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Introduction

Hydrocyanation and cyanosilylation of carbonyl compounds are among the most important strategies for C–C bondforming reactions in organic synthesis as, for instance, cyanohydrin trimethylsilyl ethers are industrially valuable and important intermediates for the synthesis of many valuable molecules such as α -hydroxy acids, α -hydroxy aldehydes and β -amino alcohols and other biologically active compounds.^{1,2}

Although there are different methods for the preparation of trialkylsilyl cyanides, the addition to carbonyl compounds of trimethylsilyl cyanide (TMSCN), which is a safe and easily handled reagent compared to HCN, NaCN or KCN,³ allows obtaining silyl protected products in high yields and readily accessible for further manipulations.⁴ However, the use of silyl cyanides requires catalytic activation by an organometallic or organocatalytic system. Thus, the traditional organometallic systems (Lewis acid catalysts) are based on the complexation of a metal to both the carbonyl group and the cyano group of TMSCN.^{5,6} However, the organocatalytic systems (Lewis basic catalysts) often react with the silicon atom of TMSCN to produce more reactive hypercoordinated silicon intermediates.

Supported ionic liquid-like phases as organocatalysts for the solvent-free cyanosilylation of carbonyl compounds: from batch to continuous flow process[†]

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Supported ionic liquid-like phases (SILLPs) are able to efficiently catalyse the cyanosilylation of carbonyl compounds using trimethylsilyl cyanide under solvent-free conditions. These organic catalysts were efficient for various carbonyl compounds including aromatic, aliphatic and α , β -unsaturated. This process perfectly conforms to the features of green chemistry: no waste regarding side-products and unconverted reactants, solvent-free, excellent catalytic activity, and no requirement for separation. Furthermore the supported nature of the SILLPs allows for the development of continuous flow synthesis of cyanohydrin trimethylsilyl ethers. The effect of the morphology of the polymer (gel-type or macroporous bead resins or, alternatively, a monolithic polymer) has also been studied, which has allowed selecting suitable materials for the efficient continuous flow single pass synthesis of cyanohydrin trimethylsilyl ethers.

The use of ionic liquids (ILs) has been demonstrated to be an efficient and environmentally friendly reaction media as well as a promoter for the cyanosilylation of aldehydes under mild conditions without the need for a Lewis acid (or base) or any other special activation.⁷ The presence of catalytic amounts of lanthanide triflates, particularly scandium triflate, in the ILs increased largely their catalytic efficiency in terms of the resulting turnover frequency and total turnover number.⁸

In the last few years, we have focused our efforts on the development of the so-called supported ionic liquid-like phases (SILLPs) prepared by the immobilization of molecules with IL-like structures onto solid supports (Fig. 1). These advanced materials allow to transfer the IL properties to the solid phase leading to either monolithic or gel supported ionic liquid-like phases (m- or g-SILLPs) sharing, therefore, the properties of true ILs and the advantages of a solid support.⁹ Catalytic processes based on the use of SILLPs allow (i) to



Fig. 1 Design vectors used to fine-tune the organocatalytic properties of supported ionic liquid-like phases (SILLPs).

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[†]Electronic supplementary information (ESI) available: GC methods and ¹H NMR spectra of the products Table 2 and calculation Table 4. See DOI: 10.1039/c3gc42238k

minimize the amount of ILs used, (ii) easy separation and recyclability and (iii) to develop mini-flow reactors for continuous processes using either conventional solvents or supercritical fluids (scFs).¹⁰ Thus, a wide range of polymer-supported ionic liquid-like phases (SILLPs) or "solid ionic solvents" with tunable properties can be easily prepared in order to (1) generate novel (bio)catalytic species, (2) improve the stability of the (bio)catalyst, (3) optimize immobilization and recyclability, (4) assist in the activation of the (bio)catalyst, (5) facilitate product isolation, and (6) influence the selectivity of the reaction, which are some of the essential roles of conventional solvents.

Taking this into account, supported ionic liquid-like materials (SILLPs) offer good potential as substitutes of bulk ILs for the cyanosilylation reaction, and here we report our efforts towards this goal. The process has been carried out by the smooth addition of TMSCN to carbonyl compounds using polymeric SILLPs as new bifunctional organocatalysts, under different batch conditions and, preferentially, under continuous flow solvent-free conditions.

Results and discussion

Different PS-DVB polymers containing alkylimidazolium chloride subunits (7–12) were prepared from commercially available Merrifield resins having different chloride loadings and crosslinking degrees as previously reported by us.¹¹ Initially, geltype microporous chloromethylated resins (1–3) in the form of beads, bearing a low crosslinking degree (2% DVB) and with chloride loadings ranging from 1.2 to 4.3 mmol Cl g–1 were used. The synthetic protocol for the preparation of the SILLPs has been previously optimized by our group and has been described in detail, allowing a quantitative transformation of the chloromethylated fragments into alkyl benzyl imidazolium groups as is shown in Scheme 1.¹²

The cyanosilylation reaction between acetophenone (13) and TMSCN (14) was selected as the benchmark reaction, as, in general, most of the reported methods for the cyanosilylation of carbonyl compounds are largely limited to aldehydes as well as to the more reactive aliphatic ketones.

First, the role of the solvent was studied by carrying out the reaction either under solvent-free conditions or in a range of solvents from a non-polar one, such as CH₂Cl₂, to polar ones



Scheme 1 Synthesis of SILLPs: (i) alkylimidazole, 90 °C; (ii) NaX or HX, H₂O. 1–3 resins are microporous beads with 2% crosslinking, 1 (1.2 mmol Cl g⁻¹), 2 (2.1 mmol Cl g⁻¹) and 3 (4.3 mmol Cl g⁻¹); 4 macroporous resin (1.2 mmol Cl g⁻¹).

Table 1	Effect of the	solvent in the	cyanosilylation	reaction	between
(14) and (15) catalysed by SILLP-7 at r.t. and 24 hours of reaction time ^a					

Entry	Solvent	$\operatorname{Yield}^{b}(\%)$	TON
1	CH_2Cl_2	64	29
2	Acetonitrile	81	37
3	2-MeTHF	29	13
4	H_2O	0	0
5	MeOH	0	0
6	_	92	41
7 ^c	—	20	—

^{*a*} 75 mg of SILLP 7, 3 mmol of acetophenone, 3.6 mmol of TMSCN and 5 mL of solvent, stirring at room temperature during 24 hours. ^{*b*} Calculated by GC. ^{*c*} Reaction in the absence of catalyst.

like MeOH or water. The SILLP-7 ($R = CH_3$, R' = H, X = Cl, low loading) was used as the initial catalyst. As shown in Table 1, the cyanosilvlation reaction was more efficient under solventfree conditions than using organic solvents or water. The reaction proceeded smoothly at room temperature to afford the corresponding cyanohydrin in 92% yield under solvent-free conditions (Table 1, entry 6). It should be noted that the reaction only led to low yields (20% yield) in the absence of the SILLP-7. Regarding the use of solvents, both MeOH and water led to non-conversion of the carbonyl compound. Low to modest vields were obtained when either CH2Cl2 or 2-MeTHF was used (Table 1, entries 1 and 3). The best solvent was clearly acetonitrile, leading to 81% yield (Table 1, entry 2). In view of these results, various aldehydes and ketones were tested under solvent-free conditions at room temperature using SILLP-7 as the catalyst to evaluate the general applicability of this protocol. All the results are summarized in Table 2.

The SILLP-7 was able to catalyse the solvent-free cyanosilylafor substituted and unsubstituted benzaldehydes tion (Table 2, entries 2-5) with similar results to those found for acetophenone. Excellent yields of the corresponding products were obtained, almost in pure form, without any additional purification step except the catalyst filtering. In addition, a cyclic ketone and an open chain aliphatic aldehyde (Table 2, entries 1 and 7) were also converted into the corresponding TMS-cyanohydrins in good yields. It should also be noted that an aromatic α,β -unsaturated aldehyde also underwent the cyanosilylation reaction efficiently (Table 2, entry 6). These preliminary results suggest that these supported ionic liquid-like phases are quite a promising system to develop simple, efficient, room temperature and solvent free cyanosilylation reactions for different classes of carbonyl compounds.

One of the potential advantages of the use of SILLPs is that, like in the bulk ILs, it is easy to vary several of their structural features (loading of IL-like units, substitution pattern, the nature of the counterion, the type of polymeric backbone, *etc.*) to fine-tune their physical and chemical properties. These changes may have a big impact on the catalytic properties of the SILLPs as organocatalysts for the cyanosilylation reaction as we have already demonstrated to apply for other (bio)catalytic systems.^{9,10,13} Hence, we studied the effects of some of

Paper

Table 2Cyanosilylation of various carbonyl compounds under solvent-free conditions catalysed by SILLP-7 at r.t. and 24 hours^a



 a 75 mg of SILLP 7, 3 mmol of carbonyl compound and 3.6 mmol of TMSCN, stirring at room temperature during 24 hours. b Calculated by GC. c A single product corresponding to the one expected for the cyanosilylation reaction was detected by ¹H NMR of the crude of the reaction.

these structural variables on the catalytic efficiency for the solvent free reaction between acetophenone and TMSCN.

First, the effect of the loading of the IL-like moieties in the polymeric backbone was tested. At long reaction times (24 hours) all the catalysts showed very good yields (ca. 90%) independent of the SILLP-loading. However, the catalytic efficiency of the SILLP measured in moles of products converted per unit of time and mole of catalyst, before completion of the reaction, was quite loading dependent. Indeed, when the same amount of solid catalysts was used, the most efficient SILLP was the one having a medium loading of imidazolium groups (SILLP-11, 40% IL-like units by weight) showing a TOF = 7.7 (mol 15 per mol cat h) calculated at two hours of reaction time, while the SILLP with higher (SILLP-8, 63% IL-like units by weight) and lower (SILLP-7, 18% IL-like units by weight) amounts of functionality only presented a catalytic efficiency (TOF) of 4.6 and 2.3 respectively. Most likely, this effect of the loading can be associated with the accessibility to the catalytic sites inside the polymeric beads. This can be difficult for low loadings, because of the formation of polar/apolar domains in the resin, but also in the resins containing a high degree of IL-like functionalization, where the IL-fragments can be strongly associated through the formation of anion-cation supramolecular structures.

Another factor that can be used to tune the catalytic activity of the SILLPs is the substitution pattern of the imidazole

moiety that can be achieved through the use of different alkyl resides (R and R'). Thus, three different SILLPs (SILLP-8, SILLP-9 and SILLP-10) were synthesized from the same starting Merrifield resin. Therefore, three different resins having the same loading (high loading) but a different substitution pattern (R = CH₃- and R' = H- (SILLP-8); R = CH₃-(CH₂)₃- and R' = H (SILLP-9) and R = CH₃-(CH₂)₉- and R' = CH₃- (SILLP-10)) were evaluated as catalysts for the benchmark cyanosilylation reaction (Scheme 2). In all the cases, the SILLPs were active to catalyze the reaction. However, the time-course profiles of the product yield (see Fig. 2) present significant differences for each of the SILLPs. Thus, the SILLP-8 was the more active one, reaching an 85% yield in *ca*. six hours, while the presence of a longer alkyl chain at the imidazolium ring led to a reduction of the catalytic efficiency.

It is noteworthy that the SILLP-8 containing the smaller substituents showed some induction time, which is not noticeable for the other SILLPs. Most likely, this observation must be related to the highly hydrophilic character of SILLP-8 that makes this resin rather hygroscopic. The observed induction time should be related to the larger amount of residual water present in this case in the polymer and that can interfere with the reaction of interest, by reacting with TMSCN instead of the chloride anion (the first step of the catalytic cycle). Indeed, the water content for these SILLPs varied from *ca*. 11% for the SILLP-8 to a maximum of 6–7% for the more hydrophobic ones SILLP-9 and SILLP-10. As can be observed in Fig. 2, after this induction period the SILLP-8 displayed the best catalytic



Scheme 2 Cyanosilylation between (14) and (15) organocatalyzed by SILLPs.



Fig. 2 Effect of the substitution pattern of the SILLPs as catalysts for the cyanosilylation reaction between **(14)** and **(15)** at r.t. and 24 hours of reaction time. • $R = CH_3$ and R' = H (SILLP-8); • $R = CH_3(CH_2)_3$ and R' = H (SILLP-9) and **=** $R = CH_3(CH_2)_9$ and $R' = CH_3(SILLP-10)$.

behavior. Thus, the exact microenvironment at the imidazolium moiety can have a key influence on the overall catalytic cycle.

Once established that the best results in terms of yield and catalytic efficiency were obtained for the SILLP based on methyl-imidazolium, we decided to study the effect of the counterion. Our previous results have proved that very significant variations in the physico-chemical properties of the SILLPs can be obtained by varying the anion of the ionicliquid-like moieties grafted onto a polymeric matrix. Therefore, SILLPs bearing five different anions and the same loading of the methyl-imidazolium cation were tested as catalysts for the cyanosilylation reaction. The nature of the anion has a significant effect on the catalytic efficiency as can be appreciated in the time-course profiles of the product yield (Fig. 3). Hence, reactions performed with catalysts based on SILLPs containing the harder Lewis bases as the anions (Cl⁻ and TfO⁻) showed a better activity than those with catalysts bearing softer Lewis base anions such as $\text{NTf}_2^{-},\,\text{BF}_4^{-}$ or $\text{SbF}_6^{-}.$ Indeed, the calculated reaction rates change followed the sequence Cl^- (r = 0.5848 h^{-1} > TfO⁻ (r = 0.0224 \text{ h}^{-1}) > NTf₂⁻ (r = 0.0417 \text{ h}^{-1}) > BF_4^- (r = 0.0065 h⁻¹) > SbF_6^- (r = 0.0050 h⁻¹) being the enhancement in the reaction rate up to ca. 117 folds going from SbF₆⁻ to Cl⁻ (see Fig. 3). According to known mechanistic data, the anion must coordinate to the Si atom to form a more reactive pentacoordinated silicate for the reaction to occur. This binding leads to a polarization of the adjacent bonds, thereby increasing the electron density at the peripheral atoms, activating the CN⁻ to attack the carbonyl group.^{14,15} Thus, the presence of a hard Lewis base, for instance the chloride in the SILLP, should facilitate this mechanism of action. On the other hand, in the catalytic cycle, the imidazolium cation may contribute to stabilize the more reactive pentacoordinated silicate through additional weak interactions such as hydrogen bonding, hydrophobic and van der Waals attraction together with ionic interactions with the anion.

The possible recycling of the catalyst was also evaluated. The nature of the support, being a gel type resin, makes it very sensitive to mechanical damage by the abrasion produced by the magnetic stirring bar. This often hampers an efficient filtration to separate the catalyst from the reagents and products, precluding the practical recycling of the supported catalyst. Therefore, we designed a simple device allowing for a reactive filtration process. The supported-catalyst was maintained in a syringe body with an adequate filter at the top and the bottom of the material, and then the solvent free mixture of the reagents (*ca.* 3 mL) was eluted through the catalytic bed and separated from the solid by simple gravimetric flow (Fig. 4). The contact time of the reagents with the SILLP-7 was long enough to achieve an average product yield of 85% for three consecutive batches of *ca.* 3 mL each. In summary, the SILLP-7 was stable enough to produce *ca.* 15 g of cyanosilylether per gram of catalyst used during three consecutive recycles, without showing any significant decrease in its activity.

The former results also suggest that these catalytic SILLPs can be stable enough as to develop a continuous flow system.^{16–18} For this purpose, a simple set-up allowing a forced continuous flow-through process was evaluated.¹⁹ The system was based on a HPLC pump, a fix-bed catalytic reactor and a continuous flow ATR-FTIR cell to facilitate the monitoring and optimisation of the process (see Fig. 5).²⁰

A careful analysis of the nature and shape of the catalyst under consideration is always needed for a proper design of the corresponding mini-flow reactors (*mfr*). Indeed, the morphology and shape of the catalyst can lead, in some cases, to significant differences in catalytic performance.^{16,21-23} Therefore, for the preparation of mini-flow fix-bed catalytic reactors, we decided to study polymers with different morphologies. First, the use of gel-type lightly crosslinked resins was evaluated for the preparation of the reactor (*mfr*-SILLP-7-*gel*).²⁴ This was the type of polymer successfully used for batch experiments. Indeed, both reagents and catalysts based on gel-type resin have been successfully used for different C–C bond formation reactions.^{25,26} However, it should be taken into account that these polymers only swell in certain solvents. In the absence of a good swelling, intraparticle diffusion of the



Fig. 3 Effect of the SILLP counterion on the cyanosilylation reaction between (13) and (14) catalysed by SILLP-8 and SILLP-13a-d at r.t. and 24 hours. \bullet (X = Cl), \forall (X = TfO), \blacksquare (X = NTf₂), \blacklozenge (X = SbF₆), \blacktriangle (X = BF₄).



Fig. 4 Recycling of the SILLP-7 for the cyanosilylation reaction between (14) and (15) at r.t. during 24 hours.



Fig. 5 Continuous flow reactor, including continuous monitoring, for the cyanosilylation reaction between (14) and (15) catalysed by SILLP-7 at r.t. (a) Photo and scheme of the set-up. (b) Evolution with time of the characteristic peaks of both reactant (14) and product (16) for the model cyanosilylation in the mini-flow reactor *mfr*-SILLP-7-*g* at r.t. and under different flow conditions. ● (C=O at 1768 cm⁻¹), ■ (C-OTMS at 1115 cm⁻¹), ▲ (Si-O at 995 cm⁻¹).

reagents and substrates can be the limiting rate factor. Therefore, suitable swelling conditions are required to allow the flow through the generated internal microchannels of the resin (usually beads).^{21,26} Furthermore, the swelling is accompanied by a change in volume that can be very important, thus affecting the packing.²¹ In this regard, a regulating device was used to properly adjust the volume of the reactor to that of the swollen resin. In this way, it is feasible to achieve a reproducible flow through systems based on gel-type polymers.²⁷

The initial results for the fix-bed reactor (*mfr*-SILLP-7-*gel*) prepared with the gel-type resin SILLP-7 are depicted in Fig. 5. The continuous monitoring of the effluent by FT-IR allowed a direct analysis of the results for this continuous flow process. The graph in Fig. 5 displays the evolution with time of the characteristic peaks for both the reactant (14) and the product (16). The data show the presence of an important induction time before the stationary regime is reached. Once this is achieved, the flow system can be maintained with the same productivity and high yields without observing any decrease in the activity of the catalyst with time. As a matter of fact, at this

Table 3Continuous flow solventless cyanosilylation reaction between14 and 15 at r.t. using different polymeric materials^a

Entry	Reactor	Flow mL min ⁻¹	Yield ^b (%)	Productivity (g 16 per g cat) $h^{-1 c}$
1	mfr-SILLP-7-gel	0.1	99	9.0
2	mfr-SILLP-7-gel	0.3	99	27.1
3	mfr-SILLP-7-gel	0.5	99	45.1
4	mfr-SILLP-12-macro	0.1	99	9.0
5	mfr-SILLP-12-macro	0.3	98	26.8
6	mfr-SILLP-12-macro	0.5	96	43.7
7	mfr-SILLP-17-molth	0.01	95	0.2
8	mfr-SILLP-17-molth	0.03	85	0.3
9	mfr-SILLP-17-molth	0.05	75	0.6

^{*a*} *mfr*-SILLP-7*-gel*: 600 mg of SILLP-7, 1.01 meq g⁻¹; *mfr*-SILLP-12*macro*: 600 mg of SILLP-12 1.09 meq g⁻¹, *mfr*-SILLP-17*-molth*: 3.38 g, 3.03 meq g⁻¹; 3.67 M of 14 in a mixture of acetophenone–TMSCN 1:1 molar. ^{*b*} Calculated by GC. ^{*c*} Calculated as [flow rate (mL min⁻¹) × concentration (mmol mL⁻¹) × (yield%/100) × Fw(16) (mg mmol⁻¹) × (1/1000)]/[cat. (g) × loading cat. (mmol g⁻¹)].

point the flow can be significantly increased (from 0.1 to 0.5 mL min^{-1}) maintaining the same outcome for the reaction. The results obtained show a productivity for the reactor with this particular configuration of 45.1 g of **16** per g SILLP-7 h⁻¹ for a flow of 0.5 mL min⁻¹ (Table 3, entry 3).

As mentioned above, proper swelling of resin is essential to provide accessibility to the catalytic sites that are embedded in the interior of the polymeric beads. The swelling of this geltype polymeric catalyst (SILLP-7, 600 mg used) is significant, with *ca*. 100% swelling in the presence of an equimolecular mixture of **14** and **15** for 24 hours ($v_i = 1 \text{ mL}$, $v_f = 2 \text{ mL}$).²⁸

Alternatively, a mini-flow reactor (mfr-SILLP-12-macro) reactor was packed with an analogous supported catalyst prepared from a macroporous resin. In contrast to gel-type or microporous resins, the beads from macroporous polymers display a permanent porosity regardless of the solvents or reagents, which usually makes them more suitable for flow processes. The reactor showed a similar behaviour as the first one, leading to yields of 99-95% of the desired product at flow rates ranging from 0.1 to 0.5 mL min⁻¹ (Table 3, entries 4–6). The slight difference observed for both reactors can be assigned to the different void volume observed for each reactor. Although the total volume occupied by the wet and swollen polymer is not very different (2 mL for mfr-SILLP-7-gel and 1.8 mL for mfr-SILLP-12-macro), there is a significant difference in the void volume due to the different swelling observed. Thus, in the case of the gel-type resin (mfr-SILLP-7gel), the void volume can be estimated to be ca. 0.4 mL, while for the reactor packed with the macroporous catalyst (mfr-SILLP-12-macro) it is ca. 1.2 mL. These differences provide slightly different residence times for each reactor. Thus, the residence time for a flow rate of 0.1 mL min⁻¹ is 4 min for *mfr*-SILLP-7-gel and 12 min for mfr-SILLP-12-macro.

Fig. 6 depicts the yield *vs.* time course for the cyanosilylation reaction between **14** and **15** using either *mfr*-SILLP-7-g or *mfr*-SILLP-**12**-*macro* at 0.1 mL min⁻¹. In both cases the induction time observed was *ca.* 3–2.5 fold the residence time



Fig. 6 Evolution with time of the yield of the product (**16**) for the model cyanosilylation between (**14**) and (**15**) obtained by the min-flow reactors (a) *mfr*-SILLP-7*-gel* and (b) *mfr*-SILLP-**12**-*macro* at 0.1 mL min⁻¹.

required to fill the reactor void volume. It must be noted that the induction time observed is much higher than that detected in the previous batch experiments. In this regard, several factors need to be taken into consideration to understand the process of catalyst conditioning before reaching the optimal operational behaviour. The first factor to be taken into consideration is the process of filling the void spaces of the system (tubing and interparticle void-spaces in the reactor) and this can be associated with the initial period for which an increase in the amount of starting material in the effluent is observed.

Volumetric calculations based on the volume spent during this period of time afforded a total volume for the system which is in good agreement with the one estimated according to the length and diameter of the tubing and to the volume of the reactor and the density (in the dry state) of the polymeric beads (ca. 0.4 mL and 1.2 mL overall void volume). On the other hand, as has been mentioned above, reaction of the chloride with TMSCN represents the first step of the catalytic cycle, but water can efficiently compete with chloride for the reaction with TMSCN when present at the polymeric beads, significantly reducing the efficiency of the process. Thus, the induction period can be associated with two main factors: (a) the wetting and swelling of the polymeric beads by the fluid containing the substrate and the reagent; 21 (b) the reaction of the TMSCN with any residual water. Indeed, if the columns are preheated in an oven at 100 °C overnight, the induction time observed is significantly reduced to 1-1.5 fold the residence time required to fill the reactor void volume.

Furthermore, the systems showed a good stability after 48 hours of continuous use without any significant catalytic deactivation, allowing the synthesis during this time of 23.8 g of the corresponding cyanosilylated compound (see Fig. 7).

Finally, the use of a mini-flow reactor prepared from a monolithic polymeric rod was also studied. The monolithic reactor was prepared as reported by us and others by polymerisation of a mixture of 4-chlorovinylbezene and



Fig. 7 Stability study: evolution with time of the yield of the product for the cyanosilylation between benzaldehyde and (**15**) obtained by the min-flow reactor (a) mfr-SILLP-7-gel at 0.01 mL min⁻¹.

divinylbenzene in the presence of the right porogenic agent.^{12,29} Further modification of the chloromethyl groups of the monolith with methylimidazole led to a monolithic reactor with an analogous chemical structure as SILLP-7 and SILLP-12.²⁹ This mini-flow reactor (*mfr*-SILLP-17-*molth*) was then evaluated using the same experimental continuous flow set-up and different flow rates ranging from 0.5 to 0.01 mL min⁻¹. In this case, only moderate yields (30%) were detected for 0.5 mL min⁻¹ flow rate and smaller flow rates (longer residence time) were needed to achieve satisfactory yields (Table 3, entries 7–9).

Table 3 summarises the results obtained for the three miniflow reactors prepared with SILLPs presenting similar functional loadings but different polymer morphologies. Although previous studies from different groups, including our own results, have revealed that monolithic flow-through reactors can provide, in some instances, significantly better performances;^{13,21,25} in this case, the fix-bed reactors prepared from polymeric beads delivered the most efficient system. No significant differences were observed between the gel-type and macroporous catalysts with a maximum productivity of 43–45 g of **16** per g cat h^{-1} . This must be associated with the very low flow rates required to achieve reasonable conversions, which suggest a reduced accessibility of the catalytic sites in the monolith. The presence of the functional groups on the surface of the porous structure of the monolith can provide a high local concentration of IL-like moieties strongly associated and ordered, substantially hampering the participation of the chloride anions in the first step of the catalytic cycle. Thus, this effect should be reminiscent of the one found for high loading resins. The use of a porogenic solvent like dodecanol is known to provide monoliths with large macropores, which is accompanied by a reduction in the total surface. Besides, polar fragments tend to be located at the interface with the porogenic agent becoming the accessible surface of the final polymer.

Table 4 shows a comparison of some of the more efficient methodologies reported up to now for the cyanosilylation reaction here considered. All these previous methods combine at

Table 4	Comparison between the	different catalytic processes	developed for the cya	anosilylation reaction of c	arbonyl compounds
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Ref	Solvent	Cat.	Conditions	Prod. ^a	E factor
7^b 8^b	[OMIM][PF ₆] [BMIM][SbF ₆]	[OMIM][PF ₆] Sc(OTf) ₃	r.t., batch, 24 h r.t., batch, 30 min	$\begin{array}{c} 0.55\\ 20000 \end{array}$	156 96
30 ^c	SolFC	PPh ₂	60 °C, flow, 0.04 mL min ⁻¹	25	0.16
c	SolFC		r.t. flow, 0.5 mL min ^{-1}	42	0.05

 a Productivity as (mol 16 per mol cat) h⁻¹. b Made with benzaldehyde. c Made with acetophenone.

least two of the elements applied in our system, namely: ionic liquids, (organo)catalysis, solventless conditions (SolFC) and flow chemistry. Two main parameters have been selected for comparison: productivity and E factor. The first one is related with the chemical efficiency of the process, while the E factor highlights its greenness. Entries 1 and 2 summarise the results obtained using ILs as the solvent. Even when the ILs could be recycled, the use of an additional organic solvent was required to isolate the product, which is reflected in the significant increase of the E factor, in spite of the really high productivity obtained when Sc(OTf)₃ is present. The use of solid/ supported catalysts (entries 3 and 4, Table 4) facilitates the isolation of the product and the reuse of the catalyst by simple filtration, which is reflected by a large reduction in the E factor (>100 fold reduction). In the case of the SILLP-7, besides, the productivity observed is twofold that of the recently reported supported phosphine.30 No additional solvent is required neither for the reaction nor for the isolation step leading to a further E factor reduction.

The two polymer-supported systems do not provide the impressive productivity of the reaction catalysed by $Sc(OTf)_3$ in ILs; however both are organocatalytic solvent-free and metal free reactions with very low E factors. Although a comparison of this type can be excessively simplistic, at the level considered, it allows illustrating how the combination of different tools from the Green Chemistry "tool box" can lead to synergies helping us to move forward towards more sustainable processes.

Conclusions

The results here presented highlight the advantages of the use of supported ionic liquid-like phases (SILLPs) to develop greener and more efficient catalytic processes. Indeed such SILLPs allowed us to design organocatalytic species for the solvent free cyanosilylation reaction of carbonyl compounds. The modular structural features of the SILLPs allow to finetune the catalytic efficiency by varying parameters such as the SILLP loading, the substitution pattern of the imidazolium units and the nature of the anion. The optimization of these parameters led to stable organocatalytic supported systems that facilitate the development of a continuous flow system implementing the productivity of the system, the product isolation and a simple catalyst recycling. The use of a flow system has also been shown to minimize the negative effects associated with the low mechanical stability of the polymeric materials employed in this work, which precludes proper recovery of the catalyst under pure batch processes. The connection of the effluent tubing to a flow-cell in a FT-IR has allowed continuous monitoring of the reaction, assisting in its optimization. This process perfectly conforms to the features of green chemistry: 100% atom economy, no waste regarding side-products and unconverted reactants, solvent-free, excellent catalytic activity, and no requirement for separation, along with continuous monitoring.

Experimental

Synthesis and characterization of SILLPs

Polymers modified with ionic-liquid-like moieties were synthesized by chemical modification of polymer-bound chloromethyl groups with the corresponding substituted imidazole (4, 5 or 6) following the experimental procedures previously described.¹² Commercially available Merrifield-gel polymers with different loadings (1.2, 2.1, 4.3 mmol Cl⁻ g⁻¹, 1-3) were used to afford the SILLPs 7–12 (Scheme 1). The metathesis of chloride by different anions (BF_4^- , TfO⁻, NTf_2^- , and SbF_6^-) yielded a new series of SILLPs with an exchanged anion (13a–d).

Synthesis and characterization of SILLP-17-monolith

A solution of divinylbenzene (2.4 mL; 80% technical grade), 4vinylbenzene chloride (1.6 mL; 90% purity grade), 1-dodecanol (4.0 mL) and AIBN (42 mg) was prepared. A 15 mm × 100 mm Omnifit® column was filled with this stock solution, both ends of the column were sealed and the system was introduced into a bath at 70 °C for 24 h. A white polymeric monolith was obtained. This monolithic column was connected to a HPLC pump and washed with THF at 1 mL min⁻¹ for 2 h at r.t. Then, methylimidazole (25 mL) was pumped at a flow rate of 0.2 mL min⁻¹ for 24 h, the column being maintained at 60 °C. The column was then washed with THF at 1 mL min⁻¹ for 2 h at r.t.

All of the polymeric materials were characterized by FT-IR spectroscopy, Raman microspectroscopy, and elemental

analysis, which confirmed the expected structures. The details of the synthesis and characterization of these compounds can be found in our previous publications.^{9,11,12,29}

Batch cyanosilylation reaction

3 mmol of the corresponding carbonyl compound were added over 75 mg of the catalyst followed by the addition of 3.1 mmol of TMSCN. The mixture was gently stirred during 24 hours at 25 °C. To determine the kinetic profiles an aliquot of 20 μ L was regularly taken (30 min, 1 hour, 2 hours, 4 hours, 6 hours, 8 hours and 24 hours) and diluted in 1 mL of CH₂Cl₂. Samples were then analysed by G.C. and ¹H-NMR (see ESI[†]).

Reactive filtration cyanosilylation reaction

A regular 5 mL syringe equipped with a nylon filter was filled with 0.4764 mg of the catalyst SILLP-7. The mixture of the reagents (1:1 mol acetophenone–TMSCN) was added to the top of the syringe and was eluted through the catalytic bed and separated from the solid by simple gravimetric flow. Aliquots were taken at constant time intervals (15 min) and analysed by G.C.

Continuous flow cyanosilylation reaction

The reactor was set up by introducing the SILLP-7 (*ca*. 600 mg) in a glass Omnifit® column (5 mm × 10 cm), which was connected at the head to a Jasco HPLC pump (PU2080 plus) and at the bottom to a continuous flow cell for a Pike-ATR MIRacleTM single reflection ATR (diamond/ZnSe) adapted to a Jasco-6300 FT-IR spectrometer by standard tubing connectors. A solution of the reagents (1:1.1 mol acetophenone–TMSCN) was pumped through the catalytic bed at different flow rates. The IR spectra were recorded at continuous intervals of time (2–4 min) during the run. In all the cases, aliquots were collected at the outlet of the reactor and were analysed by GC.

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