Divergent Multistep Continuous Synthetic Transformations of Allylic Alcohol Enabled by Catalysts Immobilized in Ionic Liquid Phases.

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Introduction

Sustainability is not only a challenge but also an opportunity to radically transform synthetic processes in new emerging technologies.[1] In this context, there is a need to develop alter- native approaches that mimic natural processes and can inte- grate multiple and consecutive catalytic sequences.[2–5] These transformations can be performed to reduce their environmen- tal impact under alternative reaction conditions by using neo- teric solvents such as water, dimethyl carbonate, ionic liquids (ILs), or supercritical fluids.[6] Indeed, these solvents can con- tribute 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, thus enhanc- ing its activity, recyclability, stability, or selectivity. At the same time, these new synthetic methodologies also face challenges related to the paradigm shifts that the chemical industry is ex- periencing. These include replacing discontinuous processes requiring multiple-unit operations by highly flexible and inte- grated continuous-flow catalytic processes.[7–11] In this regard, the development of multicatalytic platforms that allow sequen- tial and controllable processes is highly desirable. This can lead to complex syntheses through reduced external intervention and minimal environmental impact.[12–16] These platforms facili-

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tate: 1) greater reproducibility of reactions; 2) easy scaling, which facilitates the direct transfer of laboratory results to pro- duction; 3) reduction in environmental impact; 4) improved safety; 5) synthesis of new high-value chemical entities; and

6) intensification of the process. Therefore, smaller-size systems can be used, offering cost reduction and higher productivity. Furthermore, the assembly of these synthetic platforms in a di- vergent telescopic sequential fashion can lead to systems able to produce molecules with wide structural diversity.[17,18]

In this context, the main aim of this work focused on the di- vergent synthesis of a-cyano-amines and cyanohydrin trime- thylsilyl ethers, as depicted in Figure 1. Both families of com-pounds are very useful synthetic intermediates for the prepara- tion of a wide variety of organic molecules with relevant phar- macological properties.[19,20] a-Cyano-amines can be obtained through the three-component Strecker reaction by using an al- dehyde or ketone, an amine, and a cyanide source. In the ab- sence of the amine and with the selection of the appropriate catalyst, the same reactants can alternatively be transformed in cyanohydrin trimethylsilyl ethers, which can easily be convert- ed into functionalized a-hydroxy acids, a-hydroxy aldehydes, b-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 treat-ment. To overcome these problems, trimethylsilyl cyanide (TMSCN) has proven to be an effective, relatively safe, and easy to handle cyanide anion source.[20] Both reagents use ketones or aldehydes as starting materials, which can be obtained from the isomerization of readily accessible allylic alcohols in a ruthenium-catalyzed 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 two alternative families of intermediate compounds. Such platforms allow the reduction of the environmental impact and enable the simple separation and reuse of the catalysts, providing products not contaminated by traces of either the catalyst or solvent.

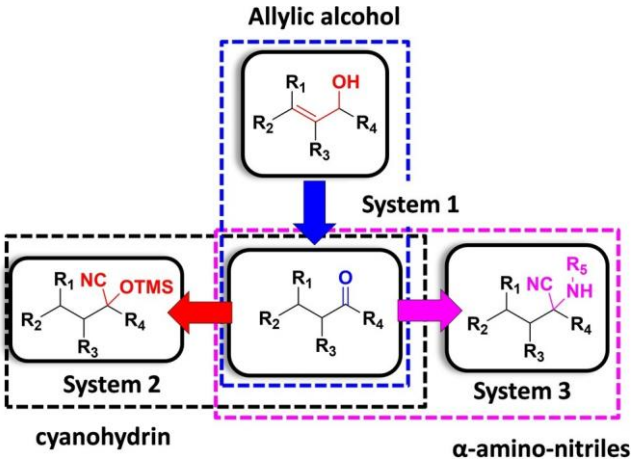
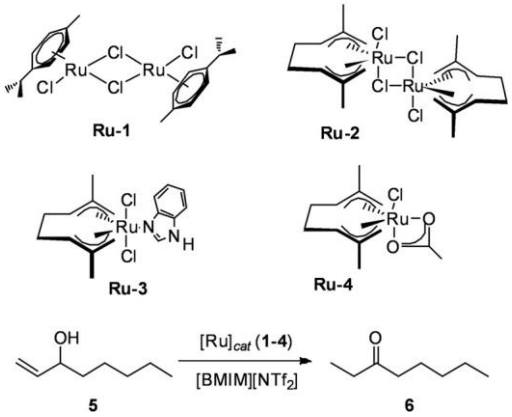


Figure 1. Divergent synthesis based on continuous-flow catalytic platforms.

Results and Discussion

Catalytic platform 1: Ru-catalyzed isomerization of allylic alcohols into ketones

Ru complexes are highly efficient catalysts for the isomeriza- tion of different allylic alcohols under mild conditions with neoteric solvents such as water,[22] deep eutectic solvents,[23] or ILs such as [BMIM][BF4] (BMIM = 1-butyl-3-methylimidazolium).[24,25] With this IL, the catalysts could be recovered during at least five consecutives batches by using hexane as the ex- traction solvent, although the catalyst showed a certain degree of deactivation upon recycling. To develop a catalytic platform based on a Ru catalyst that can efficiently work for multiple cycles and allowing a simple recycling, the combination of ILs with supercritical CO2 (scCO2) provides a relatively simple and straightforward technological solution.[26] Generally, the IL phase is used for the homogeneous immobilization of the cat- alyst (e.g., metal complexes, enzymes, and nanoparticles), whereas the scCO2 phase is intended to favor 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 optimized yields and productivities by fine-tuning of the contact time of the scCO2/IL phases through 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, and they can operate 24/7, requiring less work force for opera- tion, reducing the equipment size, and maximizing productivi- ty.



Scheme 1. Model isomerization reaction and Ru catalysts used.

To develop such a catalytic platform, four different Ru complexes were initially screened for the batch isomerization of 1- octen-3-ol in an IL phase (Scheme 1). The reaction was per- formed by using a solution of the Ru complexes in [BMIM] [NTf2] (0.5 wt%) and employing a 1 mol % loading of the cata- lyst with respect to the alcohol. The reaction was monitored at 1 and 17 h. The results are summarized in Table 1. The RuIV-ace- tate complex Ru-4 was the organometallic catalyst that showed the highest activity, reaching > 99 % of isomerization yield (Scheme 1) in only 1h [turnover frequency (TOF): 100 h@1]. The other RuIV catalysts (Ru-2 and Ru-3) led to lower yields in 1h (67 and 73 %, respectively, Table 1), whereas the RuII complex (Ru-1) showed almost no activity (< 10 %) duringthe same period. The four Ru complexes afforded good-to-excellent isomerization yields after 17 h. These results were in agreement with previous results showing that Ru-4 was an ef- ficient catalyst for this reaction in both water (0.2 mol %,> 99 %, 5 min, TOF: 6000 h@1) and [BMIM][BF4] (1 mol %, > 99 %, 5 min, TOF: 1200 h@1).[25] The lower activity observed here was most likely associated with the less polar nature of [BMIM][NTf2].

Table 1. Isomerization of 5 in [BMIM][NTf2] with 1 mol % Ru catalyst.[a]

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

[a] 5 (2 mmol), IL (1 g per mmol of reagent), catalyst (1 mol %), room tem- perature. [b] Determined by GC.

Based on these results, the reaction was studied by using an IL/sCO2 system, enabling the semi-continuous production of the ketone without the use of any additional organic solvent (Figure 2). The IL phase was used simultaneously as reaction solvent and homogenous medium for catalyst immobiliza- tion.[27] Despite the higher activity of Ru-4, the initial experi- ments were performed with the dimeric complex Ru-2, which displayed a reasonable activity and is commercially available. A schematic diagram of the reactor setup is depicted in Figure 2. The allylic alcohol was delivered by an HPLC pump, whereas a refrigerated head scCO2 pump was used to feed the CO2. Initially, the flow rates were set to 0.1 mL min@1 for 1- octen-3-ol (5) and 1.5 mL min@1 for CO2 at 75 8C and 10 MPa for an additional 7h period, achieving 95 % conver- sion of the allylic alcohol into the corresponding ketone (Cycle II; Figure 3). An additional cycle was repeated under the same conditions, leading to comparable results (93 % of the product was the 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 di- ethyl ether, confirming the presence of an apprecia- ble residual mass of the ketone (718 mg, corre- sponding to ca. 24 %). However, it is important to note that the product extracted with scCO2 was a clear uncolored oil without any trace of IL or cata- lyst, whereas the product obtained by ether extrac- tion showed traces of the catalyst (colored solution) and the IL phase (Figure S1 in the Supporting Information).

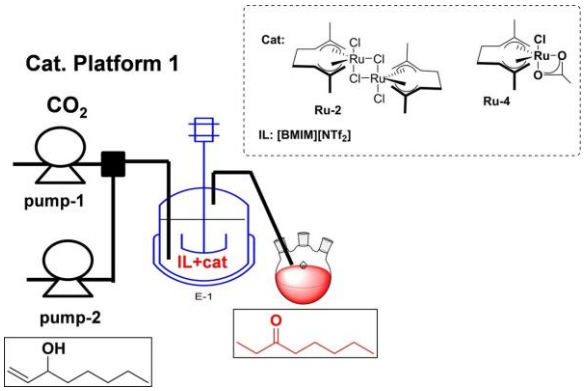


Figure 2. Schematic representation of the IL/scCO2 setup used for the isomerization of 5 catalyzed by Ru-2 and Ru-4.

Encouraged by these results, the catalyst Ru-4 was assayed under similar conditions (0.27 mol % sured from the start of the feed of the allylic alcohol 5). Ru-2 (154 mg) was dissolved in 10.5g [BMIM][NTf2] (1.5 wt%) (Figure 3). The reaction was performed by first feeding 5 (3 mL) to the reactor at a flow rate of 0.1 mL min@1. After this, the system was filled with CO2 until a pressure of 10 MPa was reached, and then, maintaining a constant flow rate of 1.5 mL min@1, samples were collected at different times and an- alyzed by GC. The initial samples showed a low degree of iso- merization owing to the short contact time of the allylic alco- hol with the complex. The degree of isomerization increased with time, reaching approximately 50 and 70 % after 3 and 4 h, respectively (Cycle I, Figure 3).

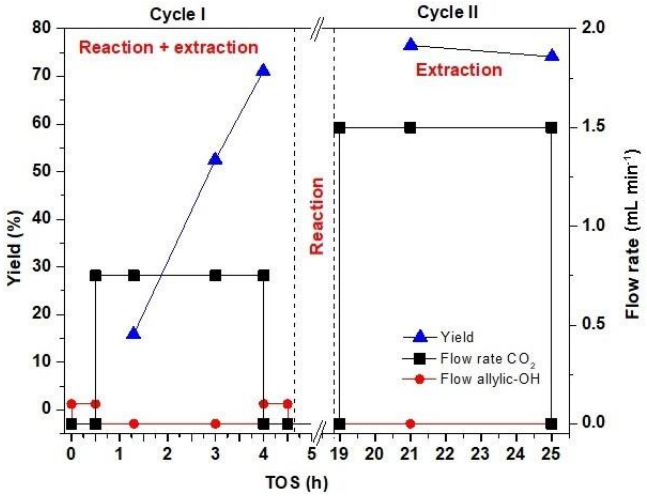


Figure 3. Results obtained for the isomerization of 5 catalyzed by Ru-2 in a [BMIM][NTf2]/scCO2 system at 75 8C and 10 MPa, (TOS: Time on stream, mea-

These results demonstrated both the feasibility of the iso- merization with the Ru complex immobilized in the homoge- nous liquid IL phase and the need for longer reaction times. Therefore, the reactor was charged again in a second cycle with 5 (3 mL), and the reaction was left to proceed for 15 h before restarting the CO2 pumping and collecting the product catalyst loading, Figure 4). When the reactor was loaded with 5 (2 mL) and left to react overnight, the extract obtained under these conditions (1.5 mL min@1 flow rate of CO2) 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. Notably, cycles II and III altogether provided a turnover number (TON) of 1425 moles 6 per mol Ru-4.

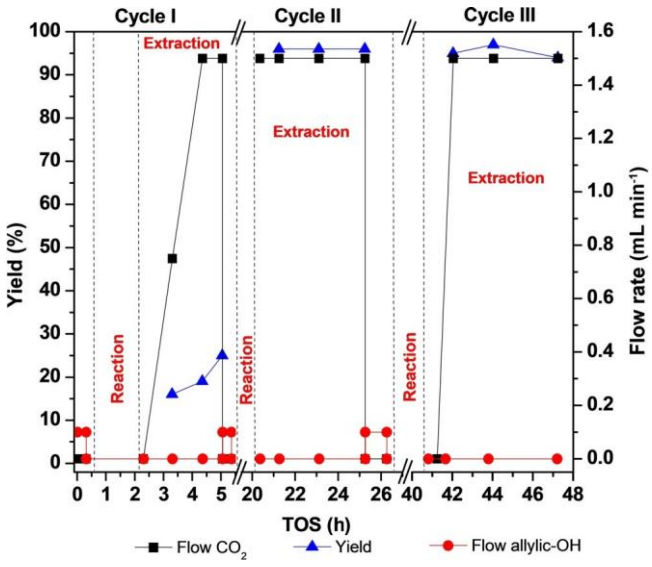


Figure 4. Results obtained for the isomerization of 5 catalyzed by Ru-4 in a [BMIM][NTf2]/scCO2 system at 75 8C and 10 MPa.

Catalytic platforms 1+2: from allylic alcohols to cyanohydrins

After we established that the Ru-4/IL/scCO2 combination can efficiently transform the allylic alcohol 5 into ketone 6, the fur- ther transformation of 6 into its cyanohydrin trimethylsilyl ether (7) by reaction with TMSCN was evaluated by using an organocatalytic system (catalytic platform 2) with the efficient catalytic system reported by us for this transformation and based on a supported IL-like phase.[28] The conversion of 6 into 7 was evaluated by directly pumping 6 through a fixed-bed re- actor containing catalyst 8 (Figure 5).

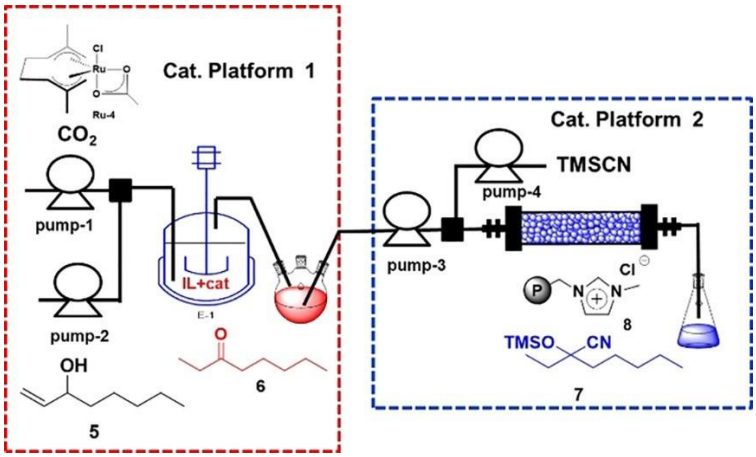


Figure 5. Schematic representation of the setup combining the catalytic platforms1 and 2 for the conversion of 5 into 7 catalyzed by Ru-4 and 8.

A summary of the results obtained with a flow rate of 0.1 mL $min^{@1}$ of a mixture of 1 equiv. of 6 and 1.2 equiv. ofTMSCN at room temperature and under solvent-free conditions is shown in Figure 6. Under this experimental setup, 6 (6 mL, from platform 1) was transformed into the corresponding cya- nohydrin 7 with an excellent yield (99 %). Therefore, the combi- nation of these two systems can be used for the efficient syn-thesis of cyanohydrins starting from allylic alcohols with pro- ductivities for both synthetic transformations of 1.08 kg of6 $g^{@1}h^{@1}L^{@1}$ and 3.8 kg of 7 $g_{cat8}{}^{@1}h^{@1}L^{@1}$ in terms of mass ofproduct obtained per gram of catalyst and per reactor volume in 1 h

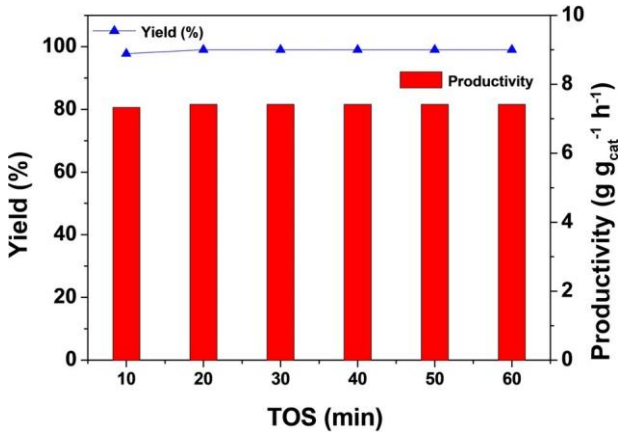


Figure 6. Catalytic platform 2. Solvent-free conversion of 6 obtained through catalytic platform 1 into 7. Flow rate: 0.1 mL min@1. 6/TMSCN 1:1.2 molar ratio. Residence time: 20 min. 600 mg catalyst 8.

Catalytic platforms 1+3: from allylic alcohols to a-amino-ni- triles

The classical Strecker reaction is one of the simplest and most economical methods for the synthesis of racemic a-aminoni- triles.[29] Polystyrene-immobilized catalysts, with either Ru or Sc as the Lewis-acid site, have been re- ported to promote this three-component reaction of aldehydes, amines, and TMSCN with excellent con- versions.[30] However, analogous reactions with ke- tones require significantly more reactive catalysts such as the polystyrene-supported gallium triflate [PS-Ga(OTf)2], which has been reported to provide the targeted a-aminonitriles in high yield and purity.[31]

Task-specific supported IL-like phases modified with sulfonic groups (9 a, Figure 7) can be used to complex lanthanide triflates, in particular scandium triflate [Sc(OTf)3].[32,33] In this regard, the presence of the imidazolium fragments in 9a can contribute to the improvement of the catalytic activity provided by the Lewis-acid units.[34–37] Such contribution is a summary of the results obtained with a flow rate of 0.1 mL min@1 of a mixture of 1 equiv. of 6 and 1.2 equiv. of TMSCN at room temperature and under solvent-free conditions is shown in Figure 6. Under this experimental setup, 6 (6 mL, from platform 1) was transformed into the corresponding cya- nohydrin 7 with an excellent yield (99 %). Therefore, the combi- nation of these two systems can be used for the efficient syn- thesis of cyanohydrins starting from allylic alcohols with pro- ductivities for both synthetic transformations of 1.08 kg of 6 g@1 h@1 L@1 and 3.8 kg of 7 gcat8@1 h@1 L@1 in terms of mass of product obtained per gram of catalyst and per reactor volume in 1 h absent in the analogous Sc-supported catalyst 9 b, prepared from a commercially available sulfonic polystyrene-divinylbenzene polymer (Amber- lyst 15).[38]

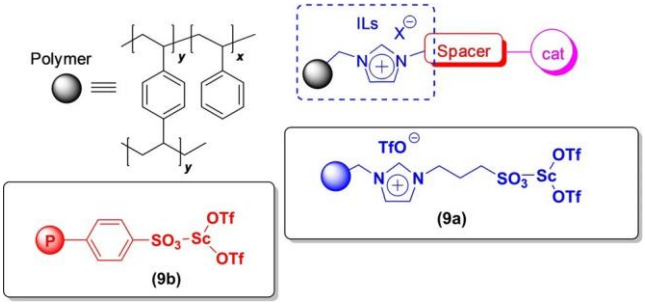


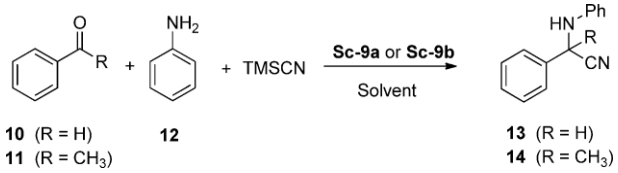
Figure 7. Polystyrene–divinylbenzene (PS-DVB)-supported Sc catalysts 9a and 9b.

Both catalysts, 9a and 9 b, were evaluated for the Strecker reaction between benzaldehyde (10), aniline (12), and trime- thylsilyl cyanide (TMSCN) (Scheme 2).[39] Under solvent-free conditions, benzaldehyde was smoothly converted in to the corresponding a-aminonitrile in the presence of 9a (entry 1, Table 2). Near-quantitative yields were achieved if the reaction was performed in the presence of an additional solvent (en tries 2–4) including the use of benign solvents such as 2- methyl-tetrahydrofuran (2-Me-THF) and dimethyl carbonate (DMC). If the reaction was performed in the presence of 9b with either acetonitrile (CH3CN) or 2-Me-THF as solvents, the yields (entries 5 and 6) were significantly lower than those ob- served for 9 a. This difference was lower for the reactions per- formed in CH3CN (99 vs. 84 %, entries 2 and 5). If the less reac- tive acetophenone (11) was used instead of benzaldehyde, the differences were even more pronounced. Catalyst 9a afforded moderate yields of 14 in 2-Me-THF (69 %, entry 8) and 20 % yield in CH3CN (entry 7), whereas catalyst 9b was not active for this reaction in any of the solvents evaluated (entries 9 and 10).

Table 2. Three-component Strecker reaction of 10 or 11 with 12 and TMSCN catalyzed by 9a or 9b.[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] 10 or 11 (1 equiv., 5 mmol), 12 (1 equiv., 5 mmol), TMSCN (1.2 equiv., 6 mmol), 9a or 9b (50 mg per mmol of 10/11), solvent (1 mL per mmol of 10/11), room temperature.



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

The different behavior of catalysts 9a and 9b highlights the key role played by the presence of IL-like fragments in 9 a. 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 9 b. As expected, this effect is more important in 2-Me-THF because CH3CN can compete with TMSCN, mini- mizing the “electrophile–nucleophile dual activation” of the re- actants with the IL-like units.

The long-term stability of catalyst 9a was studied with a continuous-flow reaction between benzalde- hyde, aniline, and TMSCN in 2-Me-THF. The flow con- ditions allow the catalyst stability to be evaluated in the absence of any physical abrasion of the polymer- ic beads associated with their extensive use under batch conditions.[40] As shown in Figure 8, when the reactants were initially pumped through a reactor packed with 9a (0.85 g) at 15 mL min@1, the obtained yield was > 99 % without any apparent activity decay during more than 24 h. Thereafter, the flow rate was increased to 30, 60, and 120 mL min@1 and still resulted in a very good activity (yield > 95 %). An intermediate flow-rate reduction to 15 mL min@1 provided yields > 99 %. No leaching of scandium firmed the stability of catalyst 9a for the Strecker reaction under flow conditions, with no detectable indication of deacti- vation for more than 75 h of continuous use. Increasing the flow rate provided important improvements in productivity. Therefore, at the higher flow rate (120 mL min@1) approximately 2.5 g of 13 per hour and gram of catalyst were produced, maintaining a 95% conversion of the reactants. Accordingly, with a small lab reactor loaded with approximately 2g of cata- lyst and using a flow rate of 0.12 mL min@1, approximately 121 g of 13 was obtained in only 24 h.

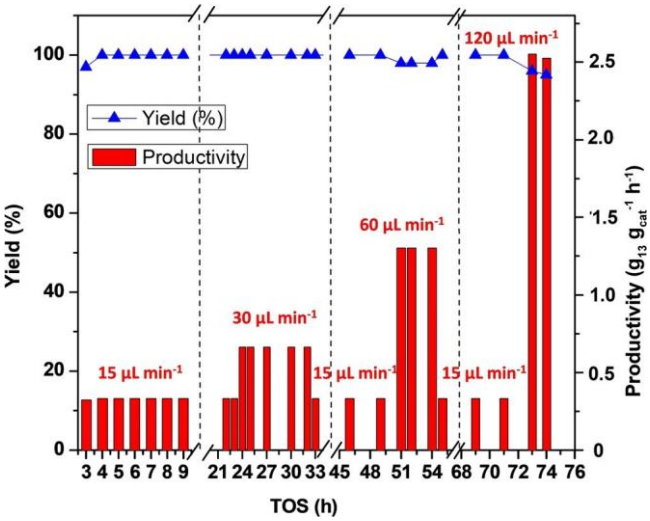


Figure 8. Yield of 13 versus TOS for the three-component Strecker reaction of 10, 12, and TMSCN catalyzed by 9a under continuous flow. 1.5 m in 2-Me- THF, 0.850 g 9a, 2.4 mL reactor volume.

The reaction of 6 with 11 and TMSCN was also evaluated under solvent-free batch conditions with catalyst 9 a, affording the corresponding a-aminonitrile 15 in 99 % yield (no traces of 7 were observed). This allowed us to study the telescoped transformation of the allylic alcohol 5 into the ketone 6 and then into the a-aminonitrile 15 by combining catalyst 9a (cat- alytic platform 3) and the Ru-4/IL/scCO2 system (catalytic plat- form 1) (Figure 9). The product extracted from platform 1 waswas detected in the liquid phase by inductively cou- pled plasma mass spectrometry. These results con-firmed the stability of catalyst 9a for the Strecker reaction under flow conditions, with no detectable indication of deacti- vation for more than

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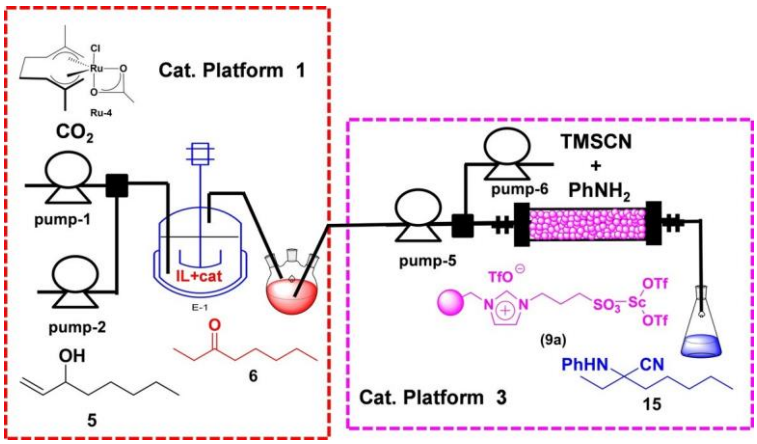

Figure 9. Schematic representation of the reactor setup combining catalytic platforms 1 and 3 for the conversion of 5 into 15 catalyzed by Ru-4 and 9a.

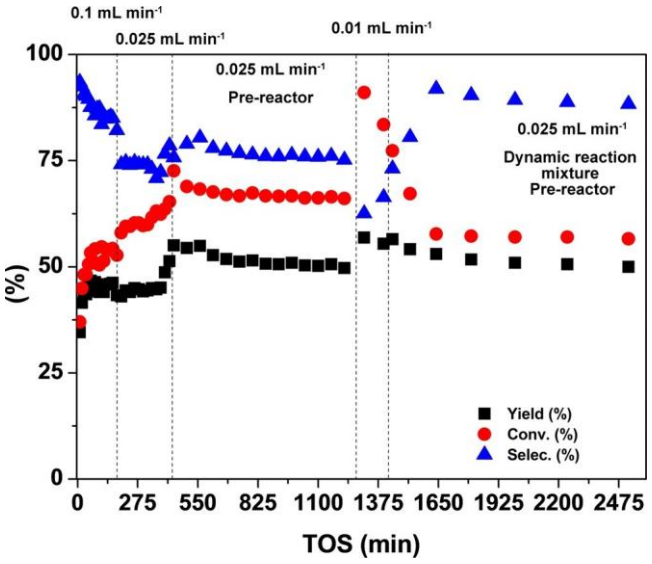

Figure 10. Results obtained by combining the catalytic platforms 1 and 3. Conversion, yield, and selectivity of 15 versus TOS for the Strecker reaction of 6, 12, and TMSCN catalyzed by 9a. 0.6 g 9a, 1.9 mL reactor volume.

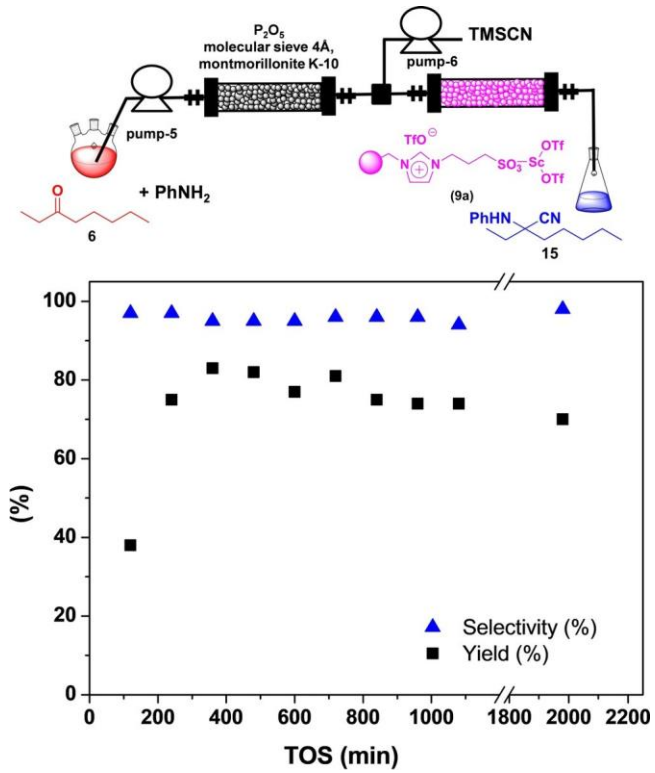

Figure 11. Yield and selectivity for 15 versus TOS for the Strecker reaction of 6, 12, and TMSCN catalyzed by 9a and setup used for the reaction. Reactor I: 4 a molecular sieves (1.2 g), P2O5 (1.2 g), and MM K10 (1.2 g), 3.9 mL re- actor volume. Reactor II: 9a (0.6 g), 1.9 mL reactor volume.

Finally, a further improvement in the formation of the keta mine was achieved by using a new fixed-bed reactor packed with equal amounts of two dehydrating agents (P2O5 and 4 a

molecular sieves) along with an acid montmorillonite (MM K10), which have been reported to promote the prepara- tion of imines under batch conditions (Figure 11).[41,42] There- fore, 6 and 12 were mixed together under solvent-free conditions for 12 h and then pumped through the first reactor heated at 60 8C (12 mL min@1 flow rate), and the solution at the outlet of this reactor was mixed with a flow of TMSCN (15 mL min@1) before entering the second fixed-bed reactor maintained at room temperature and packed with 9 a. Under these conditions, the yield was higher than 70 % and the selec- tivity was excellent (> 95 %). The final product (15) was obtained with productivities of 26.5 g 15 per day with only 0.6 g 9 a. Therefore, the combination of the catalytic platforms 1 (metal-catalyzed) and 3 (organo-catalyzed) was suitable for the telescoped preparation of a-cyanoamines from allylic alcohols.

Conclusions

The right combination of three different catalytic continuous- flow platforms, a divergent synthetic flow system for the prep- aration of both the protected cyanohydrin 8 and the a-amino nitrile 15 from the allylic alcohol 5, has been achieved. The long-term stability and the activity of each catalytic platform was evaluated and optimized. In all catalytic platforms, the ionic liquid (IL)-related species, as reaction media or as sup- ported catalysts (supported ionic liquid-like phases) played a key role. The results obtained for the Strecker reaction high- light the potential for catalytic applications of task-specific sup- ported IL-like phases containing specific functionalities (imid- azolium-sulfonic acid in this case). The three-component Strecker reaction of a non-reactive aliphatic ketone (6) was achieved by using a combination of dehydrating agents and supported catalysts in telescoped consecutive-flow mini-reactors. Therefore, the combination of allylic alcohol isomerization with the cyanosilylation and Strecker reactions, both for alde- hydes and ketones, gives access to a broad scope of valuable synthetic building blocks as protected cyanohydrins and a- amino nitriles with good yields in long-term stable continuous- flow procedures. The catalytic platforms 2 and 3 work under solvent-free conditions, and the neoteric solvents supercritical CO2 and 1-butyl-3-methylimidazolium triflate ([BMIM][NTf2]) used in platform 1 are the only solvents employed. Moreover, no purification step was needed between the catalytic plat- forms, and waste minimization was achieved in the whole pro- cess. Reasonable productivities can be obtained for the differ- ent catalytic and multicatalytic systems developed on the mul- tigram scale [gcat@1 h@1].

Experimental Section

Ruthenium complexes Ru-1–Ru-4[24] and supported ionic liquid-like phases (SILLPs) 8 and 9 a, b[28,32] were obtained according to previ- ously described procedures.

Batch isomerization of 1-octen-3-ol (5) into 3-octanone (6): 5 (0.315 mL, 2 mmol) was dissolved in [BMIM][NTf2] (2 g). The Ru cat- alyst (Ru-1–Ru-4, 0.02 mmol, 1 mol %) was added and the mixture was left at 808C under orbital stirring (220 rpm) for 1 h. Samples were periodically analyzed by GC. Batch three-component Strecker reaction of benzaldehyde (10) or acetophenone (11), aniline (12), and TMSCN catalyzed by 9a or 9b: 10 (0.515 mL, 5 mmol) or 11 (0.590 mL, 5 mmol), 12 (0.456 mL, 5 mmol), and TMSCN (0.758 mL 6 mmol) were mixed. Solvent (5 mL, except solvent-free cases) and catalyst (9a or 9 b, 250 mg) were added (50

mgmmol@1 10 or 11). The mixture was stirred for 24 h at room temperature. The samples were analyzed by 1H NMR spectroscopy.

Continuous-flow three-component Strecker reaction of benzal- dehyde (10), aniline (12), and TMSCN catalyzed by 9a: The reac- tor was set up by introducing SILLP-9a (850 mg) in a glass Omnifit column 006RG-10-10 (0.7854 V 10 cm), which was connected at its head to a KdScientifics model syringe pump. A 25 mL Hamilton sy- ringe filled with 10, 12, and TMSCN (1:1:1.2) was used. The mixture of reagents was pumped through the catalytic bed at different flow rates ranging from 0.015 to 0.12 mLmin@1. Aliquots were taken at constant time intervals and analyzed by 1H NMR spectroscopy.

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

Continuous-flow three-component Strecker reaction of 3-octa- none (6), aniline (12), and TMSCN catalyzed by 9a: The reactor was set up by introducing SILLP-9a (600 mg) in a glass Omnifit column 006RG-10-10 (0.7854 V 10 cm). The reagents mixture was pumped through the reactor by using Hamilton syringes in KdScientifics syringe pumps. Several different strategies were used to favor the previous formation of the ketimine. Method 1: A mix- ture of 6, 12, and TMSCN (1:1:1.2) was pumped through a coil reac- tor at 0.025 mL min@1 (1 m, 0.2 mL, 8 min residence time) set up before the fixed-bed reactor loaded with 9 a. Aliquots were taken at constant time intervals and analyzed by GC. Method 2: A mix- ture of 6 and 12 (1:1) was stirred at room temperature overnight (15 h). Then, TMSCN was added (1.2 molar equiv.), and the mixture was pumped through the fixed bed reactor loaded with 9a by using a 25 mL Hamilton syringe and a KdScientifics model syringe pump. Aliquots were taken at constant time intervals and analyzed by GC. Method 3: An Omnifit column 006RG-10-10 (0.7854 V 10 cm) was packed with 4 a molecular sieves (1.2 g), P2O5 (1.2 g), and montmorillonite K10 (1.2 g). The reactor was heated at 60 8C by iPrOH reflux and was connected at the head to a KdScientifics model syringe pump. A mixture of 6 and 12 (1:1) was pumped through the reactor at 0.012 mLmin@1. After this reactor, a T-piece was connected, and TMSCN was pumped at 0.013 mL min@1, join- ing the previous reagents mixture before entering the reactor packed with 9 a. Aliquots were taken at the exit of the second re- actor and analyzed by 1H NMR spectroscopy.

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Conflict of interest

The authors declare no conflict of interest.

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