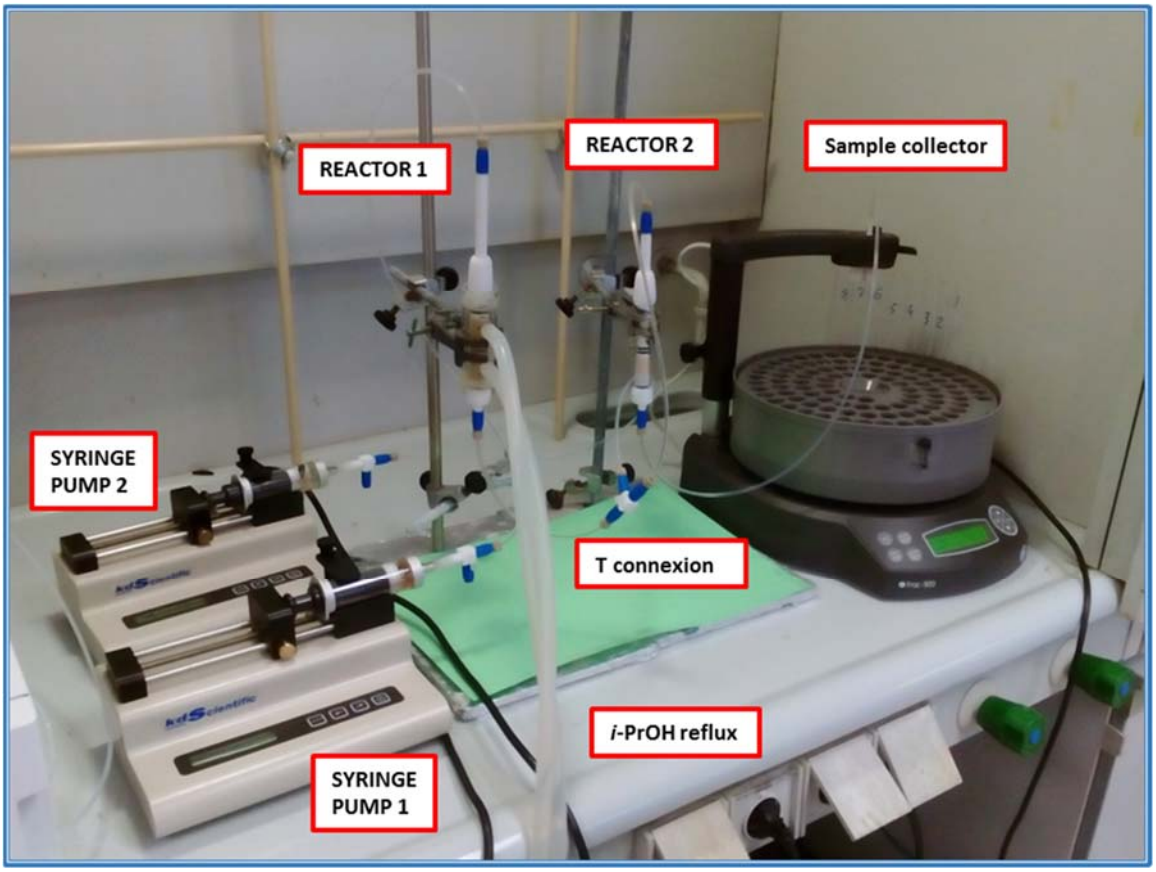

Figure S8. Set-up used to perform the three-component Strecker reaction of 3-octanone (**6**) with a previous dehydrating catalytic fixed-bed reactor to favour the formation of the imine intermediate. Syringe pumps from kdScientific and Hamilton 25 mL syringes were used. Glass Omnifit columns 006RG-10-10 (0.7854 cm diameter x 10 cm length) were used as fixed-bed reactors. Syringe 1 was filled with a mixture of 3-octanone (**6**) and aniline (**12**) (1:1). Syringe 2 was filled with TMSCN. Reactor 1 was packed with 4Å molecular sieves (1.2 g), P_2O_5 (1.2 g) and montmorillonite K10 (1.2 g). Reactor 1 was heated at 60 ºC with a *i*-PrOH reflux. Reactor 2 was packed with 600 mg of SILLP **9a**. Fractions were collected at the exit of reactor 2 using a sample collector "GE Healthcare Frac-920".

6. NMR spectra

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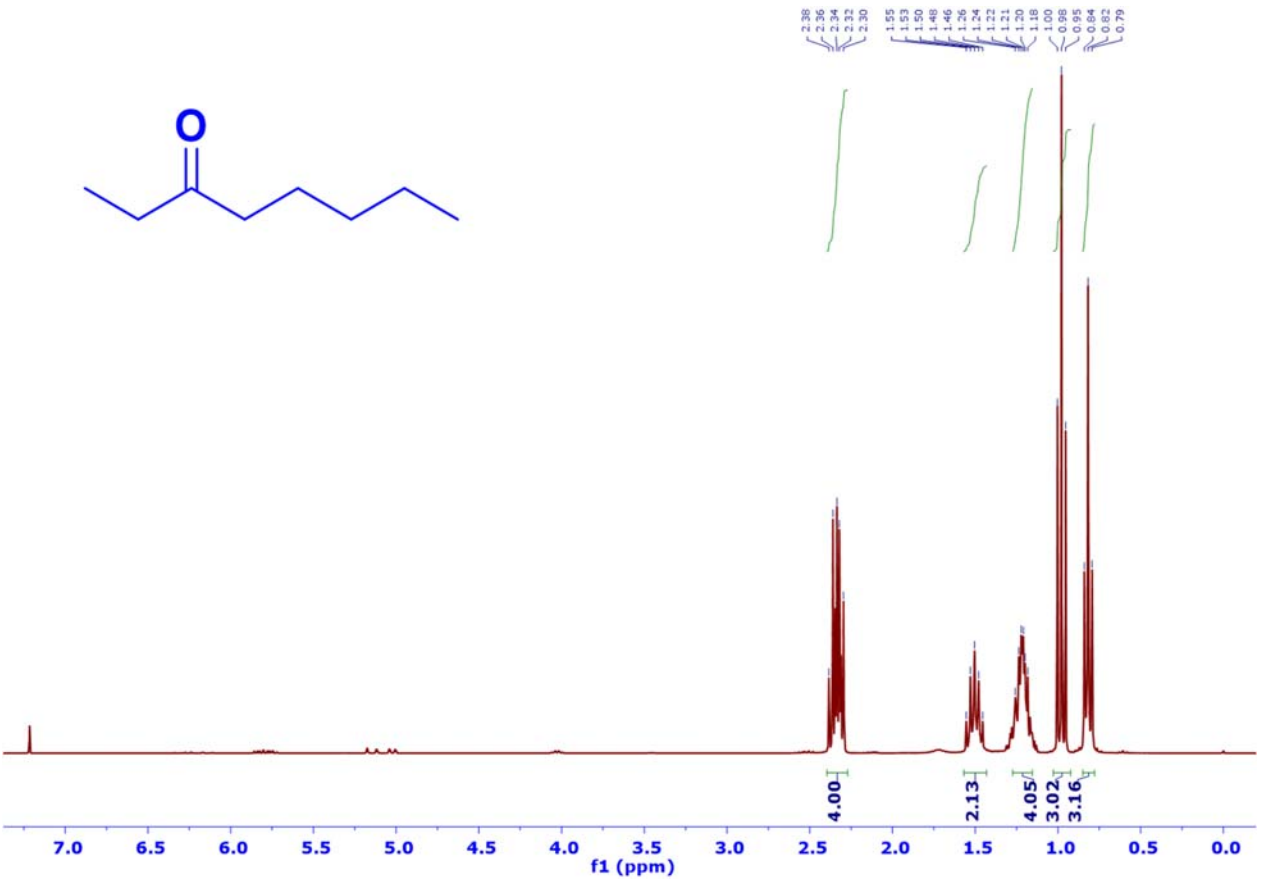
^{1}H-NMR of 3-octanone (6)



^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.38-2.30 (m, 4H), 1.50 (q, 2H), 1.26-1.18 (m, 4H), 0.98 (t, 3H), 0.82 (t, 3H)

^{1}H-NMR data of 2-ethyl-2-((trimethylsilyl)oxy)heptanenitrile (7)

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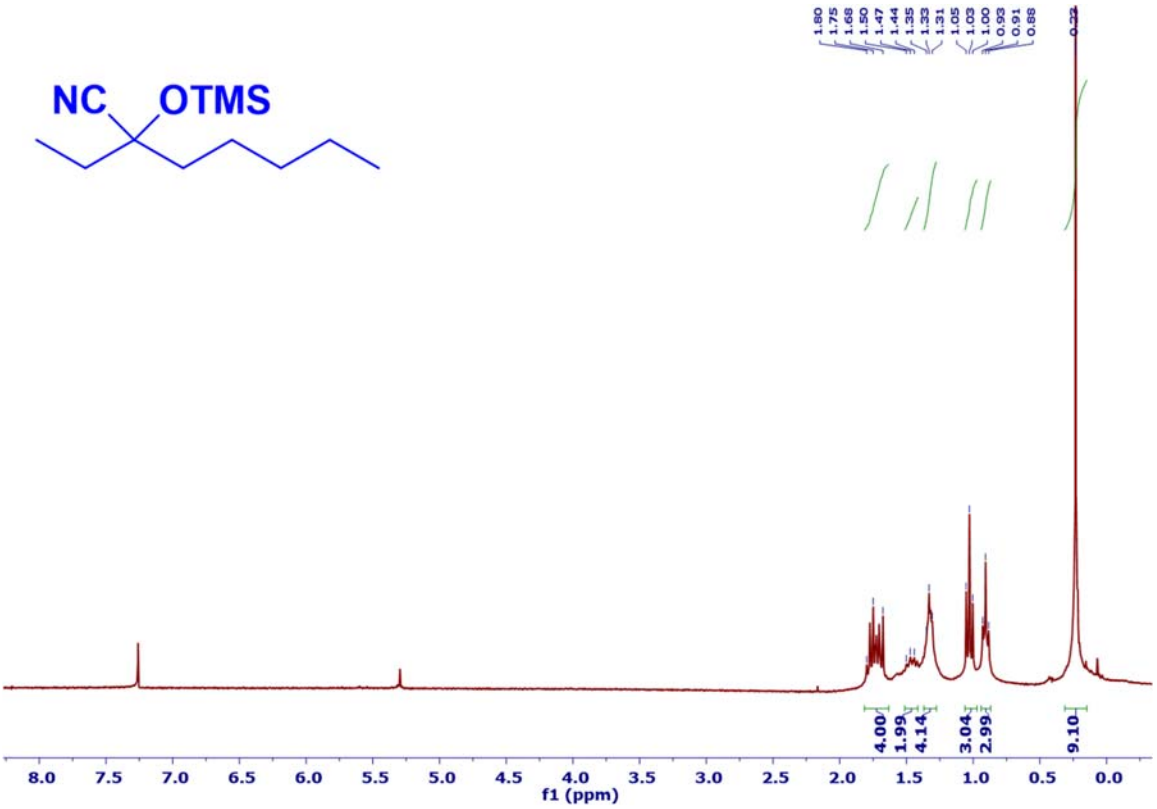

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.80-1.68 (m, 4H), 1.50-1.44 (m, 2H), 1.35-1.31 (m, 4H), 1.03 (t, 3H), 0.91 (t, 3H), 0.23 (s, 9H)

^{1}H-NMR data of 2-phenyl-2-(phenylamino)acetonitrile (13)

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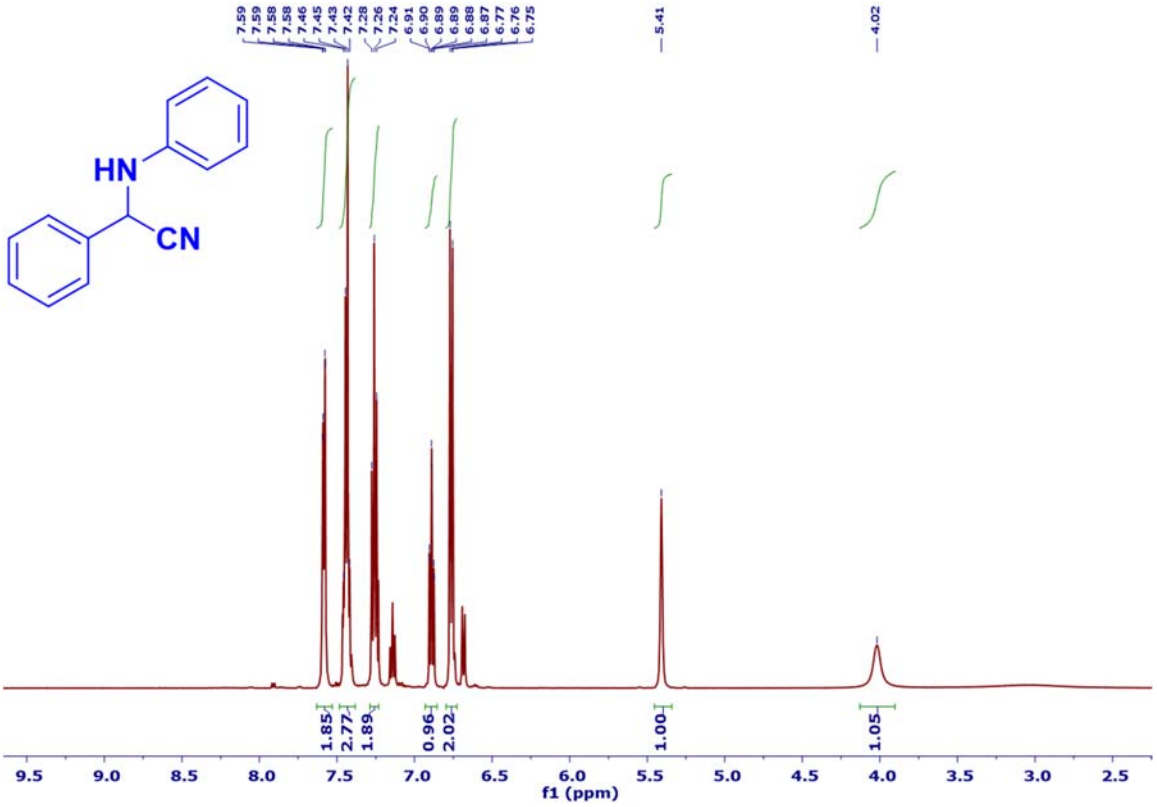

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.58 (dd, 2H), 7.47-7.40 (m, 3H), 7.26 (t, 2H), 6.89 (td, 1H), 6.76 (dd, 2H), 5.41 (s, 1H), 4.02 (bs, 1H)

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