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Supported Ionic Liquid-Like Phases (SILLPs) as Immobilised Catalysts for the Multistep and Multicatalytic Continuous Flow Synthesis of Chiral Cyanohydrins

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Supported Ionic Liquid-Like Phases have been found to be efficient organocatalysts for the synthesis of cyanohydrin esters under solvent-free conditions by an "electrophile-nucleophile dual activation" based on hydrogen bond formation. The combination of multiple and consecutive multicatalytic steps in a single and integrated cascade process of organocatalytic SILLPs with commercially available supported *Candida antarctica* lipase type B (CAL-B) has allowed developing an efficient process for the multicatalytic synthesis of enantiopure cyanohydrins under flow conditions.

Introduction

Ionic Liquids (ILs) have emerged as exceptionally interesting systems in many fields, including their use as reaction media for catalytic processes.[1,2,3] In this context, a great effort has been devoted to develop ILs with modified functionalities (Task-Specific ILs-TSILs) in order to introduce groups providing Brönsted and Lewis acidic o basic behaviour, organocatalytic or organometallic properties, all of which can display a catalytic activity.[4] In the search of practical applications of these catalytically active TSILs, the full recovery of the catalytic system needs to be always considered. Therefore, the use of supported IL-phases has gained importance in this field.[5,6,7,8] For this purpose, the covalent attachment of IL-phases to an organic polymeric support has been demonstrated to transfer to the surface of the polymer some of the main features of ILs at the molecular level (stability, tuneable polarity, etc.) while avoiding the possibility of leaching.[9,10,11] On the other hand, the presence of the polymeric backbone offers an additional design vector to optimise the macroscopic and process properties of the overall catalytic system.[12,13] Indeed, these supported ionic-liquid like phases (SILLPs) can be applied as "*solid ionic solvents*" for catalytic processes in an analogous way to bulk ILs but simplifying product isolation and recycling of the catalyst-IL-phase. As for bulk ILs, structural changes/modifications in both cation and anion result in widely varying properties of the supported ILs, allowing their tuning for the specific needs of a given catalytic process.[14,15] This approach combines the advantages of ILs as catalyst supports and modifiers with the use of solid phase chemistry, enabling not only flow processes,[16–26] but the development of one-pot multicatalytic multi-component transformations integrating several synthetic reactions in a single process.[27,28] The inspiration for this strategy is the biosynthetic machinery operating in nature, where potentially incompatible chemical transformations are separated by compartmentalisation, with reactive intermediates being passed from one unit to the next one. Although past decades have seen a significant progress in this direction, one-pot multicatalytic reactions are still not of general application.[29] The one-pot combination of catalytic and biocatalytic processes is an even more challenging issue. Although different strategies have been assayed to circumvent their mutual inactivation,[30,31] the strong potential negative interferences between the components of both systems (reagents, products and catalysts) and the conditions needed for both processes have often hampered the development of one-pot sequential telescoped synthetic processes of this nature.

Here we report a methodology for the continuous flow synthesis of cyanohydrins based on the combination of multiple and consecutive multicatalytic steps in a single and integrated cascade process, where organocatalysts based on so-called Supported Ionic Liquid-Like Phases play a key role. The combination of organocatalytic SILLPs with commercially available supported *Candida antarctica* lipase type B (CAL-B) has allowed developing an efficient process for the multicatalytic synthesis of enantiopure cyanohydrins under flow conditions.

Results and Discussion

Cyanohydrins have considerable synthetic potential as chiral building blocks allowing their transformation into a large number of chiral molecules, especially in the field of pharmaceuticals and agrochemicals.[32] Different methodologies have been developed for their synthesis in both racemic and enantiopure forms. A majority of methods reported for the preparation of enantiopure cyanohydrins are based on the

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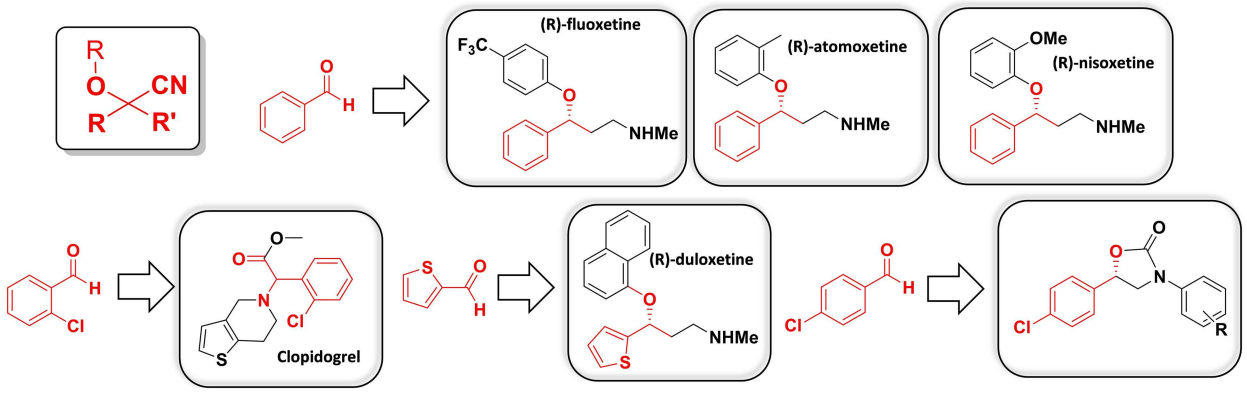
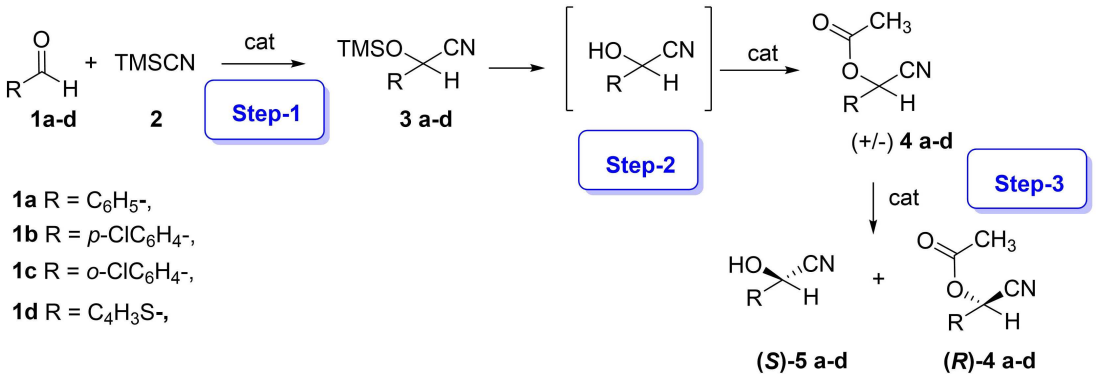


Figure 1. Structure of drugs synthesisable through cyanosilylation of different aldehydes.



Scheme 1. Synthesis of chiral cyanohydrins by multiple catalytic cascade reactions.

asymmetric addition of a cyanide derivative, such as a silyl cyanide, a cyanoformate, a cyanophosphate, or an acyl cyanide, to a prochiral carbonyl compound by using a (chiral) Lewis acid or a Lewis base catalyst or a combination of both types of catalysts.[33,34] Alternatively, HCN biocatalytic addition has been shown to provide high selectivity to a variety of prochiral aldehydes. These two methods, however, present some limitations. The first one requires the use of expensive chiral organometallic systems, while for the biocatalytic approach, albeit being more environmentally friendly,[35] the reversibility of the reaction may cause deterioration of the enantiomeric excess.[36,37] Thus, the design of simple and highly enantioselective processes with a low environmental footprint is still needed.

In this study, four specific different aldehydes (**1**–**4**) for which the corresponding cyanohydrins are key intermediates for the total synthesis of different commercial drugs (Figure 1) were selected as the starting materials.[38]

Scheme 1 depicts the general synthetic methodology proposed to obtain the corresponding chiral cyanohydrins from simple available aldehydes. The process requires three consecutive steps involving four catalytic reactions: 1) organocatalytic cyanosilylation of the aldehydes; 2) transformation into the corresponding methyl ester, which requires two consecutive reactions, first the hydrolysis of the cyanosilyl ether and then the formation of the corresponding ester; 3) the enzymatic kinetic resolution of the resulting cyanohydrin ester by transesterification in presence of alcohol. In this way, at least three different catalysts are required to develop a single-pot process.

It has been recently reported that Supported Ionic Liquid-Like Phases (SILLPs) can efficiently catalyse the cyanosilylation reaction of aldehydes and ketones (step-1).[39] Table 1 shows that by using **6** (Figure 2) as a simple supported organocatalyst the four aldehydes considered could be converted into the corresponding cyanosilyl ethers (**3a**–**d**) with excellent yields.

Table 1. Batch multistep consecutive synthesis of cyanohydrins.

	Substrate	Step-1[e]	Step-2[f]	Step-3[g]	
Entry	R	Yield [%][a]	Yield [%][b]	Yield [%][c]	*ee* [%][d]
1	C_6H_5-	99	99	56	>99
2	*p*-ClC_6H_4-	95	99	57	>99
3	*o*-ClC_6H_4-	95	99	51	>99
4	C_4H_3S-	95	99	52	>99

[a] Conditions: 1 eq RCHO, 1.2 eq TMSCN; rt, 24 h, Cat: 25 mg per mmol of RCHO. [b] Conditions: 1 eq substrate, 2 eq Ac_2O, 40 °C, 24 h, 50 mg of cat. per mmol of substrate. [c] Conditions: 9.8 mL 2-Me-THF, 0.15 mL n-propanol and 100 mg CAL-B (Novozym 435) per mmol of substrate, 60 °C, 24 h, yield for **5a**–**d**. [d] *ee* for **4a**–**d**; *ee* > 95% for **5a**–**d**. [e] Catalysed by **6**. [f] Catalysed by **11**. [g] Catalysed by Novozym 435.

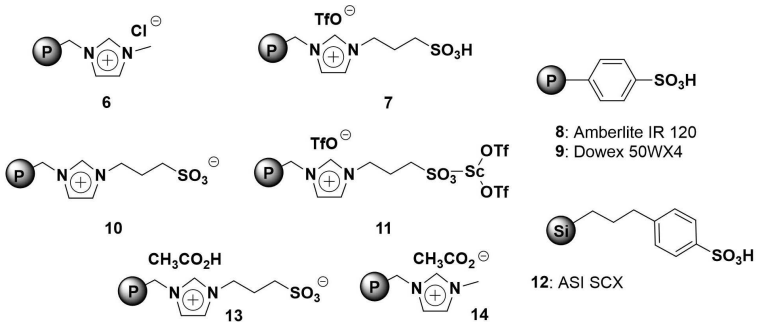


Figure 2. Catalysts assayed for the different steps of the overall process.

This methodology allows the first synthetic step to proceed with excellent yield, 100% atom economy, no waste regarding the side-products formation and unconverted reactants, use of solvent-free conditions, excellent catalytic activity, and no requirement for purification before performing the next step.

Step-2 involving the consecutive hydrolysis of the cyanosilyl ether and the formation of the corresponding acetyl ester requires a catalyst able to facilitate both reactions. Figure 2 illustrates the structure of the catalysts **7**–**14** evaluated for this step under batch conditions. The screening was performed in the absence and presence of acetic anhydride (Ac_2O) to evaluate the intrinsic activity of the catalyst for the silyl ether hydrolysis (in the absence of Ac_2O) and, alternatively, for the two consecutive reactions (in the presence of 2 eq. of Ac_2O). The trimethylsilyl cyano ether (**3a**) derived from benzaldehyde (step-1) was used as the model substrate for such screening under solvent free conditions.[40]

The commercially available polymeric supported sulfonic acids assayed (**8** and **9**) were able to promote the quantitative hydrolysis of the silyl ether group, but not the acetylation of the resulting cyanohydrin (<10%). The water absorbed on the catalyst is likely to favour the hydrolysis of the silyl ether while inhibiting ester formation (Table S1, entries 1 and 3). Indeed, the opposite trend was observed when these catalysts (**8** and **9**) were vacuum dried for 24 hours. The reaction performed in the absence of Ac_2O was inhibited (<15%), while in the presence of Ac_2O the consecutive catalysed desilylation and ester formation took place (>90%, Table S1, entries 2 and 4). The related silica-immobilised sulfonic catalyst (**12**) was also an active catalyst displaying a good performance for the two tested reactions (>90%, Table S1, entry 5).

In the search of alternative catalytic systems, ILs and task specific ILs have been used to catalyse both ester formation,[41,42] and the desilylation reaction.[43] It has been also reported that $Sc(OTf)_3/Ac_2O$ mixtures can be efficient systems for the consecutive desilylation and acetylation of sugars and this mixture was also very efficient in our case (entry 6 in Table S1).[44,45] In view of these precedents, we prepared a series of task-specific SILLPs (**7**, **10**, **11**, **13**, **14** Figure 2) as potential catalysts for the second step. Unfortunately, the initial screening of the catalyst **7** indicated that it was neither efficient for the hydrolysis nor for the esterification in the presence of Ac_2O (Table S1, entry 8). However, the related Sc complex formed by reaction with Sc $(OTf)_3$ and the zwitterionic SILLP **10** led to moderate results for the consecutive desilylation and acetylation reactions (Table S1, entry 7). In the case of catalyst **13**, prepared by treating SILLP **10** with acetic acid, initial results showed also a moderated activity (Table S1, entry 9) for both coupled reactions. Interestingly, while for catalyst **10** a significant loss of activity was observed with reuse (Figure S1b), the reuse of catalyst **13** under the same conditions showed an increase in its activity in such a way that after four reuses yields >95% were obtained for the synthesis of the corresponding cyano ester (Figure S1a). The catalyst **14** was also active for synthesis of the cyano ester **4a** (Table S1, entry 11). Summarising, at least four supported catalytic systems (**11**, **12**, **13** and **14**) were effective for the consecutive desilylation and acetylation reactions required for the step 2 of our proposed telescoping synthesis.

We also evaluate the direct preparation of cyanohydrin acetal ester (**4a**) by the reaction of benzaldehyde with acetyl cyanide under solvent free conditions and using different catalysts (Table S3, SI). The catalysts tested were less efficient providing lower yields than the two step reaction using TMSCN and Ac_2O as reagents and the catalysts based on SILLPs.

The final step can be achieved by the use of an enzymatic catalyst.[46] Thus, the enantioselective hydrolysis of the racemic mandelonitrile acetate ((±)-**4a**) in the presence of *n*-propanol and using 2-methyl-tetrahydrofurane (2-Me-THF) as the solvent was considered. The immobilised commercially available Lipase B from *Candida antarctica* (Novozym 435) could be used to transform the racemic cyanohydrin acetate into a mixture of (*S*)-cyanohydrin and (*R*)-mandelonitrile acetate (>99.9% ee), with a conversion slightly higher than 50% (Table 1, entry 1). The effect of the concentration of the racemic mandelonitrile acetate was then investigated (Table S2). Concentrated solutions, up to 1 M, of *rac*-mandelonitrile acetate could be used with good conversions (55%) and enantioselectivities (>99% ee for **4a**, Table S2, entry 2). The use of more concentrated solutions of *n*-propanol (2 M in 2-Me-THF), however, produced a decrease on the enantioselectivity of the kinetic resolution (KR) (52% ee for **4a**, Table S2, entry 3).

Table 1 summarises the results obtained when the catalysts **6**, **11** and Novozym 435 were applied for the synthesis, under batch conditions, of the corresponding cyanohydrins from

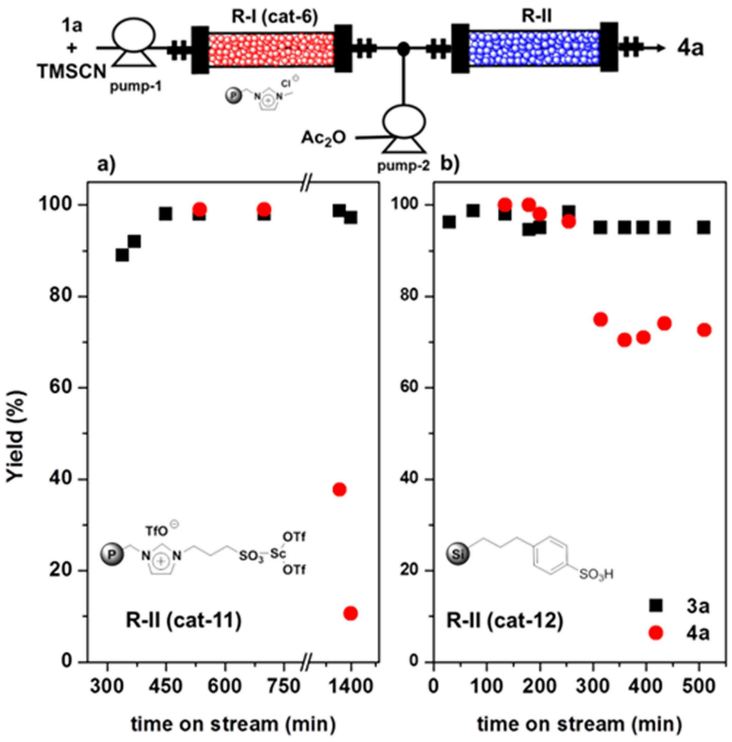


Figure 3. Evaluation of the catalyst stability for the two-step synthesis of racemic mandelonitrile acetate (**4a**) under continuous flow conditions. Black squares: yield for step-1 after **R-I**; Red dots: yield for step-2 after **R-II**. a) step 1: **RI**: 1 g catalyst **6**, 0.01 mL min^{-1}, r.t; step 2: **R-II**: 1 g catalyst **11**, 0.019 mL min^{-1}. b) step 1: **R-I**: 1 g catalyst **6**, 0.01 mL min^{-1}, r.t.; step 2: **R-II**: 1 g catalyst **12**, 0.02 mL min^{-1} **1a**:TMSCN:Ac_2O 1:1.1:1.2 (molar ratio).

aldehydes **1**–**4**. The results demonstrate that it is possible to obtain the corresponding cyanosilyl ethers (**3a**–**d**) and the corresponding racemic cyanohydrin esters (**4a**–**d**) with excellent yields (>90%) independently of the aldehyde used. Noteworthy, the first and second steps were performed under solvent-free conditions, where the single purification performed before the subsequent step was the filtration of the corresponding solid catalysts. The kinetic enzymatic resolution of the cyanohydrin esters was able to selectively hydrolyse the racemic esters to yield the (*S*)-enantiomer of the cyanohydrins and leaving the corresponding (*R*)-cyanohydrin acetates (with an enantiomeric excess >99.9%).

These results demonstrate that it is possible to perform the synthesis of the enantiopure cyanohydrins by three consecutive catalytic steps under batch conditions. However, when the single-pot multicatalytic cascade reaction was evaluated, using a combination of the different catalytic systems, the single process fails. Indeed, even when different protocols were assayed for the consecutive addition of the catalysts and/or reagents, the global process proceeded with low conversion and/or low enantioselection. Thus, the single-pot multicatalytic process is not feasible under batch conditions due to the incompatibility between the enzymatic catalyst and some of the reagents and/or catalysts involved in the global synthetic sequence.

A simple approach to enable cascade or concurrent chemoenzymatic reactions to occur without mutual inactivation is to compartmentalise the different catalytic systems. This approach shields the catalytic centres from one another.[30,31,47,48] The use of consecutive fix-bed reactors can provide the required isolation of the catalysts by compartmentalisation and to favour the simple and continuous production of the chiral target without the need for isolation of any intermediates and without requiring the separation of any catalysts, co-products, by-products, and excess reagents.[16,27,28,49,50]

Thus, the use of a continuous flow process using benzaldehyde as the starting material to perform a telescopic synthesis of the corresponding cyanohydrin was evaluated. Accordingly, the continuous synthesis of the cyanohydrin esters using two fixed-bed reactors coupled together in-line was initially evaluated. The first reactor (**R-I**) was packed with catalyst **6**, and a neat mixture of benzaldehyde and TMSCN (1:1.1 molar ratio) was pumped at 0.01 mL min^{-1}. A second reactor (**R-II**) filled with catalyst **11** was connected at the exit of **R-I** by means a T-piece, which also allowed to mix the silyl ether coming out from **R-I** with a stream containing acetic anhydride. The flow of this steam was adjusted to a flow rate (0.009 mL min^{-1}) matching to 2 equivalents of Ac_2O per each equivalent of the silyl ether coming out from **R-I**. Although catalyst **11** was able to simultaneously hydrolyse the silyl ether and to form the corresponding ester yielding the desired rac-mandelonitrile acetate, it did not show a long-term stability. A strong deactivation of **11** was observed after 24 hours of continuous use on stream (Figure 3a). After this time, the main product collected at the outlet of the two reactors was the cyanosilyl ether, indicating that though the second reactor was not stable

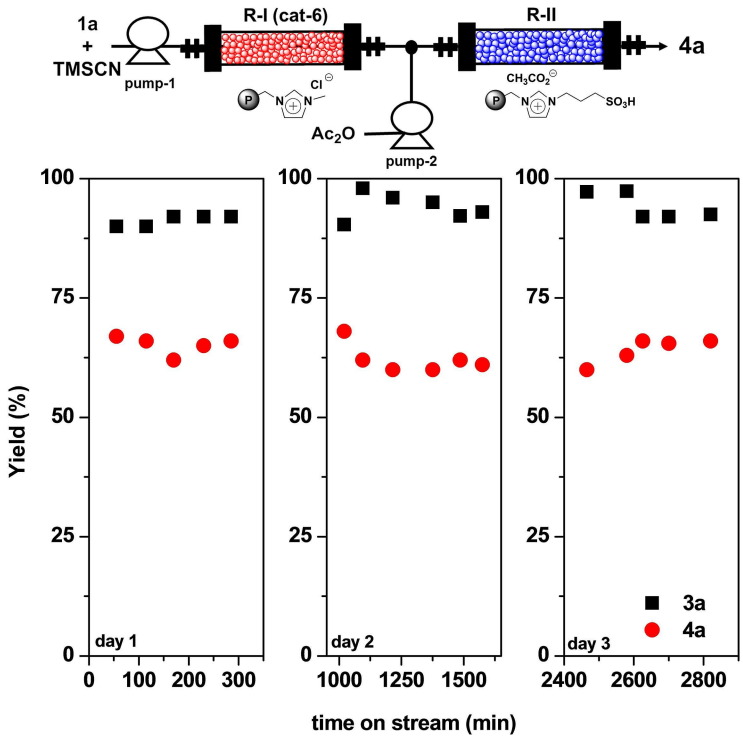


Figure 4. Evaluation of the catalyst stability for the two-step synthesis of racemic mandelonitrile acetate (**4a**) under continuous flow conditions. Black squares: yield for step-1 after **R-I**; Red dots: yield for step-2 after **R-II**. a) step-1: **R-I**: 1 g catalyst **6**, 0.01 mL min^{-1}, rt; step-2: **R-II**: 1 g catalyst **13**, 0.019 mL min^{-1}. **1a**:TMSCN:Ac_2O 1:1.1:2.

enough, **R-I** was still active. Indeed, this reactor (**R-I**) was stable for at least 50 hours, with >95% yields, with the productivity for this period being ca. 24 g of product / g of catalyst.

In order to confirm the deactivation suffered by the catalyst **11**, a mixture of the cyanosilyl ether (**3a**) and Ac_2O (1:1.2 eq.) was pumped directly through **R-II** at 0.02 mL min^{-1}. The catalyst was stable during the 3 first hours with yields >99%. However, after an additional period of 24 hours on stream, the yield dropped to <30%. These results highlight the importance of assessing the long term stability of the catalyst for flow processes. Even catalysts that are active for consecutive runs under batch conditions might be not suitable for prolonged used under continuous flow. In the light of the former results, other active catalysts were evaluated for step-2 taking into consideration the results previously discussed (according to results in Table S1). Thus, an alternative **R-II** fix-bed reactor was prepared with the commercially available silica-based sulfonic acid catalyst **12** and the reaction mixture was pumped through it at a flow rate of 0.02 mL min^{-1}. The catalyst was still active after 20 hours of continuous use, although after 5 hours on stream the activity dropped from >95% to 70% (Figure 3b).

Finally, catalyst **13** displayed a constant catalytic performance with a stable yield for **4a** of ca. 65% for more than 40 hours of continuous use under flow conditions (Figure 4). At the view of the stable performance of this catalyst, the improvement in the obtained yield was assayed by adjusting the experimental conditions. Indeed, an increase of the excess of the Ac_2O used from 1.2 to 2 equivalents rendered an improvement of the yield from ca. 65% to ca. 90%, suggesting SILLP **13** as a suitable catalyst for step-2.

The different stability of the catalysts can be rationalised attending their differences at the molecular level. The catalyst **11** is a metallic salt with Lewis acid properties that in the presence of an excess of acetic acid can lead to a significant scandium leaching. Indeed, an increase in the amount of Ac_2O used in the reaction from 1.2 to 2 equivalents led to a faster catalyst deactivation. Regarding the solid sulfonic acid catalyst **12**, its partial deactivation can be associated to the lack of efficient regeneration of the Brönsted acidity in the catalytic cycle.

On the contrary, the bifunctional SILLP **13** can work as a dual catalyst with a dramatic anion-cation cooperative effect and a catalytically efficient combination of acidic and basic sites. As detected by TGA SILLP **13** contains *ca.* 5% of water and *ca.* 2% of acetic acid (see Figure S2). The acid sites, in the presence of some water, can hydrolyse the cyanosilyl ether to yield the corresponding alcohol.[51] On the other hand, the C-2 hydrogen at the imidazolium moiety can also contribute to the electrophilic activation of the carbonyl group of Ac_2O through hydrogen bond formation. The efficient transformation of the initially formed trimethyl silyl alcohol (TMSOH) into the corresponding ether (TMS_2O) is essential to regenerate the catalytic water needed for the hydrolysis, which seems to be facilitated by the presence of acetic acid molecules in **13**. An acetic acid molecule can also play a key role in the acylation step by activating the Ac_2O through hydrogen bonding.[52,53]

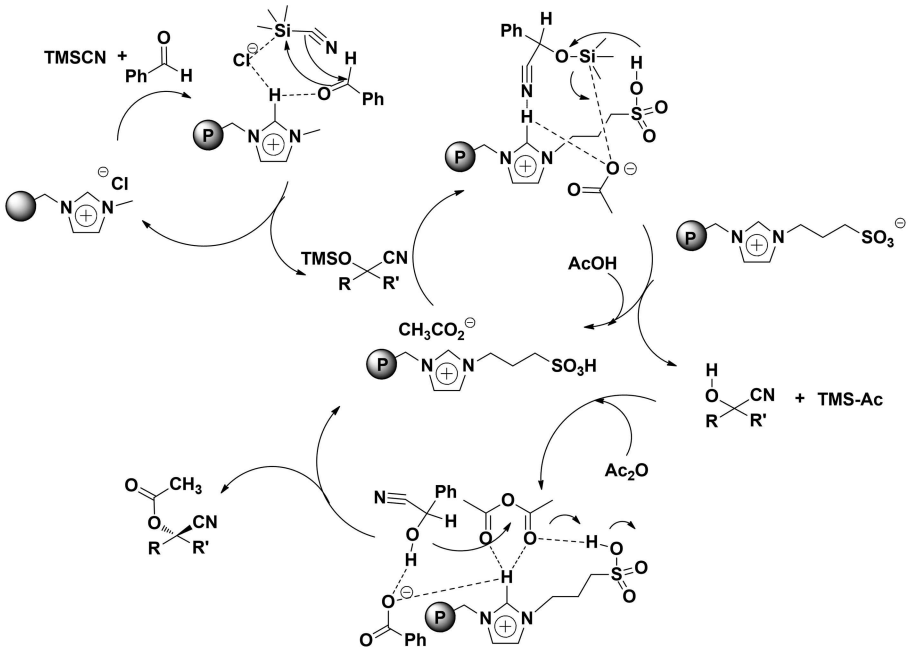


Figure 5. Mechanistic model for the consecutive processes involved in the synthesis of cyanohydrin catalysed by SILLPs **6** and **13**.

Therefore, the cation of the SILLP and the acetic acid activate the electrophile, as hydrogen bond donors, while the anion activates the nucleophile, as hydrogen bond acceptor. The importance of the dual nature of catalyst **13** is demonstrated by comparing its catalytic activity with the one for a mixture of **8** and **14**, a SILLP containing acetate as the counteranion. The mixed system is catalytically active but its activity decreases with the reuse (Figure S3a) and the same is observed for **14** (Figure S3b).

A plausible reaction mechanism is presented in Figure 5 based on this dual activation effect. Here the SILLP is acting in a similar fashion than related ILs in solution by an "electrophile–nucleophile dual activation" through a cooperative hydrogen-bonded network.[54,55,56,57] These results confirmed that supported ionic liquid phases are able to mimic the catalytic behaviour found for bulk ILs with the additional advantages of needing a smaller amount of IL, an easier isolation and recycling and the possibility to work under continuous flow conditions.

The last step to complete the process is the continuous kinetic resolution of the cyanohydrin ester obtained after the second step. This process is a well stablished reaction under batch conditions.[58] A bioreactor was prepared as a fix bed reactor with Novozyme 435 (**R-III**) to evaluate the feasibility of this approach. A solution of the racemic cyanohydrin ester **4a** in 2-Me-THF (0.1 M) and n-propanol as the transesterification agent (2 equiv., 0.2 M) was pumped through the catalytic bed (**R-III**) at 60 °C and 40 bar. Thus, for a total flow rate of 0.35 mL/min, an excellent and selective conversion of the cyanohydrin ester to the corresponding alcohol (ca. 48% yield for the alcohol) was found, with excellent enantiopurities for both the (*R*)-acetylated mandelonitrile (95% *ee*) and the hydrolysed (*S*)-mandelonitrile. (>99% *ee*, Figure S4). Thus, these results demonstrated the feasibility of the KR of the racemic acetylated mandelonitrile under continuous conditions. At the view of these results, the telescoped synthesis of cyanohydrin was assayed by using three consecutive fix bed reactors (**R-I**, **R-II** and **R-III**) packed respectively with the organocatalytic SILLPs **6** and **13** and with Novozym 435 as the supported biocatalyst. The results obtained for this set-up are summarized in Figure 6.

The reactors were coupled sequentially after each reactor had reached the steady state without including any separation step. Thus, the reactor **R-II** was connected to **R-I** after 1000 min, when the first reaction was taking place with yields >90% to afford the cyanosilyl ether **3a**. In a similar way, **R-III** was attached to the two previous ones after 3700 min, when the corresponding acetate ((±)-**4a**) was obtained with >90% conversion. In the last reactor, the racemic acetate was kinetically resolved by the action of the enzyme, which selectively hydrolysed the racemic esters to yield the (*S*)-enantiomer of the cyanohydrin **5a** and the corresponding (*R*)-cyanohydrin acetate (**4a**) (with an enantiomeric excess >99% for a conversion to **5a** slightly higher than 50%).

Noteworthy, it was possible to achieve efficiently a coupled process involving four consecutive reactions, which was not feasible as a single-pot process under bath conditions. The system was stable at least for two days (>3000 minutes) of continuous use. Our results suggest that the combination of continuous flow processes, SILLPs as organocatalytic phases and biocatalysts can lead to an efficient process in terms of catalytic efficiency but also regarding the process productivity and sustainability. In this context, it should be mentioned that step-1 and its combination with step-2 (step1 + step-2) have remarkably low E factors (0.1 and 0.93 respectively, Table S4), which highlight the greenness of these two steps performed

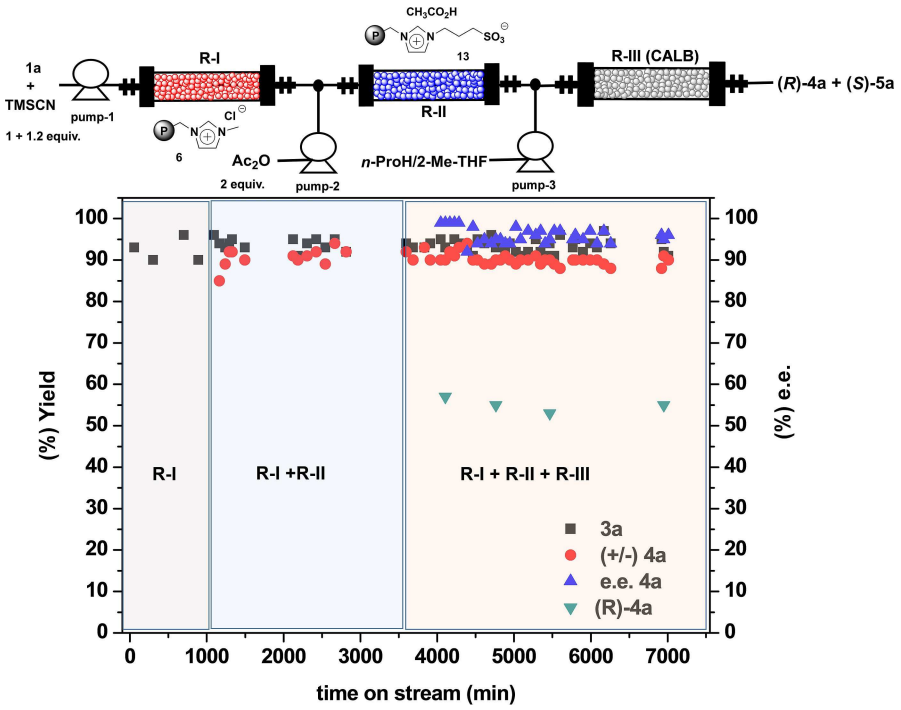


Figure 6. Evaluation of the catalyst stability for the multicatalytic synthesis of enantiopure mandelonitrile acetate ((*R*)-**4a**) under continuous flow conditions. Black squares: yield for step-1 after **R-I**; red dots: yield for step-2 after **R-II**; green triangles: yield for step-3 after **R-III**; blue triangles: enantioselectivity for the final product ((*R*)-**4a**) after **R-III**. Step-1: **R-I**: 1 g catalyst **6**, 0.01 mL min^{-1}, rt; step-2: **R-II**: 1 g catalyst **13**, 0.019 mL min^{-1}. **1a**:TMSCN:Ac_2O 1:1.1:2; step-3: **RIII**: 1 g Novozym 435 (CALB), 60 °C, flow 0.35 mL min^{-1}, 0.1 M **4a** in Me-THF:IPA (0.85:0.15).

under solvent free conditions. The use of an additional organic solvent required in the KR step is reflected in the significant increase of the E factor (21.8 without considering solvent recovery). These values are however lower than those reported for other catalytic and biocatalytic methods (see Tables S5 and S6 in the SI) being inferior to the usual E values for a pharmaceutical product ranging from 25 to 100.[59] Regarding productivity, the obtained values for the individual steps range from 100 to 200 mg g^{-1} h^{-1}, being the biocatalytic step the one displaying the higher productivity. Overall, the space-time-yield (STY) for the final step of the process, including the two chiral products of interest formed, is 124 g g^{-1} cat. h^{-1} L, a value that compares well for related biocatalytic processes described for the synthesis of cyanohydrins using hydroxynitrile liases and HCN, a more hazardous chemical reagent than TMSCN.[60,61]

Conclusions

In summary, the right combination of organocatalysts based on Supported Ionic Liquid-Like Phases with a biocatalyst allows successfully developing a valuable flow protocol for the multi-catalytic, multistep, single-pot and metal-free synthesis of chiral cyanohydrins with good yield and enantioselectivity. Our studies also highlight the potential for catalytic applications of SILLPs designed with specific functionalities. An "electrophile–nucleophile dual activation" through a complex network of hydrogen bonding seems to be essential, in a similar way to that observed in bulk ILs. Hence, SILLPs might be regarded as "solid ionic solvents" or as nanostructured materials with microenvironments displaying the same characteristics, at molecular level, as their analogous ILs phases. Besides, their insoluble nature enables their use under continuous flow, allowing the possibility of combining organocatalytic and biocatalytic successive reactions to facilitate complex synthetic syntheses to occur in a single process, avoiding deactivation/incompatibility issues found in the related single-pot batch syntheses.

Experimental Section

Experimental details are provided in the electronic supplementary information

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: continuous flow · supported ionic liquids · biocatalyst · organocatalyst · cyanohydrin

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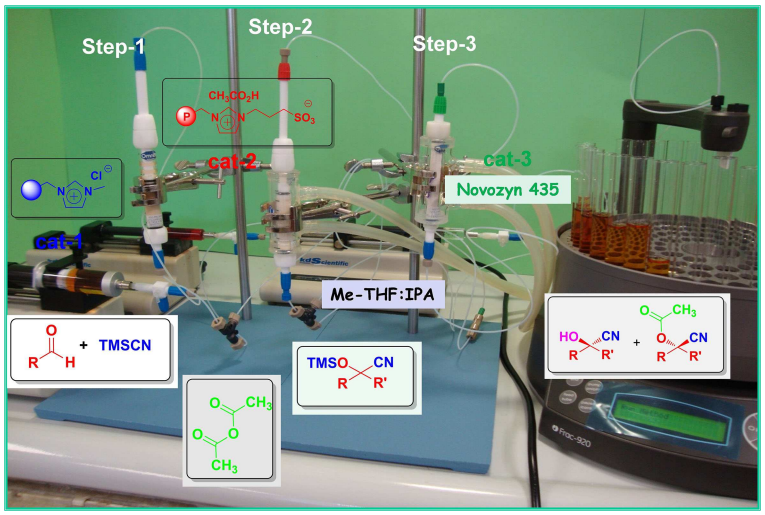

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Step it up: An integrated cascade multicatalytic multiple step flow process based on the appropriated combination of organocatalytic supported ionic liquid-like phases (SILLPs) together with commercially available supported *Candida antarctica* lipase type B (CAL-B) is reported for the efficient synthesis of enantiopure cyanohydrins.