Base supported ionic liquid-like phases as catalysts for the batch and continuous-flow Henry reaction†

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New solid basic catalysts immobilised onto supported ionic liquid-like phases have been prepared, having suitable mechanical stability for their use for the continuous-flow Henry reaction.

Introduction

The need to reduce the amount of toxic waste and by-products arising from chemical processes requires an increasing emphasis on the use of less toxic and environmentally compatible materials and the design of new synthetic methods.¹ Base catalysed reactions are widely employed in the bulk and fine chemical industries. Examples include the aldol,² Knoevenagel,³ Henry⁴ and Michael⁵ reactions. Under the former perspective, this requires achieving selective processes yielding the desired product and reducing the salts formed as a result of neutralisation of soluble bases. Within this context, the design and development of environmentally friendly basic catalysts for C–C bond formation in organic transformations is highly important.

To catalyse these processes organic amines, alkali alkoxides, and alkali hydroxides are commonly used in a homogeneous phase with the reagents. Although the approach is effective, these reagents are difficult to separate and, in many cases, are not recycled. Moreover, the presence of acids in the work up may catalyze side reactions, like dehydration, leading to lower selectivities. To alleviate these problems, solid basic catalysts have been developed utilizing either inorganic solid materials, such as basic metal oxides and carbonates, or by supporting organic bases, for example amines, on inorganic or polymeric supports. This approach has attracted intense interest. Effective heterogeneous basic catalysts have been found for aldol, Knoevenagel, Henry and Michael reactions and, in many cases, the solid base is recyclable.⁶

Recently, ionic liquid technology has been utilized to enable base catalysed reactions to occur, allowing the base to be recycled and, in some cases, showing higher selectivities compared with molecular solvents.⁷

Although ILs have become commercially available, they are still relatively expensive compared to traditional solvents. Besides, some of them show evidence of low biodegradability and (eco)toxicological properties.⁸ Hence, the immobilisation of ILs onto a support is a highly attractive strategy to minimize

the amount of ILs used, maintaining their catalytic properties. Additionally, supported ILs have the advantage of an easy separation and recyclability as well as the potential for the development of continuous processes.⁹

We have recently reported the preparation of supported ionic liquid-like phases (SILLPs) by the modification of either macroporous or gel type polystyrene-divinylbenzene (PS-DVB) resins.¹⁰ As these materials are not able to adsorb ILs as films onto the surface, as occurs in the case of silica gel,¹¹ our approach was based on the immobilisation by covalent binding of IL-like units (alkyl-imidazolium cations). In our approach, ILs properties are transferred to the solid phase leading to either monolithic supported ionic liquid-like phases (M-SILLPs) or gel supported ionic liquid-like phases (G-SILLPs), with similar characteristics than the homogeneous analogues.¹² Furthermore, their controlled solid nature enable them to be used to develop mini-flow reactors for continuous processes.¹³

In this paper, we report the preparation of new solid base catalysts with suitable mechanical stability for their application for continuous-flow processes. The catalytic systems are based on basic anions immobilised by metathesis onto SILLPs, and were applied for batch and continuous nitroaldol reactions. This approach synergically combines the advantages of supported ionic liquids as a “supported liquid solvent”, those of an immobilised base as a “green” catalyst and those of solventless reactions with the advantages of a continuous flow process, easy product separation and catalyst reuse.

Experimental

General considerations

All the reagents were used as received, without any further purification. Raman spectroscopy was done by means of a JASCO NRS-3100 dispersive spectrometer. Conditions: 785 nm laser with a single monochromator, grating 600 mm^{−1}, slit 0.2 mm, resolution 12.75 cm^{−1}; with a center wavenumber of 1200 cm^{−1}, a laser power of 90.1 mW and 10 accumulations of 5 s. The IR spectra were recorded on a Perkin-Elmer 2000. NMR spectroscopy was done by means of a Varian Mercury 500 MHz with chemical shifts expressed in ppm. Mass spectra were recorded on a Quattro LC (quadrupole–hexapole–quadrupole) mass spectrometer with an orthogonal Z-spray electrospray

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interface. Elemental analysis were performed on an Elemental Carlo Erba 1108 apparatus.

General procedure for the synthesis of G-SILLPs

A Merrifield resin (2 g, 1.1 mmol g⁻¹, 1% DVB) was suspended in 25 mL of a 1 M solution of 1,2-dimethylimidazole in DMF. The system was heated at 80 °C and periodically, samples of *ca.* 20 mg of polymer were extracted, washed with MeOH and dried under vacuum for Raman analysis. After 3 h, the polymer was filtered, washed with DMF (3 × 20 mL), MeOH (3 × 20 mL), CH₂Cl₂ (3 × 20 mL) and dried under vacuum at 60 °C.

General procedure for the synthesis of M-SILLP 3

Monolithic materials were prepared by copolymerization of the corresponding monomeric mixture inside a HPLC column (stainless column, 15 cm–1/4 inch id) as has been described elsewhere.^{10a} Monomeric mixture 40 : 60 CIVB : DVB mass%; porogenic mixture toluene : dodecanol 10 : 50 mass%; monomers: porogens ratio 40 : 60 mass%. 1% AIBN, 24 h, 70 °C.

G-SILLP 4a

IR (cm⁻¹) KBr. 3053, 3023, 2920, 1602, 1587, 1535, 1512, 1451, 1421, 1269, 1239, 1162, 1112, 1081, 1019, 855, 823, 762, 695, 665, 607, 545, 471. **Raman (cm⁻¹):** 1595, 1575, 1506, 1442, 1323, 1192, 1177, 1148, 1064, 1024, 995, 900, 825, 788, 755, 720, 663, 637, 616, 540, 401, 310. **Elemental analysis observed:** %N 2.5. **Calculated for** (C₁₀H₁₀)_{0.02}(C₈H₈)_{0.87}(C₁₄H₁₇ClN₂)_{0.11} %N 2.6. **Loading:** 0.91 mmol functional group g⁻¹ resin.

G-SILLP 4b

Elemental analysis observed. %N 4.3. **Calculated for** (C₁₀H₁₀)_{0.02}(C₈H₈)_{0.74}(C₁₄H₁₇ClN₂)_{0.24} %N 4.8. **Loading:** 1.78 mmol functional group g⁻¹ of resin.

G-SILLP 4c

Elemental analysis observed. %N 8.05. **Calculated for** (C₁₀H₁₀)_{0.02}(C₈H₈)_{0.46}(C₁₄H₁₇ClN₂)_{0.52} %N 8.10. **Loading:** 2.89 mmol functional group g⁻¹ of resin.

SILLP 5

Elemental analysis observed. %N 2.35. DVB content estimated by Raman spectroscopy.¹⁴ **Calculated for** (C₁₀H₁₀)_{0.55}(C₈H₈)_{0.26}(C₁₄H₁₇ClN₂)_{0.14} %N 2.83. **Loading:** 1.07 mmol of functional group g⁻¹ of resin.

M-SILLP 6

A 1 M solution of 1,2-dimethylimidazole in DMF was pumped into a monolithic column by means of a HPLC pump. After filling the column, the system was closed and heated at 70 °C for 24 h in an oven. Afterwards, the system was washed with DMF and MeOH. **IR (cm⁻¹) KBr:** 3053, 3023, 2920, 1602, 1587, 1535, 1512, 1451, 1421, 1269, 1239, 1162, 1112, 1081, 1019, 855, 823, 762, 695, 665, 607, 545, 471. **Raman (cm⁻¹):** 1595, 1575, 1506, 1442, 1323, 1192, 1177, 1148, 1064, 1024, 995, 900, 825, 788, 755, 720, 663, 637, 616, 540, 401, 310. **Elemental analysis**

observed: %N 4.68. **Calculated for** (C₁₀H₁₀)_{0.64}(C₁₄H₁₇ClN₂)_{0.36} %N 6.0. **Loading:** 2.14 mmol functional group g⁻¹ of resin.

General procedure for anion metathesis

The resin (1 g) was suspended in 15 mL of a 1 M solution of the corresponding salt in MeOH or MeOH : H₂O. For the introduction of hydroxyl groups in the resin, it was suspended in 10 mL of an aqueous solution of NH₃. The system was stirred for 24 h at room temperature. Afterwards the polymer was filtered and washed with MeOH, MeOH : H₂O (1 : 1), H₂O and MeOH.

G-SILLP 7a (X = OH)

IR (cm⁻¹) KBr. 3023, 2921, 2849, 1707, 1670, 1587, 1534, 1513, 1452, 1420, 1269, 1239, 1160, 1112, 1018, 965, 823, 762, 695, 665, 543. **Raman (cm⁻¹):** 1595, 1575, 1506, 1442, 1323, 1192, 1177, 1148, 1064, 1024, 995, 900, 825, 788, 755, 720, 663, 637, 616, 540, 401, 310. **E. analysis calc:** %N 2.4. **Calculated for** (C₁₀H₁₀)_{0.02}(C₈H₈)_{0.86}(C₁₆H₂₀N₂O₂)_{0.11} %N 2.6. **Loading:** 1.04 mmol functional group g⁻¹ of resin.

G-SILLP 7b (X = OH)

Elemental analysis observed. %N 4.2. **Calculated for** (C₁₀H₁₀)_{0.02}(C₈H₈)_{0.74}(C₁₄H₁₈N₂O)_{0.24} %N 4.9. **Loading:** 1.78 mmol functional group g⁻¹ resin.

G-SILLP 7c (X = OH)

Elemental analysis observed. %N 7.56. **Calculated for** (C₁₀H₁₀)_{0.02}(C₈H₈)_{0.46}(C₁₄H₁₈N₂O)_{0.52} %N 7.66. **Loading:** 2.71 mmol functional group g⁻¹ resin.

G-SILLP 7d (X = proline)

Elemental analysis observed. %N 2.6. **Calculated for** (C₁₀H₁₀)_{0.02}(C₈H₈)_{0.86}(C₁₉H₂₅N₃O₂)_{0.11} %N 3.6. **Loading:** 0.86 mmol functional group g⁻¹ of resin.

Characterization of 8 (X = OH)

IR (cm⁻¹) KBr. 3053, 3023, 2920, 1602, 1587, 1535, 1512, 1451, 1421, 1269, 1239, 1162, 1112, 1081, 1019, 855, 823, 762, 695, 665, 607, 545, 471. **Raman (cm⁻¹):** 1595, 1575, 1506, 1442, 1323, 1192, 1177, 1148, 1064, 1024, 995, 900, 825, 788, 755, 720, 663, 637, 616, 540, 401, 310. **Elemental analysis observed:** %N 2.38. **Calculated for** (C₁₀H₁₀)_{0.55}(C₈H₈)_{0.26}(C₁₄H₁₈N₂O)_{0.14} %N 2.88. **Loading:** 1.05 mmol functional group g⁻¹ of resin.

Characterization of 9 (X = OAc)

IR (cm⁻¹) KBr. 3053, 3023, 2920, 1602, 1587, 1535, 1512, 1451, 1421, 1269, 1239, 1162, 1112, 1081, 1019, 855, 823, 762, 695, 665, 607, 545, 471. **Raman (cm⁻¹):** 1595, 1575, 1506, 1442, 1323, 1192, 1177, 1148, 1064, 1024, 995, 900, 825, 788, 755, 720, 663, 637, 616, 540, 401, 310. **Elemental analysis observed:** %N 4.68. **Calculated for** (C₁₀H₁₀)_{0.64}(C₁₆H₂₀N₂O₂)_{0.36} %N 5.56. **Loading:** 1.99 mmol functional group g⁻¹ of resin.

Synthesis of 1-benzyl-2,3-dmim[Cl]

1,2-dimethylimidazole (1.5 g, 15.6 mmol) was dissolved in 20 mL of EtOH in a 50 mL flask. Then, benzyl chloride (2.4 mL, 20 mmol) was added. The solution was heated at 80 °C for 5 h. The product was washed with CH₂Cl₂/H₂O and later the organic phase was evaporated under vacuum. The product was recrystallized in CH₂Cl₂ to obtain 1.57 g of solid (7.07 mmol, 45% yield). ¹H (CD₃OD, δ): 2.66 (s, 3H), 3.86 (s, 3H), 5.44 (s, 2H), 7.36–7.44(m, 5H), 7.55(s, 2H). ¹³C (CD₃OD, δ): 9.11, 34.67, 51.68, 121.44, 122.75, 127.95, 128.85, 129.24, 134.08, 145.15. IR (cm⁻¹) KBr: 3067, 2851, 1572, 1497, 1456, 1364, 1334, 1162, 1082, 1030, 873, 823, 723, 699, 663, 624, 470, 449, 433. Raman (cm⁻¹): 1597, 1578, 1505, 1444, 1375, 1328, 1265, 1198, 1150, 1084, 1042, 1024, 994, 874, 811, 715, 668, 612, 562, 425, 308. MS (*m/z*): 187. MP 125–130 °C. Elemental analysis calculated for (C₁₂H₁₅ClN₂): %C 64.71 %H 6.79 %N 12.58 observed %C 64.57 %H 6.91 %N 12.47.

General procedure for the Henry reaction in batch

p-Nitrobenzaldehyde (0.25 g, 1.66 mmol) was dissolved in 2.25 g of nitromethane (25 equiv.). Later 0.5 mmol of the supported base were added to the solution, and the system was stirred at room temperature. Periodically, liquid samples were taken and analyzed by Raman spectroscopy. At the end of the reaction, the polymer was filtered, the excess of aldehyde evaporated and the product was characterized by ¹H NMR.

General procedure of the Henry reaction in continuous flow mode

A Gilson HPLC pump was used to carry out the Henry reaction in continuous flow mode. The column was connected and the solution of aldehyde into nitromethane was pumped through the column at room temperature. The samples were later analyzed by Raman spectroscopy and also by ¹H NMR. Once the reaction was finished, the system was washed with MeOH pumped through the column.

Synthesis of base-SILLPs

The SILLPs were prepared by modification of a series of Merrifield resins with microporous nature (2% of crosslinking) and different functionalisation degrees (1.2, 2.1 and 4.3 mequiv. Cl g⁻¹) (Scheme 1). Besides, macroporous polymers were also used in either beads or monolithic form. The synthesis of base-SILLPs were carried out by reaction of 1,2-dimethylimidazole (1,2-DMIM) with the different chloromethylated resins at a constant concentration of 1 M of 1,2-DMIM in DMF. The

Scheme 1 Synthesis of base-SILLPs. **1a–c** gel type polymer, **1a** (1.1 mequiv. Cl g⁻¹), **1b** (2.1 mequiv. Cl g⁻¹), **1c** (4.3 mequiv. Cl g⁻¹); **2** macroporous, beads (1.2 mequiv. Cl g⁻¹); **3** macroporous monolith (2.1 mequiv. Cl g⁻¹). (i) 1,2 dimethylimidazole, 90 °C. (ii) NaX or HX, H₂O.

reaction was followed by Raman spectroscopy. Monitoring reactions by means of spectroscopic techniques provide us a structural information of reagents and products, as well as information about reaction mechanisms.¹⁴

Fig. 1 shows the variation of four different peaks with the reaction time. The band at 647 cm⁻¹ (C–Cl stretching band) and at 1265 cm⁻¹ (down arrows) (wagging bands of CH₂–Cl) disappearing with time and being substituted by IL-like moieties. The peaks at 1506 cm⁻¹ and 720 cm⁻¹ (up arrows) correspond to symmetric and antisymmetric stretching of methyl group in the C₂ position of 1,2-DMIM increasing with time. The grafting of the imidazole moieties onto the polymer can be monitored through such variations. The kinetics plots (conversion vs. time, Fig. 2d) were calculated by following the evolution with time of the area of each characteristic peak.

Fig. 1 Raman spectra vs. time for the alkylation of **1c** (4.3 mequiv. Cl g⁻¹) with 1,2-DMIM to yield to **4c**.

First, the effect of the amount of alkylating agent used for the synthesis of SILLPs was investigated. The reaction was followed by the disappearance and appearance of the above mentioned bands. When the synthesis of SILLPs was carried out with a Merrifield resin (1.19 mmol g⁻¹) using a 3 or 6 fold excess of 1,2-DMIM at 90 °C in DMF, no differences in the reaction kinetics were found. In 2.5 h the quantitative grafting of the IL-like groups was achieved. By contrast, less than 10 min were needed if the reaction was performed using melt 1,2-DMIM as solvent and reagent. However, the solidification of 1,2-DMIM in excess makes the thorough washing of the final resin difficult.

The loading and structure (macroporous/gel type) of the polymer may have an effect on kinetics for the grafting of the IL-like moieties.¹⁵ Hence, the synthesis of four different (**4a–c**, **5** and **6**) supported ionic liquid-like phases were studied. Besides, the synthesis of the analogous ionic liquid in solution was also performed in order to compare the reaction kinetics, the future applications, and the behaviour of the homogeneous vs. supported ionic liquid. The reactions were followed by Raman spectroscopy, as in the previous cases.

Some of the results are displayed in Fig. 2 showing the disappearance of the CH₂–Cl band (1265 cm⁻¹) for the polymers in each studied case. Surprisingly, under similar conditions, the homogeneous reaction was slower than the heterogeneous ones (Fig. 3). It is likely that as the grafting of the IL-like moieties

Fig. 2 (a) Raman onset for the 1530–1480 cm^{-1} region. (b) Raman onset for the 1270–1240 cm^{-1} region. (c) Raman onset for the 740–640 cm^{-1} region. (d) Kinetics plot conversion vs. time for the different peaks for the synthesis of **4c**.

Fig. 3 Conversion vs. time plot for the synthesis of SILLPs in DMF. (●) Homogeneous alkylation of 1,2-DMIM with chloromethylbenzene. (★) Alkylation of 1,2-DMIM with **1a** (gel type 2.1 mequiv. Cl g^{-1}). (▼) Alkylation of 1,2-DMIM with **1b** (gel type 1.2 mequiv. Cl g^{-1}). (▲) Alkylation of 1,2-DMIM with **1c** (gel type 4.3 mequiv. Cl g^{-1}). (■) Alkylation of 1,2-DMIM with **2** (macroporous 1.2 mequiv. Cl g^{-1}).

progressed the polarity of the support was also modified. Thus, the un-reacted $\text{CH}_2\text{-Cl}$ groups were surrounded by a more polar environment favouring the substitution reaction. Such effects are less efficient in the homogeneous system. Kinetics for the different supports did not show important differences due to either loading or nature of the backbone matrix. The reaction was slightly faster at the beginning in the case of the macroporous polymer. This polymer has a rigid structure with

some functional groups placed in the outer surface, and therefore more accessible to the alkylating agents. Other groups, however, are located in the non-swollable crosslinked region being thus less accessible. This fact explains why the reaction is faster in the beginning, but slower afterwards, showing an almost complete functionalization in approximately 150 min. In the microporous resins, this phenomenon is not of importance, the appropriate swelling of the polymer controlling the accessibility of the reactive sites.¹⁵ This is in fact reflected by the results obtained using different solvents with differing swelling properties as can be seen in Fig. 4.

Henry reaction catalysed by base-SILLPs

The classical nitroaldol reaction is usually performed in the presence of a base (Scheme 2) in an organic solvent. Since basic reagents are also catalysts for the aldol condensation and for the Cannizzaro reaction when aldehydes are used as carbonyl sources, it is necessary to adopt appropriate experimental conditions to suppress these competitive reactions.¹⁶ To obtain better yields of 2-nitro alcohols a careful control of the basicity of the reaction medium is necessary, and long reaction times are demanded. Furthermore, the α -nitroalknols formed may undergo base-catalyzed elimination¹⁷ of water to give nitroalkenes that readily polymerise. This elimination is difficult to avoid when aryl aldehydes are employed.

We decided to investigate the Henry reaction between *p*-nitrobenzaldehyde and nitromethane under solventless conditions using the supported ionic liquid-like phases as basic

Fig. 4 Conversion vs. time plot for the synthesis of SILLPs. (●) Alkylation of 1,2-DMIM with **2** (macroporous 1.2 mequiv. Cl g⁻¹) in water. (▲) Alkylation of 1,2-DMIM with **2** (macroporous 1.2 mequiv. Cl g⁻¹) in DMF. (■) Alkylation of 1,2-DMIM with **1a** (gel type 1.2 mequiv. Cl g⁻¹) in water. (▼) Alkylation of 1,2-DMIM with **1a** (gel type 1.2 mequiv. Cl g⁻¹) in DMF.

Scheme 2 Henry reaction.

catalysts. The corresponding bases were prepared by methathesis of Cl⁻ by different basic anions (Table 1). The SILLPs based on 1,2-dimethylimidazole groups were chosen to avoid the C-2 basic protons in the imidazole group. Indeed, when the reaction was performed with base-SILLPs derived from 1-methylimidazole, products derived from both Cannizzaro and elimination reactions were observed. Table 1 summarised some of our results for the batch Henry reaction for different basic anions. No side products were observed for any of the basic anions assayed. Acetate and

hydroxy anions were the most efficient catalyst in terms of yield and reaction rate. The catalyst can be reused without losing activity. No chiral induction was observed when L-proline was used.

We also studied the influence of the base loading onto the SILLPs. Thus, supported bases with different amount of IL-like moieties were used (**7a–c**, X = OH⁻). All the reactions were performed for 30% catalysts/aldehyde molar ratio. As it can be seen in Fig 5 no significant differences on reaction rate were found. However, both yield and rate were reduced by decreasing the amount of base from a 30% to a 16%.

Fig. 5 Conversion vs. time for the batch Henry reaction catalysed by different SILLPs. (●) 30% cat, **7a** 1.04 mequiv. cat g⁻¹. (▲) 30% cat, **7b** 1.78 mequiv. cat g⁻¹. (▼) 16% cat, **7b** 1.78 mequiv. cat g⁻¹. (■) 30% cat, **7c** 3.02 mequiv. cat g⁻¹. Conversion followed by the disappearing of the carbonyl band in Raman spectroscopy.

Therefore, once the efficiency of base-SILLPs was proved under batch solventless conditions, we decided to evaluate their behaviour under continuous-flow conditions.¹⁸ An experimental set-up as shown in Fig. 6 would allow the easy recovery of the excess of nitromethane as well as the easy separation

Table 1 Henry reaction catalysed by basic-SILLPs^a

Entry	X ⁻	Loading/mequiv. g ⁻¹	Time/min	Yield ^c (%)	TON/g g-cat ⁻¹	TOF/g g-cat ⁻¹ h ⁻¹
1	Cl	1.05	405	26	0.6	0.09
2	AcO	1.04	30	97	2.2	4.4
3	AcO ^b	1.04	30	98	2.2	4.4
4	OH	1.09	30	99	2.2	4.4
5	L-Proline	0.98	420	75	1.7	0.2
6	Merrifield	—	420	0	—	—
7	Cl im	0.99	420	2	—	—

^a All reactions were performed using 250 mg *p*-nitrobenzaldehyde, 150 mg of base-SILLP and 1 mL of nitromethane. ^b 2nd use. ^c Yield determined by NMR.

Fig. 6 Continuous-flow solventless Henry reaction catalysed by basic-SILLPs.

and isolation of the product from the catalysts. The recycling of nitromethane was done by evaporating under vacuum the product phase.

Although the initial screenings under batch condition were performed using gel type SILLPs, the flow experiments were run using a macroporous polymer. When gel type polymers were packed in a column and reactants were pumped, the high swelling of the materials led to high back pressures. However, basic-SILLPs based on either a macroporous beads polymer or a monolith did not show this technical inconvenient. Therefore fixed-bed mini-flow reactors with different amounts of catalyst and volumes can be easily prepared. Table 2 summarises some of the results achieved for the continuous-flow Henry reaction using such reactors.

The fixed-bed mini-flow reactor based on a monolithic material (Entry 1, Table 2) was attached to a high pressure pump. Then, a solution of *p*-nitrobenzaldehyde in nitromethane was pumped through the reactor at a constant flow rate ($100 \mu\text{L min}^{-1}$) over *ca.* 7 h. Aliquots were analyzed for the product content at regular time intervals by both NMR and Raman spectroscopy. Fig. 7 displays the observed behaviour during this period of time. Thus, the reaction proceeded continuously with 95% yield at room temperature with no noticeable changes on both product yield and selectivity after 342 min (*ca.* 47 bed-volumes) of continuous use under the same conditions. However, after this time some decay on activity was observed. At that time, the reactor was washed and regenerated by pumping a solution of NaOAc in water. Once the reactor was washed, a new reaction cycle was performed under the same conditions. The catalyst showed the same performance than before washing (Fig. 6 and Entry 2 Table 2). Accordingly, deactivation of the catalyst could be due to the slow exchange of the catalytic anion (AcO^-) by other less active anions such as $^-\text{CH}_2\text{NO}_2$.

Fig. 7 Solventless continuous-flow Henry reaction.

Different flow rates, reactants, concentrations, type of materials (monolith vs. beads) and basic anions were tested (Table 2). All the conditions assayed led to full conversion of the aldehyde into the product. However, changes in the conditions were reflected in the presence of different deactivation patterns of the catalyst. Best results were achieved when using OH^- as anion (Entry 6). The use of hydroxyl as anion is advantageous since

Table 2 Continuous-flow Henry reaction catalysed by basic-SILLPs

Entry	X ⁻	G cat.	Type	Loading cat/ mmol g ⁻¹	[RCHO]/M	Flow/ mL min ⁻¹	Vol./mL	LHSV/ g g-cat ⁻¹ h ⁻¹	Residence time ^e /min	TON cycle/ g g-cat ⁻¹	Cycles ^c	Productivity/ g g-cat ⁻¹	Final product/g
1	AcO	0.48	Monolith	1.99	0.33	0.10	0.72	0.87	7.2	0.10	47.22	4.81	2.4
2	AcO	0.48	Monolith	1.99	0.33	0.10	0.72	0.87	7.2	0.10	41.67	4.28	2.1
3	AcO	0.23	Monolith	1.99	0.20	0.50	0.35	5.43	0.7	0.06	86.21	4.88	1.3
4	AcO	0.31	Beads	1.05	0.72	0.10	0.48	2.95	4.8	0.24	24.84	5.85	1.8
5	AcO	0.31	Beads ^a	1.05	0.72	0.25	0.48	7.39	1.9	0.21	7.76	1.66	0.6
6	OH	0.47	Beads	1.10	0.72	0.50	0.81	9.64	1.6	0.26	31.06	7.95	3.8
7	AcO	0.48	Monolith	1.99	0.73	0.10	0.58	1.95	5.8	0.17	17.24	2.92	1.6

^a Recycle of entry 4. ^b Calculated according to standard literature.¹⁹ ^c Number of bed volumes per cycle with a yield higher than 90%.

the recycling is facilitated by just using an aqueous solution of ammonia.

Conclusion

The use of SILLPs allowed us to prepare efficient basic catalysts using a basic anion. The reaction can be carried out either in a batch or continuous flow system. The latter one proved to be more suitable for the easy separation and isolation of the final product. In flow systems, a small amount of the substrate is actually forced into intimate contact with an “excess” of the catalyst. Thus, a total conversion of product can be achieved with residence times as short as 1–3 min, using a monolithic mini-reactor with a free-volume of ca. 500–800 μL . Indeed, if the TON for batch and continuous flow process are compared, higher values are obtained for the flow systems. The base-supported systems present a high throughput and are advantageous to the upscale of the process. Although the activity of catalysts decays with time, the continuous flow set-up allows an easy and efficient washing and recycling of the catalytic system. Indeed, a set-up with parallel reactors would allow the continuous production for long periods of time, by switching from one to other when the catalytic activity decreased.

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